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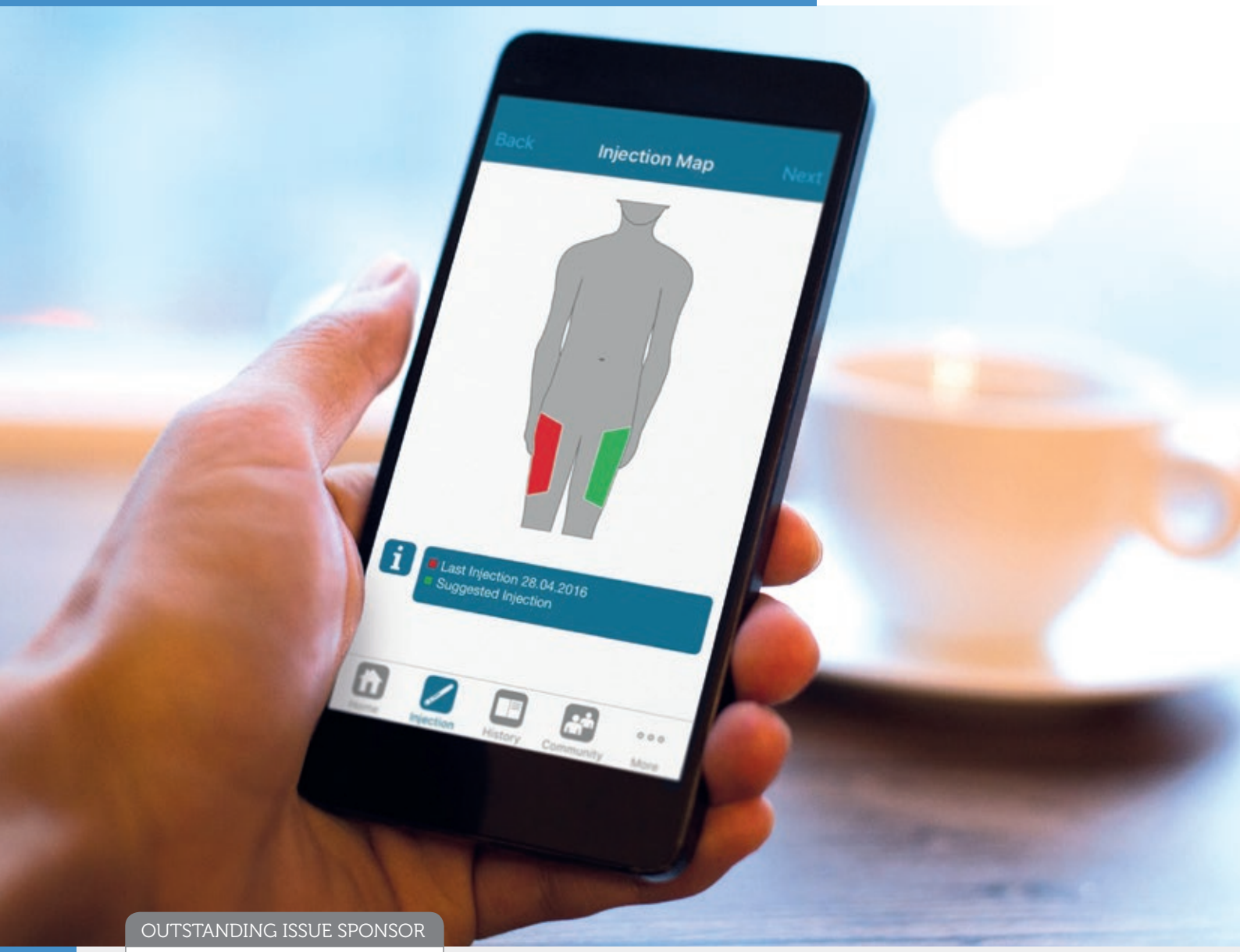

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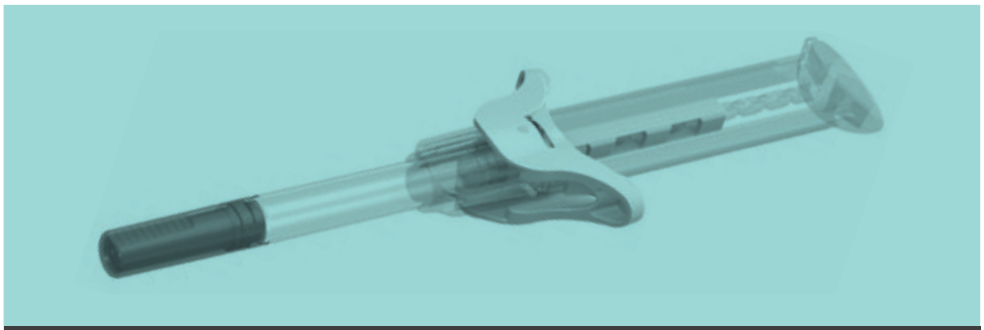

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France
Tel: +33.(0)4.76.68.36.36

U.S. Headquarters
1, Becton Drive
Franklin Lakes, NJ 07417-1886
USA
Tel U.S.: (1).800.225.3310
Outside of U.S.: (1).201.847.4017

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PREFILLED SYRINGES

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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Nov Pulmonary & Nasal Delivery

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EDITORIAL AND ADVERTISING:

Contact: Guy Furness, Proprietor & Publisher
T: +44 (0) 1273 47 28 28
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

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Front cover image, adapted from SmartPilot™ mobile app concept "Injection map advising patient where to inject next", supplied by Ypsomed. Reproduced with kind permission.

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February 2017	Prefilled Syringes	December 19th
March 2017	Skin Drug Delivery: Dermal, Transdermal & Microneedles	January 23rd
April 2017	Pulmonary & Nasal Drug Delivery	February 20th
May 2017	Injectable Drug Delivery: Devices Focus	March 20th
June 2017	Connected Drug Delivery Systems	April 17th
July 2017	Novel Oral Delivery Systems	May 22nd
September 2017	Wearable Injectors	July 24th
October 2017	Prefilled Syringes	August 21st
November 2017	Pulmonary & Nasal Delivery	September 25th

SMARTPILOT FOR YPSOMATE: TRANSFORMING A PROVEN AUTOINJECTOR INTO A FULLY CONNECTED DEVICE

In this article, Orfeo Niedermann, Business Development Director, Ypsomed Delivery Systems, provides insights into how connectivity enhances existing autoinjectors and adds value for users, physicians, pharma companies and insurers. Specifically, he sheds light on how SmartPilot, a re-usable add-on with built-in wireless communication and advanced sensors, transforms the standard YpsoMate 2-step autoinjector into a fully connected self-injection system. The article then illustrates how smart devices offer new possibilities to monitor adherence patterns during clinical testing and improve therapy outcomes with real-time, in-use patient guidance and tracking of injection history and success.

With the large number of new biologics the demand for devices for the subcutaneous (SC) self-injection of biopharmaceuticals continues to grow and develop. The need for simpler self-injection procedures and improved patient adherence for autoinjectors, pens and large-volume patch injectors is increasing. Smart technologies offer new possibilities to improve patient adherence and therapy outcome. There are a number of drivers stimulating the development and use of smart and connected devices.

> "For connected devices the necessary sensor, transmission and power sources are not yet affordable to be fully integrated into disposable pens and autoinjectors. This is why Ypsomed is developing solutions to combine the strengths of a ready-to-use disposable device with the technical possibilities of reusable devices."

LESS FREQUENT INJECTIONS

With improved formulations and larger injection volumes, new biologics typically require weekly, biweekly or even monthly SC injections. On the one hand, less frequent injections reduce patient exposure to the moments of injection discomfort and the hassle of storing and preparing the drug product. The lack of injection routine, on the other hand, calls for even simpler use of the device and need for more guidance and feedback before, during and after injection.

CHANGES IN DRUG REIMBURSEMENT MODELS

With healthcare costs soaring for newer biologic therapies health insurers are looking to move away from unit priced payment towards outcome-based compensation models for therapies aligned with superior clinical results. This also drives the need for technical solutions that automatically record whether, and how successfully, the patient follows therapy guidelines.

Orfeo Niedermann
Business Development Director
Ypsomed Delivery Systems
E: orfeo.niedermann@ypsomed.com

Ypsomed AG
Brunnmattstrasse 6
CH-3401 Burgdorf
Switzerland

www.ypsomed.com

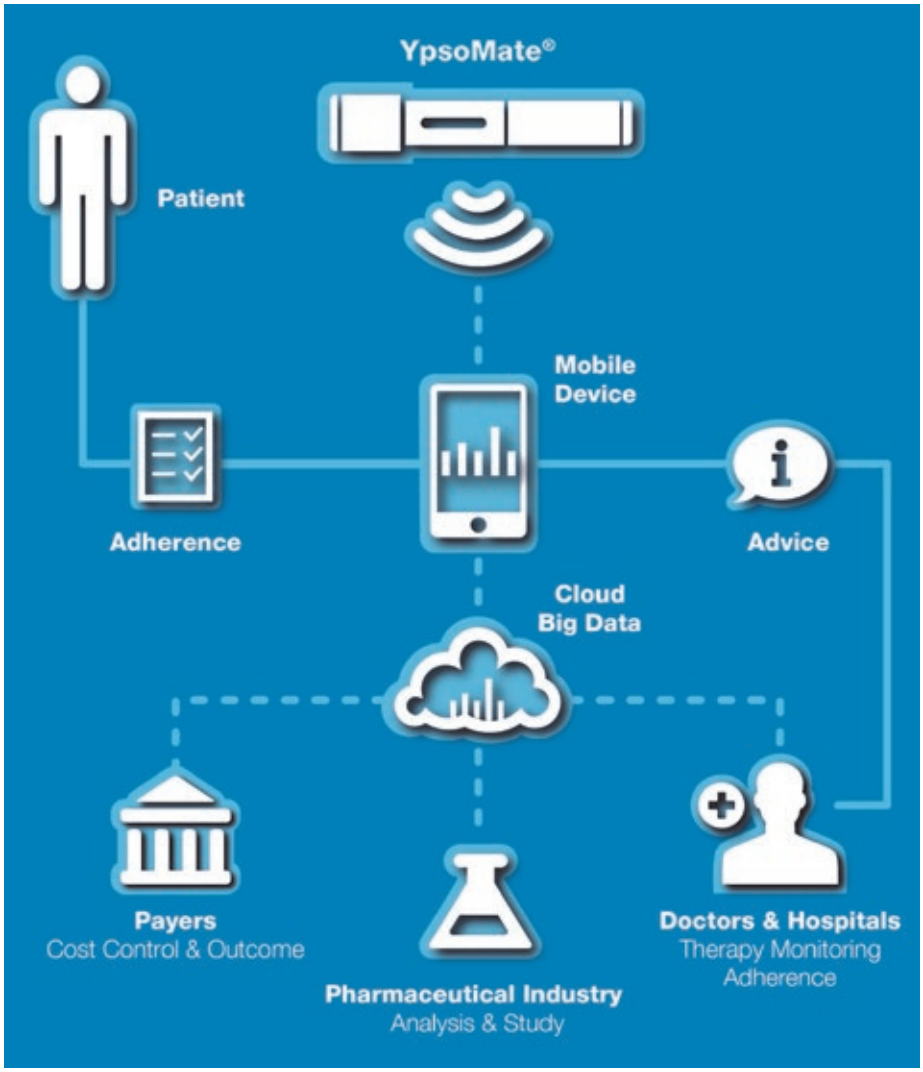

Figure 1: Environment and network interacting with the patient.

ANALYSIS OF REAL-WORLD DATA

Pharma companies are accumulating vast amounts of data about therapies and disease states during clinical trials and post-market surveillance. However, one important factor in the equation is whether patients in self-care environments have correctly administered their medicine. This also calls for a simple and automatic log book for all patient administered doses.

PATIENT & HEALTHCARE INVOLVEMENT

As the internet, mobile devices, social networks and patient forums gather information, patient awareness for their therapy status and effectiveness increases significantly. The acceptance and demand for electronic, connected devices and software is growing quickly and further supporting the need for smart self-injection devices (Figure 1).

SMART ADD-ON TRANSFORMS AUTOINJECTOR INTO A FULLY CONNECTED DEVICE

The world of self-injection pens and autoinjectors has seen a clear trend to prefilled disposable devices. Key drivers are simplicity of use in combination with pharma company needs to improve efficiency of the supply chain and simplify device replacement.

For connected devices the necessary sensors, transmission and power sources are not yet affordable to be fully integrated into disposable pens and autoinjectors. This is why Ypsomed is developing solutions to combine the strengths of a ready-to-use disposable device with the technical possibilities of reusable add-ons.

At this year's PDA Universe of Prefilled Syringes & Injection Devices Conference (Huntington Beach, CA, US, October 17-18, 2016), Ypsomed presents its latest advancement in smart devices that

> "The device detects and communicates different use states and allows the smartphone to provide real-time step by step instructions in written, animated and audible formats."

Figure 3: Illustration of a patient loading a standard YpsoMate 2-step autoinjector into the fully connected SmartPilot add-on.

leverages the proven and fully industrialised YpsoMate autoinjector platform.

SmartPilot (see Figure 3) is a reusable add-on for the standard YpsoMate autoinjector that not only tracks and wirelessly transmits the success of injection events but also pilots the patient in real-time throughout the injection process. This is achieved with advanced visual and audible feedback from the add-on, display of complementary information on a related mobile app, and individualised ergonomics. SmartPilot flexibly transforms a standard YpsoMate autoinjector into a fully connected device.

As SmartPilot is compatible with YpsoMate autoinjectors without further modification, it offers an ideal solution for existing and future YpsoMate customers who want to equip their device with connectivity flexibly as part of product lifecycle activities. SmartPilot may also be used as a means for monitoring and analysing progress of and patients' adherence patterns during clinical trials. In addition, the complementary mobile app may be enriched with questionnaires for patients to self-report their wellbeing and other disease-relevant parameters.

IN-USE GUIDANCE INCLUDING HOLDING TIME INFORMATION

In conjunction with the use of a smartphone and the related mobile app, SmartPilot can provide patients with video-enhanced instructions on how to use the autoinjector. The device detects and communicates different use states and allows the smartphone to provide real-time step by step instructions in written, animated and audible formats. This includes the option of providing precise advice on recommended holding time to reach complete delivery of the drug.

SmartPilot identifies handling errors and instructs patients on corrective actions with the help of the mobile app. As such, the technology complements conventional training methods and trainer devices. Data exchange between SmartPilot for YpsoMate and a patient smartphone is established via Bluetooth Low Energy (BTLE), an emerging standard compatible with all available smartphones and standard operating systems.

ADVANCED TECHNICAL SOLUTION

A key challenge when developing SmartPilot was to identify relevant device status information without physically modifying the existing YpsoMate autoinjector platform.

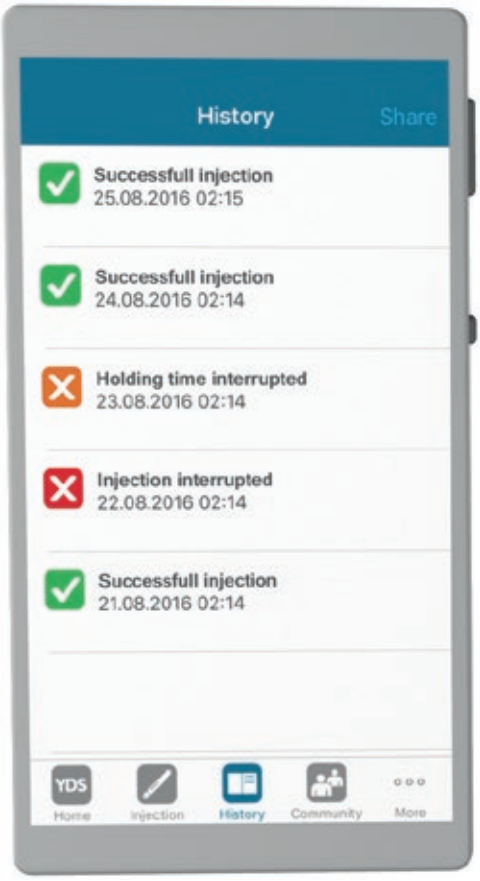

Figure 4: Illustration of information displayed on SmartPilot mobile app: the injection history provides an overview of injection events and indicates handling errors.

Ypsomed has developed a concept based on a contactless sensor solution that detects and differentiates between:

- Pushing the device on skin
- Completion of needle insertion and start of injection
- End of injection
- Removal of device from skin
- Locking of needle shield.

SmartPilot can therefore distinguish and recognise errors such as removing YpsoMate from the skin during injection or interruption of the holding time. Such information is recorded, transferred to the smartphone and processed for subsequent analysis (see Figure 4). Availability of such data not only instructs patients on how to use YpsoMate correctly but assists healthcare professionals, caregivers, and pharmaceutical companies. For instance, it may be used specifically to further improve patient training materials, to explain previous unexplained variations in clinical studies, or to support outcome-based payment scenarios.

USE WITH OR WITHOUT SMARTPHONE

SmartPilot also directly provides visual and audible feedback to patients on injection success or errors, without needing to have a smartphone connected during the injection process. SmartPilot provides integrated visual and audible feedback that guides the patient through the injection process and indicates use errors. It even advices the user on the recommended holding time by means of a flashing LED light and audible feedback (Figure 5).

Figure 5: SmartPilot for YpsoMate, ready for injection.

In addition, SmartPilot has built-in memory to record and store information covering multiple injection events. It saves use data including date, time and potential use errors on the device itself. Such information then can be read out either by patients and caregivers at a later point in time or by HCPs during a periodic check-up.

LEVERAGING SMART TECHNOLOGIES & INTERNET

The possibilities to enlarge the benefits of the associated smartphone app and internet connectivity are countless and will certainly evolve. The patient can easily be reminded when to perform the next injection. If an injection was not performed as scheduled, the patient will receive a reminder or a friendly personal call to motivate adherence for the next injection.

SmartPilot-related software may also track other health-relevant information around the patient or log patient self-reported health status or wellbeing. For more frequent or larger injections it may be helpful to track and recommend the subsequent injection site (see Figure 6). The patient may also have access to virtual patient forums and online communities to share experiences or injection-relevant information.

CONCLUSION

The YpsoMate family of 1 mL and 2.25 mL devices is enjoying significant success for both originator and biosimilar biologics due to their ease of use based on 2-step, button-less, push-on-skin technology. This is reinforced by Ypsomed's focus on well thought out, flexibly customisable designs manufactured on fully automated manufacturing infrastructure.

The development of SmartPilot for YpsoMate provides pharma companies with the ideal clinical and marketing tool to pioneer the next phase of self-administration device development in a connected world.

SmartPilot allows YpsoMate to be flexibly upgraded into a fully connected device and also provides advanced real-time user feedback. The related mobile app further enables display and analysis of complementary information, such as instructing patients on how to avoid use errors or advising on where to inject next. SmartPilot is suitable to monitor patient behaviours and adherence patterns during clinical trials. However, it also reflects a tool to transform the proven 2-step autoinjector into an internet-of-things enabled device to accelerate further the transition towards outcome-based payment models.

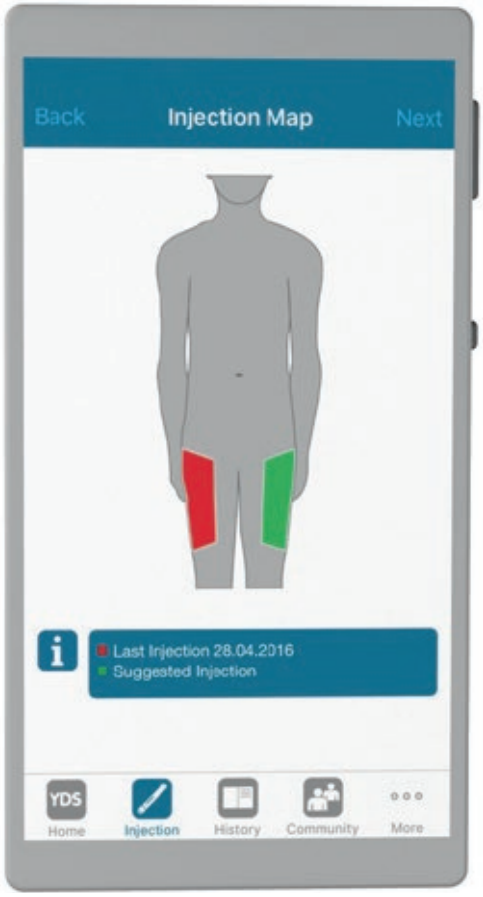

Figure 6: Injection map advising the patient where to inject next.

> "The development of SmartPilot for YpsoMate provides pharma companies with the ideal clinical and marketing tool to pioneer the next phase of self-administration device development in a connected world. SmartPilot allows YpsoMate to be flexibly upgraded into a fully connected device and also provides advanced real-time user feedback."

> "SmartPilot-related software may also track other health-relevant information around the patient or log patient self-reported health status or well-being. For more frequent or larger injections it may be helpful to track and recommend the subsequent injection site."

ABOUT YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed is the leading independent developer and manufacturer of innovative autoinjector and pen injector systems for self-administration of injectable drugs. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, 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. 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 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 ISO13485 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 companies 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 working relationships with numerous leading pharma and biotech companies.

Medicom
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EARLY & HOLISTIC DEFINITION OF THE OPTIMUM PRIMARY PACKAGING STRATEGY: ORPHAN/RARE DISEASES FOCUS

In this article, Kate Hudson-Farmer, PhD, and Niels Kure, MBA, both Directors of Front-End Innovation at Medicom Innovation Partner (a Phillips-Medisize Company), reveal conflicting pressures on the product development process in orphan indications which potentially lead to products in this category – especially emerging biotech products – being left with suboptimal drug delivery systems and primary packaging, and the consequent negative impact on patients. The authors explain how overcoming these pressures and paying proper attention to the development of the primary packaging and delivery systems for orphan products early on in the development process is worthwhile, with benefits arising as early as during clinical development as well as in the longer term.

Development of a new therapy is a very complex process, and many of the important decisions taken in the earliest stages will eventually follow the drug all the way through its lifecycle, and subsequently also appear in the hands of the patient, caregiver and/or healthcare practitioner.

The complexities of many orphan diseases in terms of treatment options (or lack of), their chronic manifestation and the management of symptoms, make them among the most challenging diseases to manage. A growing number of potential orphan disease therapies are being developed as biologics requiring injection as the dominant route of administration. Moreover, a significant majority of these are likely to be delivered by some form of injection by either the patient themselves or the caregiver. Getting the drug on the market and into the hands of the patient as quickly as possible, as well as defending its position against future potential entrants, is paramount for pharmaceutical companies in order to secure both short and long-term return on investment. This time pressure on products for orphan indications means that it is often decided just to put the drug in a vial and give the patient a syringe, which gives rise to poor adherence, poor administration, lower safety and ultimately lower efficacy.

> "If the drug molecule is designed specifically to meet the needs of the patient, surely a drug delivery solution optimised to fit the needs of the target patient group and orphan disease area is of critical significance too?"

This multi-layered complexity calls for strategic thinking where options for drug delivery solutions are considered against potential market needs, the strong scientific

Dr Kate Hudson-Farmer
Director, Front-End Innovation
T: +45 70 30 16 00
E: khf@medicomip.com

Mr Niels Kure
Director, Front-End Innovation
T: +45 70 30 16 00
E: nku@medicomip.com

Medicom Innovation Partner a/s
(A Phillips Medisize Company)
Gimsinglundvej 20
DK-7600 Struer
Denmark

www.medicomip.com

"Even for those orphan drugs that have achieved formulation into liquid preparations, the further application of prefilled syringes and even an auto injector, which is becoming more of the norm for many chronic diseases, is still lagging in the orphan arena."

drivers which normally characterise orphan drug development and the pharmaceutical company's own internal expectations. In order to retain a lead position over the longer term, thus creating competitive advantage beyond the orphan drug exclusivity period, one needs a thorough understanding of the lifecycle management strategies related to the drug packaging and delivery device options. It requires a "top down" and holistic approach to defining the treatment solution from a specific disease need perspective, capturing all the elements from therapeutic efficacy to optimal drug delivery to service-related benefits.

Ideally such a strategy process is carried out early enough in the drug development phase so that the required tests involving the primary packaging can be performed on the option that gives the required commercial and technical opportunities and positioning.

What is clear is that the drugs being developed to treat orphan diseases are not "off-the-shelf" but highly developed compounds tailored to the patients' needs. However, most of the drug delivery devices, which are supplied with the drug, are the complete opposite: off-the-shelf vials and syringes without any real thought as to the patients' needs. If the drug molecule is designed specifically to meet the needs of the patient, surely a drug delivery solution optimised to fit the needs of the target patient group and orphan disease area is of critical significance too?

Underestimating the importance of instilling confidence and wellbeing in such patient populations is crucial to long-term compliance with treatment. The healthcare world is shifting towards payment for outcomes and the orphan disease area is unlikely to escape this.

Carefully designed device solutions can be aimed at specific needs of a patient population and, vitally, to improving dosing consistency and accuracy. These factors lead to improving not only safety and efficacy but also the patients' adherence and compliance, aspects of utmost importance for improving outcomes. Improving outcomes leads to greater overall success of the drug both in clinical trials and on the market, justifying pricing decisions and creating a stronger, longer-term competitive position.

"The arguments are strong for making self-injection as simple and user-friendly as possible. Indeed, there is growing evidence that reducing the number and complexity of steps required for self-injection improves not only consistency of dose delivered but also overall adherence to treatment."

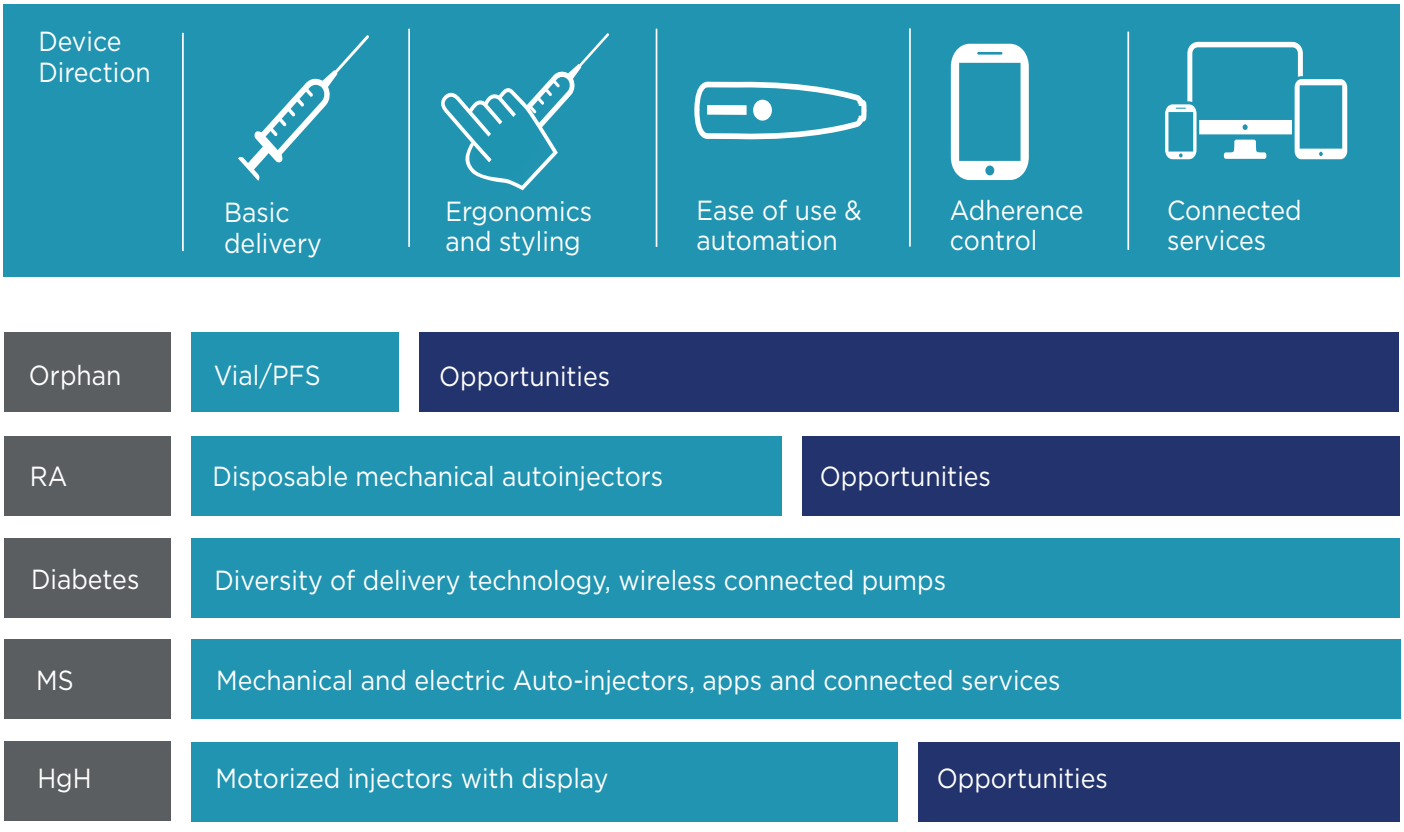

Figure 1: Examples of device and service maturity across therapies.

Fast-to-market approaches often involve formulating drugs that require reconstitution from lyophilised powders in a vial prior to injection. The reconstitution process requires the patient to carry out numerous steps whilst maintaining sterility and may potentially result in inconsistent reconstitution from dose to dose. Additionally, there are safety and emotional issues to contend with such as exposed needles not only posing a hazard to the user or caregiver, but creating fear and unease, often leading to lack of compliance in terms of continuing treatment. The arguments are strong for making self-injection as simple and user-friendly as possible. Indeed, there is growing evidence that reducing the number and complexity of steps required for self-injection improves not only consistency of dose delivered but also overall adherence to treatment.

> "...the overarching benefits that can be offered by such delivery systems to the orphan diseases sector are significant, and should be considered, as many have compound effects."

Using more advanced delivery systems to reconstitute drugs within the device, hide the needle from the user, as well as enabling a more consistent, easier and less fearful delivery is possible, but it is by far from being the norm.

Even for those orphan drugs that have achieved formulation into liquid preparations, the further application of prefilled syringes and even an auto injector, which is becoming more of the norm for many chronic diseases, is still lagging in the orphan arena.

Getting the drug on the market and into the hands of the patient as quickly as possible is a key driver for pharmaceutical companies, and this is extremely important for such orphan diseases where there is often such a lack of therapies. Unfortunately, thinking about the way such therapies are to be delivered is often not a dominant part of the total disease solution. Many view the utilisation of more advanced delivery systems as a diversification mechanism in a competitive market and thus do not see the need for such offerings for new market entrants where there may be a lack of significant competition. Additionally, due to the low volume of patients in any one orphan disease, a further perceived barrier is the ability to get a device manufacturer involved for such low volumes cost effectively.

However the overarching benefits that can be offered by such delivery systems to the orphan diseases sector are significant (see Figure 1), and should be considered, as many have compound effects. By their very nature orphan diseases have small patient numbers and clinical trial respondent numbers are allowed to reflect this. Consistent dosing within such small sample sizes, particularly. in later stage trials, where efficacy and improvements over other therapies is under scrutiny, is very important. Advanced delivery systems that can deliver doses repeatedly and accurately, in a user-friendly, non-threatening format, have the ability to provide results regarding actual efficacy more accurately for smaller populations, and are more likely to ensure adherence, compounding the effect of gaining accurate results.

> "Unfortunately, thinking about the way such therapies are to be delivered is often not a dominant part of the total disease solution. Many view the utilisation of more advanced delivery systems as a diversification mechanism in a competitive market and thus do not see the need for such offerings for new market entrants where there may be a lack of significant competition."

Coupling this with the ability to add connectivity to the device in addition to making it look and feel high quality, results in a range of extra values to patient, clinician and pharmaceutical company, both pre-market and post-launch. Training patients and caregivers to use such devices is simpler and cuts down time required with each patient. Devices can be made that offer obvious and simple user-steps that monitor usage, instil confidence and educate the user about the importance of certain aspects of their condition. All of these factors drive improvements in outcomes and the overall validated success of the treatment.

Complementing current early market access activities and programmes conducted in orphan drug development, the improved early interaction and careful understanding of care journey needs, together with strategic thinking about the drug delivery solution, will benefit patients, HCP, payers and pharmaceutical companies. Moving away from basic delivery mechanisms to more user-friendly, intelligent devices will add value to all stakeholders and must be the future for the orphan drug world in much the same way as the mainstream biopharmaceutical world.

ABOUT THE COMPANY

Medicom Innovation Partner (a Phillips-Medisize Company) is a leading global innovation, development and low-volume production provider focused on drug delivery devices and connected health solutions for the high-value rare disease and orphan drug market. Medicom Innovation Partner was established as a technology venture of Bang & Olufsen A/S back in 1989 and the company has been a dominant player within the drug device world for more than 25 years. Medicom holds a dedicated staff of more than 90 high-calibre innovation specialists, mechanical, hardware, software, quality assurance, regulatory and production engineers based in Struer, Denmark, and Cambridge, UK. Medicom has experienced considerable growth over the last five years.

As of May 31, 2016, Medicom is part of Phillips-Medisize Corporation. Phillips-Medisize is a leading global outsource provider of design and manufacturing services to the drug delivery and combination products, consumable diagnostics and medical device, and specialty commercial markets. The company has annual sales of over US$700 million with 80% of the total revenue coming from drug delivery, medical device, primary pharmaceutical packaging and diagnostic products such as: disposable insulin pens, glucose meters, specialty inhalation drug delivery devices, single-use surgical devices and consumable diagnostic components.

Together Phillips-Medisize and Medicom will become one of the leading players within the growing drug delivery device and connected health market.

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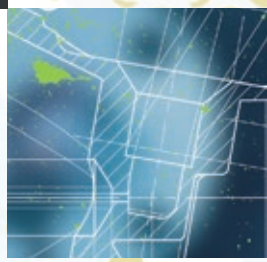
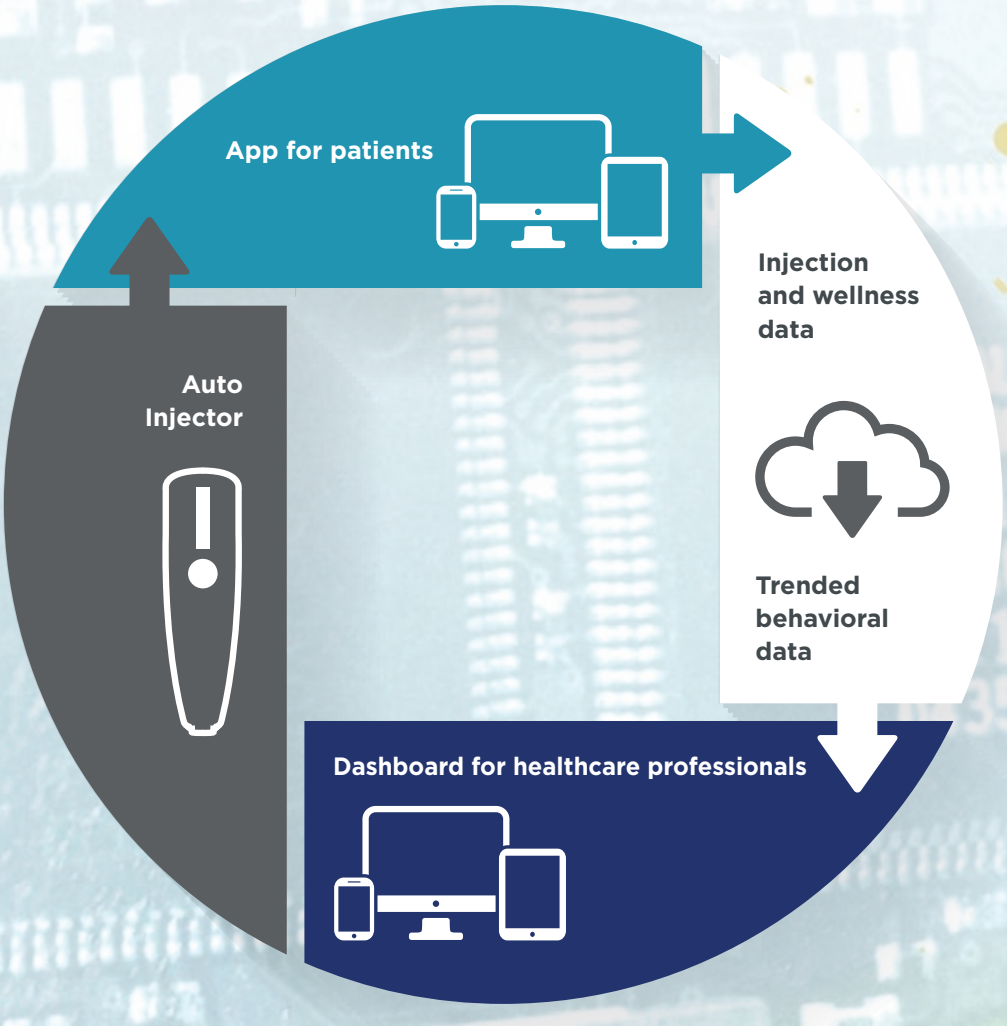
in patient centric drug delivery systems



Devices
Connectivity
Connected Health Service Solutions



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Medication delivery systems are vital for the survival of patients. New technologies and the expertise it takes to understand and use them are a must for designing absolute reliability into these systems, which will remove risk and reduce costs for hospitals and users alike.

Market drivers for delivering automated and semi-automated drug delivery systems are many. The growth over the past few years in e-health is a primary one. More and more applications are coming into the marketplace that provide e-health services, from setting a smart phone app to remind a person when to take their pills, to providing a device to deposit those pills, to collecting physical data about a person's body in order to sound an alarm when a problem occurs.

Another important focus has been in the growing move towards the creation of liquid medications to make delivery simpler, as well as fully automatic. At the moment, pharmaceutical companies are involved in the research and production of a variety of liquid forms of medication that can easily be tailored to a specific person's needs.

> "Liquid dosing is not new, but through the use of the right delivery systems – ones that are accurate, repeatable, long lasting and quiet – medicines can be delivered locally."

The impact of protein- and gene-based therapies has also been limited by the need for better methods of delivery into cells within tissues. The ability to provide medication in this way will affect a variety of fields, including micro-molecular delivery of proteins, hormonal injections and even specialised genetic therapies, all of which will revolutionise the potential to provide services in the medical industry.

Liquid dosing is not new, but through the use of the right delivery systems – ones that are accurate, repeatable, long lasting and quiet – medicines can be delivered locally. What this means is that the whole body does not have to be medicated in order to deal with a local ailment. For example, why take a painkiller for your whole body if your only problem is a sore knee or elbow. Local, automatic delivery will decrease the overall amount of medication that has to go into a person's body, which will eliminate a lot of unnecessary side effects and decrease the amount of the medication being used. Plus, for serious patient care, the ability to deliver medication locally will eliminate the possibility of someone becoming addicted to the painkiller or other drug.

User requirements for drug delivery systems include comfort for the user, which means it must be super compact to fit seamlessly into a person's life. The device must produce very low noise, offer extremely long battery life and be flexible enough to fit into all aspects of the person's life. The new systems must be water resistant, chemical resistant, and mechanically and electronically robust in every way.

Some of the devices already on the market include ambulatory infusion pumps, patch pumps for insulin delivery, linear peristaltic pumps, rotary peristaltic pumps and tiny implantable pumps for those with chronic pain (Figures 1 and 2).

maxon offers their expertise in finding the perfect drive solution for whichever drug delivery system chosen. For example, it has designed an artificial pancreas with a dual pump that measures the blood sugar amounts and delivers insulin and glucagon to balance those blood sugar levels. Such a device needs to be the size of a

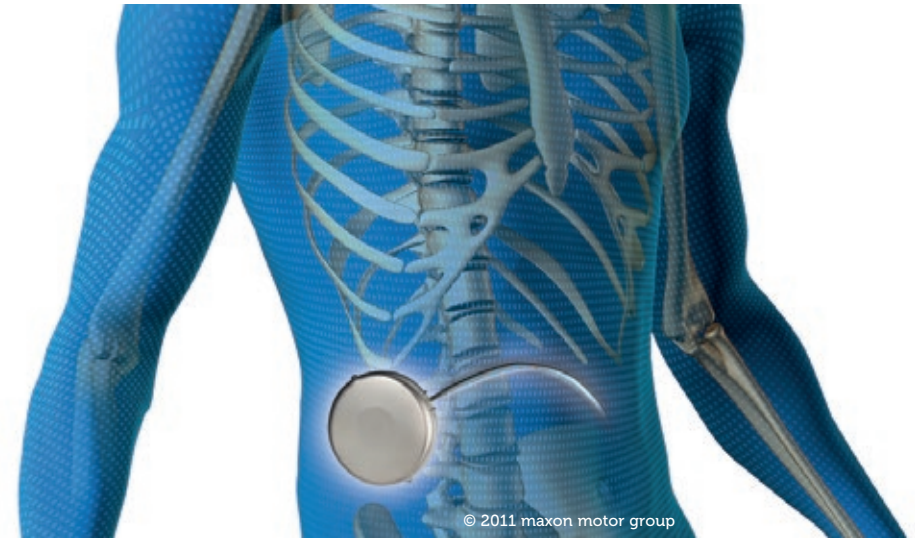
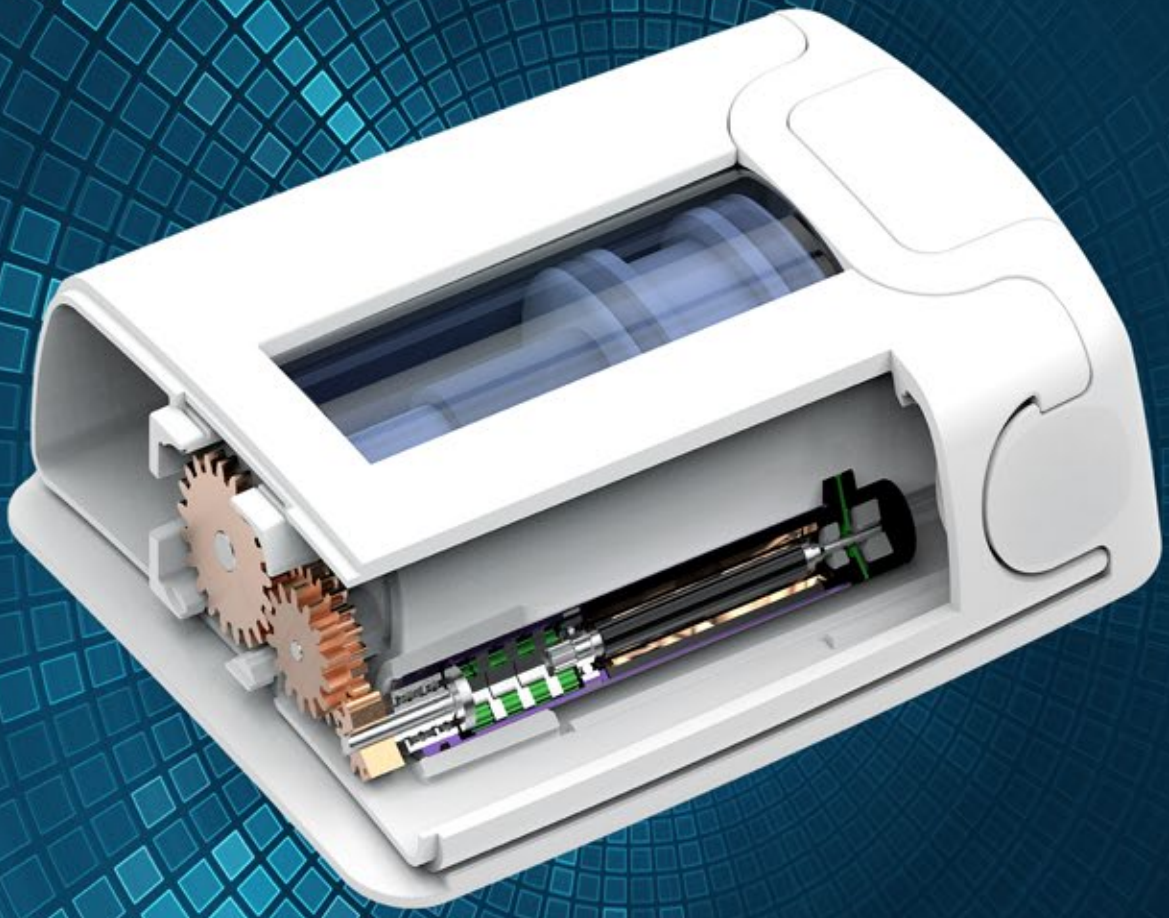


Figure 1: The active implant is implanted in the lower abdomen directly underneath the skin.

Beyond
Drive Solutions...



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> "maxon continues to create delivery systems for medical use that offer some of the smallest micro drives – that are not only compact but offer low noise and provide high-efficiency – while maintaining a user-friendly interface to control systems of all types."

match box and mounted as a patch pump or wearable to the body.

For more invasive, implantable pumps, maxon has designed and manufactured a device using biocompatible materials in the manufacturing process. For example, the company uses titanium, which requires a high level of expertise to machine and laser weld. The entire assembly of the implantable microdrive takes place under cleanroom conditions.

maxon continues to create delivery systems for medical use that offer some of the smallest micro drives – that are not only compact but offer low noise and provide high-efficiency – while maintaining a user-friendly interface to control systems of all types. There must never be any concern over the ability for the systems to co-operate, especially in life-or-death situations in which drug delivery systems must often serve their function. Trust in the components being used is a requirement.

Presently, maxon has specialist teams working on the next generation of drive solutions for drug delivery as well as permanent and disposable devices for numerous applications based on syringes as well as needle-free solutions. The company's expertise allows it to design and manufacture complete systems for a multitude of specific applications.

Since 1961, maxon motor has researched and developed a growing line of products and services, including integration of many systems for the medical and pharmaceutical industries. More than 2,100 employees work worldwide, with production sites in Switzerland, Germany, Hungary and South Korea, as well as sales companies in more than 30 countries.

Carsten Horn
Executive Manager/Product Manager
E: drugdelivery@maxonmotor.com
T: +49 7641 9114 0

maxon motor GmbH
Untere Ziel 1
79350 Sexau
Germany

www.maxonmotor.com

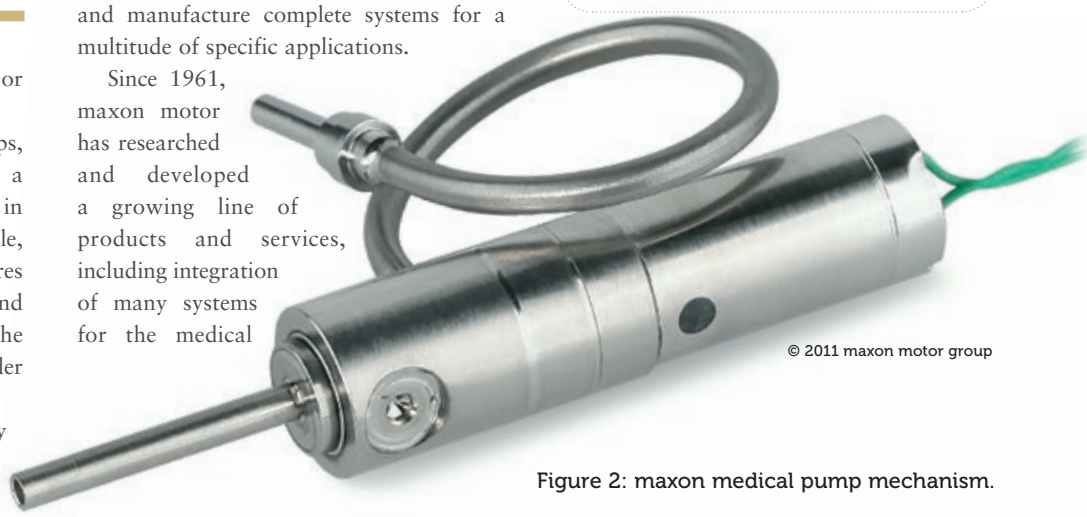

Figure 2: maxon medical pump mechanism.

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Reliable incorporation in injection devices

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- Homogeneous siliconization results in smooth plunger movement

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THE DEVELOPMENT OF THE MOLLY® PLATFORM

SHL Group explores the growth of the Molly® family of drug delivery devices as an example of how the auto injector market has changed over the last five years, and looks to the future – with the growing interest in adding connectivity to the devices to improve the way data can be captured, stored and analysed for the benefit of patients.

The trends in drug delivery are set by the pipelines, technologies and innovations from the pharmaceutical, biotech and healthcare industries. However, when it comes to catching up on the latest technological, societal and regulatory changes, drug delivery companies are often ahead of their customers.

> "...both device manufacturers and pharma companies have to stay well informed of the most important and innovative device features on the market and co-operate in order to bring the best value to the patient."

Recent years have witnessed significant global market growth for injectable drug delivery devices. This trend is expected to continue well into the future. One research study suggests that it will grow from 68.6 million annual units in 2016 to 142 million annual units in 2026.[1] Self-injection devices are expected to grow at a compound annual growth rate (CAGR) of 16.1%, continuously increasing the market share.[2]

What explains this growth? What puts self-injection devices, such as auto injectors and pen injectors, in such a high demand among patients, payers and pharma companies?

There are several explanations behind this trend:

- Growing life expectancy means that people require longer and better care than before. Living longer, we are also suffering more from chronic diseases. According to the WHO estimate, the prevalence of chronic disease will increase by 57% by the year 2020.[3] As chronic disease management is a life-long process, many treatments are moving from hospital to home to increase patients' comfort and to reduce the healthcare spending burden as well as the workload of healthcare professionals.
- Yet another change associated with chronic disease management is the rise of biological drugs. These were already providing 22% of big pharma sales in 2013 and are expected to account for 32% by 2023.[4]
- A steady rise is evident in biosimilars of many top-selling biologics as patents for the original drugs are expiring. Pharmaceutical companies developing both biologics and biosimilars use auto injectors not just as a convenient and user-friendly delivery method, but also for drug lifecycle management and product differentiation.

DEVICE TRENDS

These industry trends mean that delivery devices are becoming an integral part of the healthcare industry. Therefore, both device manufacturers and pharma companies have to stay well informed of the most important and innovative device

SHL Group
#136, Kuo Sheng 2nd Street
Taoyuan
Taiwan
T: +886 3 217 0303
E: info@shl-group.com

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features on the market and co-operate in order to bring the best value to the patient. Some of the current focal points for self-injection devices are:

- **Patient-centricity:** powered by human factors engineering and usability studies, today, both device and drug companies consider satisfying end-user needs to be one of the most important requirements for their products.
- **Seamless commercialisation:** with growing competition in the market of biologics and biosimilars, product differentiation and speed-to-market offers are as important in drug-device product development as technical specifications.
- **The biotech challenge:** the next generation of large molecule biological drugs often requires devices to accommodate larger dose volumes or higher viscosities.
- **Quality and regulatory control:** to ensure safety of patients and avoid financial losses by pharma companies, it is important for device companies to maintain highest quality standards and support their customers throughout the regulatory approval process.
- **Digital health:** the advance of the Internet of Things and availability of connected technologies mean that delivery devices are also entering the digital era.

THE MOLLY FAMILY

Some of these trends are very recent; some have been in the making for quite some time. SHL has always been a pioneer in drug delivery solutions and is very familiar with all the latest tendencies. To follow the development of the market in the last five years, you don't have to look further than the history of one of our most successful projects – the Molly® family. As a family of devices based on the same platform, but responding to different needs and requirements, Molly devices are the perfect reflection of the auto injector market history and direction.

THE NEW PLATFORM

The inspiration behind the first Molly device – Molly® 1.0 – came from both pharmaceutical industry and end-user needs. On the one hand, there was a clear supply vacuum for pharma and biotech companies who wanted to launch the device quickly and with minimum investment. From the patient perspective, the device had to be as safe and convenient as possible. Therefore, we needed a device that offered faster development timeline without sacrificing any essential design features. Also, we needed to minimise the complexity for the patient experience, to make the device intuitive and really simple to use.

> "As Molly® 1.0 has now been approved, our customers can use this device with secure knowledge that it is readily "approvable" from a regulatory perspective. This is a major advantage compared with new devices where there is always some risk of issues being highlighted during regulatory review."

The solution, as the problem itself, was twofold. The two-step operation was a revolutionary solution that simplified the injection process to two simple steps – uncap and inject – without compromising injection experience or patient acceptance. The device is easily activated by pressing down on the needle cover, with activation force optimised precisely for the ultimate user control.

From the engineering point of view, every detail of the mechanical design was thought through to guarantee that all injection requirements could be met. We developed a range of spring options adapted for various drug characteristics and took into consideration potential glass breakage issues by designing Molly® to hold the prefilled syringe by the neck instead of at the flange. Most importantly, SHL's engineers designed a unique power pack that offered the same functionality with significantly reduced number of components. Owing to this innovative solution, Molly® measures only 13 cm – not bigger than a regular prefilled syringe.

BENEFITS

What real value and benefits were created by applying this creative design and engineering? Fredrik Stromvall, Project Leader at the time for the Molly® project, emphasises: "Every feature of this product has been thought out and developed for the benefit of either the drug company or the end-user."

The ultra-compact design makes the device appealing, less frightening for patients and also extremely portable. It makes Molly® more acceptable as a disposable product, reducing the environmental impact during development, manufacturing, transportation and disposal. It even makes the storage easier for the patient, since most biologics need to be stored in the limited space of a fridge.

The simple two-step injection process is extremely easy to learn, requiring less explanation and training (Figure 1). To ensure safety for the patient, the protective needle shield locks as soon as the device is removed from the injection site. Not only does this mean that the risk of

Figure 1: Molly® 1.0 – easy two step injection process.

Figure 2: Molly® becomes a branded platform – Molly® RNS..

needle injuries is reduced, but also that the patient never has to see the needle exposed, eliminating needle phobia concerns. Jochen Ratjen, Director of Industrial Design at SHL, concludes: "We have observed very high acceptance for the Molly® device in several user studies. Human factors experts also have pointed out that that Molly® is a positive example for good usability."

For pharmaceutical companies the benefits are also numerous. To minimise upfront investment, the platform device business model allows for significant savings on additional tooling, assembly and testing equipment. Molly® consists of a minimal number of components, making the manufacturing process less expensive and more efficient.

As a pre-configured device, Molly® requires significantly reduced timeline for development compared with a completely new bespoke device. At the same time, it still offers customisation of the spring and colour to answer the drug specifications and product differentiation requirements.

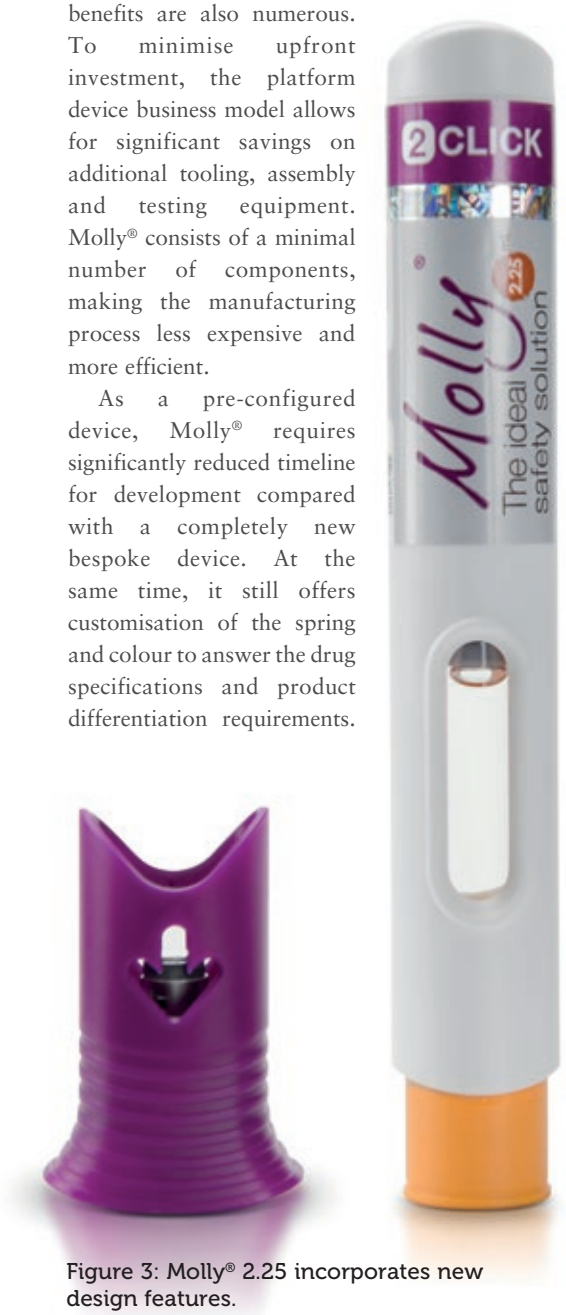

Figure 3: Molly® 2.25 incorporates new design features.

Moreover, as Nicholas Heaton, Executive Director for Business Development Europe, points out: "As Molly® 1.0 has now been approved, our customers can use this device with secure knowledge that it is readily "approvable" from a regulatory perspective. This is a major advantage compared with new devices where there is always some risk of issues being highlighted during regulatory review."

To ensure smooth market launch, SHL also offers robust final assembly, packaging and labelling services to keep all these important stages in-house, thus guaranteeing faster communications, tighter quality control and continuous support of the project management team for our biopharmaceutical partners.

MEETING NEW CHALLENGES

The success of Molly® as a technological solution led to the creation of the whole new branded platform. First, Molly® 1.0 became available with a rigid needle shield – Molly® RNS (Figure 2). However, industry needs kept evolving, and so did the Molly® platform. Mats Persson, Executive Vice-President of SHL, elaborates: "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 large 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."

To enhance the device's usability and user-friendliness, several design changes were made. Molly® 2.25 has a new rear end and a double-curved cap (Figure 3). They give the auto injector a more natural and ergonomic feel, at the same time ensuring anti-roll features. The new pull- or twist-off design of the cap, enlarged with two flanges, makes it easier to grasp and take the cap off for patients with diminished physical ability.

The result of combining the successful Molly® platform with a larger volume syringe and new design features is a robust and reliable drug delivery solution for larger volume formulations. Due to the success of previous Molly® devices, our partners can be sure that this branded auto injector will be just as safe, easy-to-use and quick to market as Molly® 1.0.

ADDING CONNECTIVITY

The latest big topic in the healthcare industry is digital health and the connected solutions associated with it. Even though the pharmaceutical industry, being quite conservative in its nature, is only taking slow steps in this direction, it is forecasted to be one of the next significant trends in the near future.[5] Connectivity works by providing means to capture, save and share data from an injection device.

Rasmus Renstad, the Vice-President of Innovation at SHL, explains how it could help all stakeholders: "One of the biggest hurdles is low adherence to medication. It contributes to unnecessary suffering for patients and their families. It also results in growing avoidable healthcare expenses and losses for pharma industry. A connected drug delivery device can support all stakeholders by providing real data to analyse. It can be used to enhance patient experience and support and will lead to healthier outcomes and benefits for all parties."

When developing an innovative concept, such as a connected auto injector, it is best to base innovation on a solid foundation of experience. Molly® platform was the perfect choice for the development team to start working with, due to its proven efficiency, usability and reliability.

To connect (C) the device, Molly® has been adjusted with a proprietary interface at the rear end. This interface connects to a reusable recording unit (RU) equipped with Bluetooth technology to transmit the injection data to the user's mobile device.

The injection data saved can be further shared through the Cloud with as many parties as necessary and used to personalise and enhance patient support programmes.

The Molly® C and RU concept (Figure 4) combines the trusted branded platform device with the breakthrough technology. In addition to all the benefits of the auto injector platform, such as safety, ease-of-use and reliability, this concept also offers benefits of connectivity for multiple stakeholders in the age of digital health.

Figure 4: Molly® C and RU concept combines the trusted branded platform device with breakthrough technology.

THE FUTURE

The Molly® platform has been evolving together with the market – incorporating the most important and necessary design features, finding creative technical solutions, devising new business models to expedite commercialisation and integrating cutting-edge innovation. As we believe that continuous improvement is possible even when the device is already a success, there are already plans to develop the platform in the future. The design of Molly® is going to be further improved for better manufacturability, high speed assembly and next-generation connectivity solutions.

The story of the Molly® family is the story of the self-injection devices market. However, none of this would be possible without SHL's comprehensive in-house capabilities and services and, most importantly, the knowledge and experience of our team.

Drug delivery devices will keep developing hand in hand with biopharmaceutical industry. To keep up with the advance of the next generation healthcare, we will continue to develop solutions for today on the path to tomorrow.

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NOVEL APPROACHES & TECHNOLOGIES TO INCREASE PATIENT CONFIDENCE & DECREASE ANXIETY

Building on his previous articles in ONdrugDelivery on training devices and drug delivery device education, here, Joe Reynolds, Research Manager at Noble, introduces some of the latest approaches Noble is pioneering, and technologies it is developing – such as needle simulators – to equip patients for confident, anxiety-free self administration of parenteral drugs, with positive knock-on effects on adherence and treatment outcomes.

As one of the oldest forms of drug delivery, the first medical application of syringes can be traced back to the ninth 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 19th 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.

> "Training and educational initiatives were largely supported by IFU, package inserts and other content-based collateral... only 12% of patients have proficient health literacy and the ability to manage their health and wellness with these materials.[5]"

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 (Phases 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 determines a patient's ability to safely and effectively use prefilled syringes and adhere to therapy.

According to the 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, 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] As a consequence of these avoidance behaviours, many patients fail to realise the full therapeutic benefits of medications and ultimately discontinue treatment.

Mr Joe Reynolds
Research Manager
T: +1 888 933 5646 Ext. 147
E: jreynolds@gonoble.com

Noble
121 South Orange Avenue
Suite 1070 North
Orlando, FL 32801
United States

www.gonoble.com

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 they 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]

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 cornerstones to effective onboarding strategies by allowing patients and healthcare providers to learn how to use prefilled syringes and other forms of drug delivery devices safely. Based on the findings of a recent user study, training devices can increase patient confidence by 86% and decrease anxiety by 15%; two variables that research suggests are closely related to adherence and outcomes.[6]

BUILDING MUSCLE MEMORY

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°) and depth into a pinched or stretched injection site, as required
5. Fully depressing the plunger to deliver the prescribed dose
6. Removing and properly disposing of the used syringe.

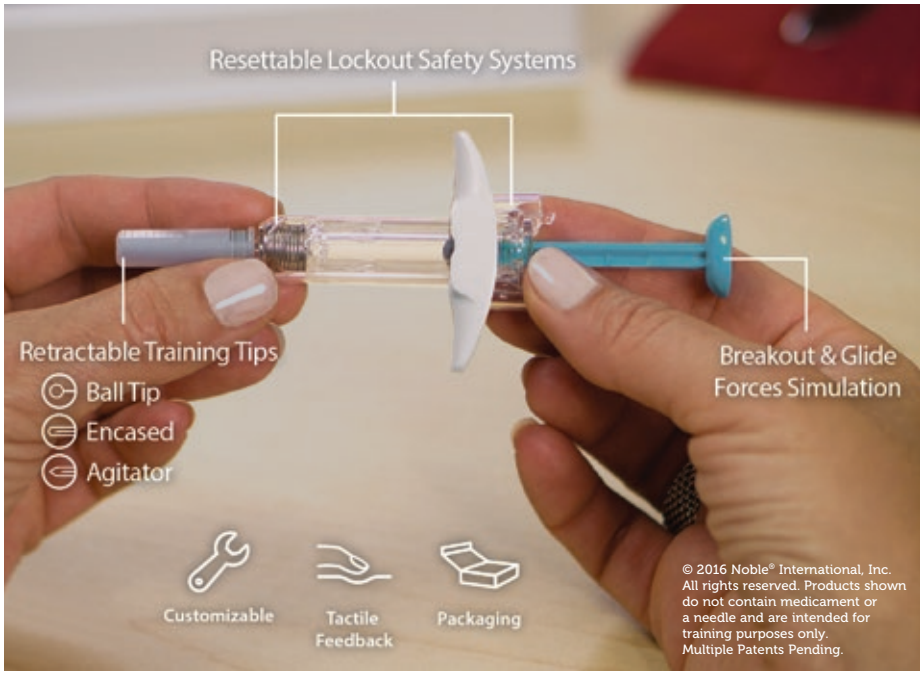

Figure 1: Training syringes simulate attributes of real syringes including: plunger break-out, glide forces for varying viscosities, volumes, resettable safety systems and other product-specific features to build confidence and proper administration behaviours.

To maximise the value and consistency of training, training syringes (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 REDUCING 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 perception 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 mimic fully the deformation, puncture and insertion force characteristics of various needle gauges, bevel geometries and other key attributes (Figure 2). When applied to prefilled syringe training, these proprietary technologies allow patients to learn in safety the force and technique required to insert needles into the skin.

Key insertion behaviours captured in needle simulators include the following:

- Deformation. Induced when needle tip is in contact with 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. The insertion force continues to increase in relation to the insertion depth and injection site characteristics.

ANGLE AID TRAINING SOLUTIONS IMPROVE DEPOSITION & TECHNIQUE

Subcutaneous (SC) 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 SC 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 tech 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", and adds that "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 errors, while improving satisfaction and outcomes.

ABOUT THE COMPANY

Noble, the leader in onboarding and device training, is a patient-centred product development and manufacturing company. Noble works closely with the world's leading pharmaceutical and biotechnology companies to develop educational and training solutions that improve the patient journey. Cross-disciplinary designers and engineers provide fully customised solutions from the first concept sketch through production in both regulated and non-regulated environments. Noble is headquartered in Orlando, FL, US.

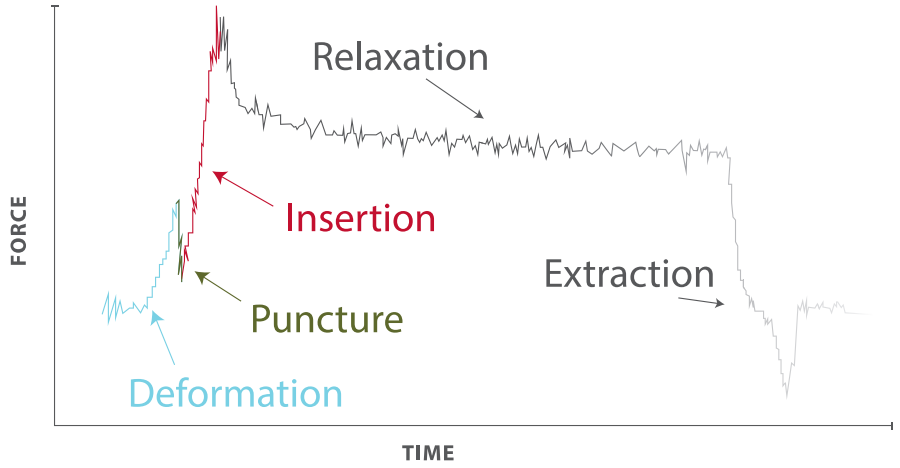

Figure 2: Needle insertion force from injection beginning to completion.

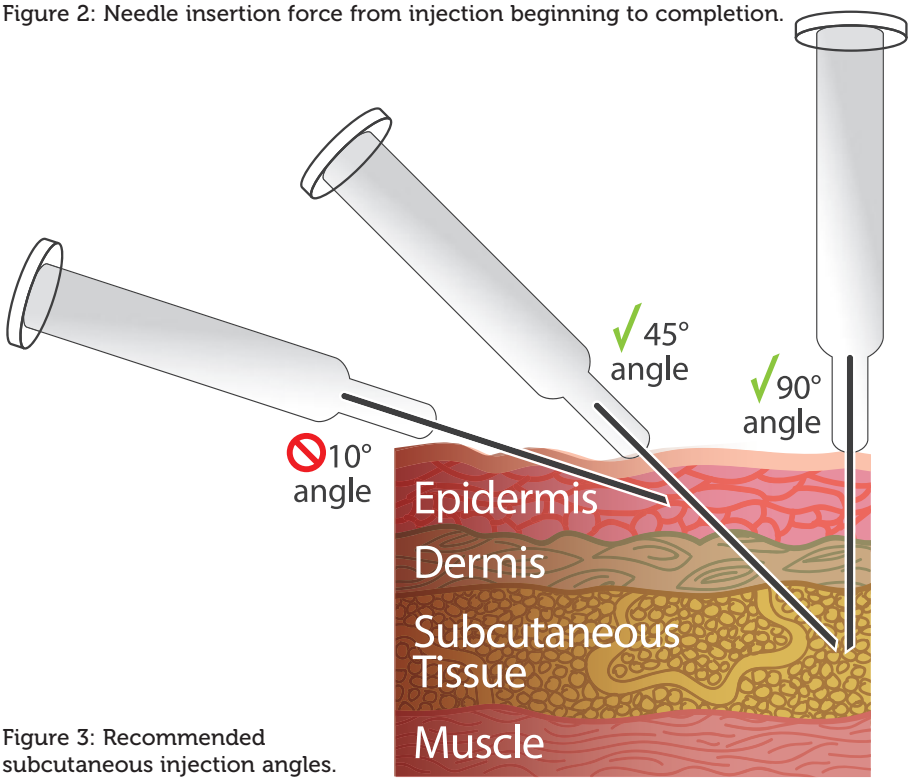

Figure 3: Recommended subcutaneous injection angles.

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ABOUT THE AUTHOR

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, pharma and biopharma brands. Mr Reynolds holds a BS in Business Administration from the University of Central Florida, an MS in Marketing from the University of South Florida and an MS in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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PRODUCT SHOWCASE: SCHOTT's SyriQ® and TopPac® Rigid Caps

SCHOTT
glass made of ideas

SCHOTT'S RIGID CAPS ADD NEW TWIST TO PREFILLED SYRINGES

Schott has added new closure systems to its already extensive portfolio of prefillable syringes (PFS), offering more flexibility for pharma companies while keeping patients safe. syriQ® Rigid Cap (SRC), shown in Figure 1, and Schott TopPac® Rigid Cap (TRC), shown in Figure 2, feature an intuitive twist-off mechanism. The caps ensure the integrity of the container, yet can easily be opened by healthcare professionals or patients.

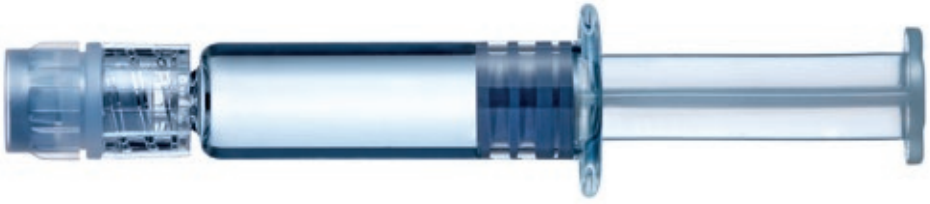

Figure 1: The syriQ® Rigid Cap (SRC) for glass prefillable syringes.

Figure 2: The TopPac® Rigid Cap (TRC) for polymer prefillable syringes.

> "Container closure integrity (CCI) is one major concern in the pharma industry. Another one is usability. Our new closure systems deliver in both areas."

These advanced closure systems for glass and polymer syringes improve patient safety while securing packaging supply chain. They offer a seamless fit for Schott's prefilled glass syringes known under the brand name syriQ®, and Schott TopPac®, its polymer equivalent. SRC is already commercially available, with TRC to follow later this year.

"Container closure integrity (CCI) is one major concern in the pharma industry. Another one is usability. Our new closure systems deliver in both areas," said Anil Busimi, Global Product Manager at Schott Pharmaceutical Systems. "The design of SRC, our solution for syriQ® glass PFS, matches a closure system the industry is already familiar with. This adds a great deal of flexibility to our customer's supply chain, and it speeds up time to market for new or already existing drug products."

SRC combines a rubber tip-cap with a rigid cap screwed in a Luer lock adapter. The closure system comes pre-assembled with Schott's high-quality syriQ® glass syringe barrels, all pre-sterilised and in a standard nest-and-tub configuration. Thanks to standardisation and since the materials are similar to Schott's existing product line, drug manufacturers can quickly integrate SRC into existing production set-ups.

Schott is also ready to support drug developers in product documentation and the regulatory approvals process. This will help drug manufacturers get their product to market faster.

Schott developed TRC, the rigid cap for the Schott TopPac® polymer PFS portfolio, simultaneously with SRC. The rigid cap, fitted with a rubber tip-cap and twist-off mechanism, offers superior CCI during filling, processing, transportation, and shelf life. TRC, like CRS, is easy to open and easy to connect with hypodermic needles, IV connectors, or vial adapters, and reduces the risk of contamination while opening the closure system.

COMPLETE SYRINGE PORTFOLIO

New solutions like SRC and TRC derive from Schott's broad experience in syringe manufacturing. The company has been producing syringes in Europe since 1996. Today, the production is concentrated in Switzerland and is supported by an R&D team based at the site. From here Schott has developed a complete portfolio of both glass and polymer syringes, which is now even further expanded by the rigid closure systems. This offers pharma companies a broad range of solutions, suitable for a variety of applications like heparin, vaccines, biotech, and special applications such as intensive care.

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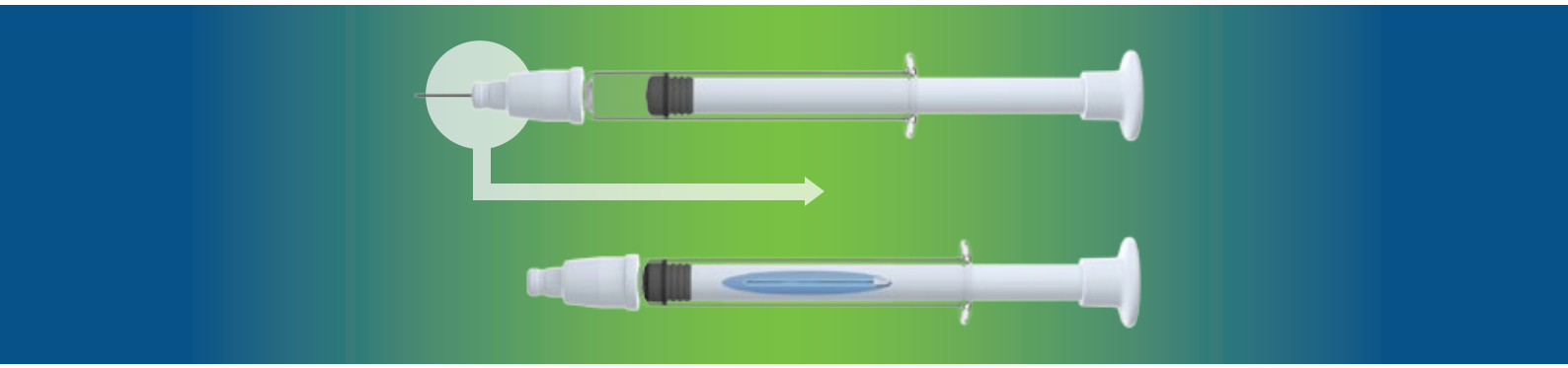
INNOVATION WITHOUT CHANGE

Innovation Without Change simplifies the development 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 and 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.



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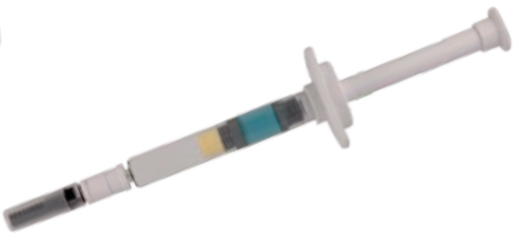
- Marketable Differentiation
- Uses Existing Syringe Components
- Simplified Commercialization Path
- Reduced Supply Chain Risk
- Standard Filling & Assembly
- Glue-Free Design

The Companion Product Family

Companion Staked Needle Syringe

Companion Luer Syringe



Companion Dual Chamber Reconstitution Safety Syringe

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Note: This product has not been evaluated by FDA.

COMPANY PROFILE: NEMERA (INJECTABLES OFFERING)

Nemera

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

Parenteral administration of a drug exposes users (patients and healthcare professionals) to numerous hazards. In designing a medical device, it is critical to consider the device failure and use-related hazards to ensure the product is safe to use and fits patients' needs. Through good design, patients are empowered with intuitive, easy-to-use, ergonomic and reliable medical devices.

Nemera and its partners empower patients through good design with Nemera's extensive experience in developing and manufacturing parenteral drug delivery devices.

The company leverages decades of manufacturing and development experience in the parenteral device segment to offer patients premium products and customers a complete service. With the support of its global centre of expertise comprising more than 60 engineers and experts in creative design and human factors activities, Nemera is able to drive an idea from concept all the way to large-scale manufacturing.

Nemera's balanced business model includes: full proprietary product development, contract manufacturing and customised solutions. This model gives flexibility to customers, being able to enter the development and manufacturing process at any stage. Depending on their needs, pharmaceutical companies can leverage Nemera's knowhow and expertise to develop customised solutions based on either their own or Nemera's intellectual property.

NEMERA INNOVATIONS

Safe'n'Sound®

In the parenteral industry, needlestick injuries are a global concern. According to the WHO, more than two million exposures to blood occur every year, resulting in health, psychological and cost issues. Safe'n'Sound® (shown in Figure 1) is Nemera's fully passive solution to needlestick injuries for prefilled syringes that patients can count on.

US FDA 510k cleared, the system

Adrien Tisserand
Global Category Manager,
Parenteral & CMO
T: +33 4 74 94 06 54
E: adrien.tisserand@nemera.net

Isabelle Delcroix
Strategy Director
T: +33 4 74 94 06 54
E: isabelle.delcroix@nemera.net

Nemera
20, Avenue de la Gare
38290 La Verpillière
France

www.nemera.net

	Off-the-shelf range		Customised 1 mL & 2.25 mL	Concept
	1 mL Long	2.25 mL Long		
Component				
Sub-Assembly	Cut/Round Flange Small Round Flange* Luer Lock**	Extra Small Round Flange* Small Round Flange* Cut/Round Flange*	Customers' specific syringes	1 mL short staked 0.5 mL long staked
Plunger Rod	White/Transparent	White/Transparent	Colour specific	N/A
Option				
Add-on Extended Finger Flange	Portfolio of colours	Portfolio of colours	Colour specific	N/A

Table 1: Specifications and customisation options for the Safe'n'Sound® platform. (* In 2017. ** With BD Syringes)

protects healthcare professionals, patients who self-inject doctor-prescribed medications, and individuals that assist self-injecting patients, from accidental needlesticks. Not only does Safe'n'Sound® improve users' safety and injection conditions, but also the device complies with the recommendations of the WHO and the EU Council Directive 2010/32/EU.

Some of the specifications and customisation options for the Safe'n'Sound® platform are summarised in Table 1.

There are a numerous reasons to add Safe'n'Sound to a prefilled syringe, including:

- **Drop test.** Protects against drops thanks to its design holding the syringe in every orientation
- **Activation extra force.** Low extra force (<8N) required to activate
- **Override PUSH.** Requires high force (>100N) after the safety activation to break the safety feature by applying pressure on the plunger rod
- **Override PULL.** Requires high force (>100N) after the safety activation to disassemble the body and the sleeve
- **Device labelling surface.** Increased labelling surface thanks to safety device
- **Syringe loading.** Requires low force to snap the syringe into the safety device, lowering the risks of potential syringe breakage during insertion.
- **Syringe unloading.** Once the syringe is inserted into the device, the clips hold the syringe firmly

Expected benefits	Standard AI	Safelia	Safelia Features
Creating possibilities for viscous injections with the same AI platform as for standard glass syringes	x	✓	Injects fluid and viscous drugs up to several 100 cP
Risk of syringe breakage eliminated Possibility of using all (or no) syringe flanges	x	✓	No stress on syringe flanges
Enables increased spring force and use of small gauge needles (less patient pain) without risk of glass breakage	x	✓	No stress on syringe flanges
Reduction of injection force peaks	x	✓	Cam design to adjust injection speed
Drug is delivered at the right depth	x	✓	Needle insertion disconnected from injection

Table 2: Summary of Safelia® benefits and features compared with standard auto injector.

Figure 2: 1 mL and 2.25 mL versions of the Safelia® auto injector.

- **Residual volume.** Minimises residual volume variability due to its efficient design.
- **Patented product.** Freedom to operate performed
- **On the market.** Available for Luer and staked versions
- **Open platform.** Compatible with syringes of different filling volume and flange type from multiple suppliers.

Additionally, Safe'n'Sound® is a safe and easy to use, convenient and ergonomic system. It is a robust device, and provides audible feedback to indicate that the safety mechanism has completed final locking.

Safelia® Two-Step Auto Injector

Nemera's two-step auto injector platform, Safelia™ (Figure 2), eases the patient self-injection experience. It delivers a variety of drug products in glass syringes, ranging from more fluid formulations to the most challenging drugs such as viscous, sustained-released, concentrated

Figure 3: Nemera's two solutions for RNS removal are A) an integrated device pre-assembled to Safe'n'Sound®; and B) a stand-alone, multiple use solution into which Safe'n'Sound® is inserted.

Figure 4: Solution for one-handed SC injection at 45° angle.

Figure 5: To prevent accidental removal of the stopper or plunger rod, Nemera developed a back-stop feature.

formulations, products for subcutaneous and intramuscular injection, and including larger volumes.

The benefits and features of Safelia® compared with a standard auto injector are summarised in Table 2.

Safelia® administers a large range of formulations and injection volumes; the platform can adapt by design to handle both fluid and highly viscous formulations, taking care specifically of biologics, sustain-released formulations and sheer-sensitive molecules, of up to 2.25 mL injection volumes. The device improves the patient experience, with the possibility to reduce needle gauge, reduce injection time, and slow down the needle penetration inside the body tissues, and gives the possibility of a delayed retraction, for viscous injections especially.

A detailed article focusing on the Safelia® platform, by Nemera Business Development Director Isabelle Delcroix, appeared in ONdrugDelivery Magazine, Issue 67 (May 2016), pp 38-42.

Rigid Needle Shield Removal Concepts

Removing the rigid needle shield (RNS) of the syringe requires dexterity and minimum force. In order to facilitate device usage and overcome the issues of gripping or sticky RNS, Nemera has developed several solutions. Two options are available (see Figure 3):

A) Integrated: single use solution to remove the RNS pre-assembled to Safe'n'Sound®
B) Stand-alone: multiple use solution in which Safe'n'Sound® is inserted to remove the RNS.

One-Handed SC Injection with Half-Inch Needle

Performing a subcutaneous injection requires the user either to pinch the skin and inject at 90° or inject at 45°. As these steps are inconvenient, they can lead to injection in the wrong skin layer. With Nemera's solution for subcutaneous injections (Figure 4), only part of the needle is exposed, allowing:

- One-handed subcutaneous injection (patient convenience)
- Drug delivery in the correct tissue layer (reduction of pain)
- Standard syringe usage while differentiating (cost & time to market/ no competition).

Backstop Concept

In order to prevent accidental removal of the stopper or plunger rod, Nemera developed a back-stop feature comprising an add-on part (Figure 5) clipped at customer's facility after syringe insertion.

Implanters

Sustained-release parenteral formulations are delivered subcutaneously through implants in order to provide slow release of the drug. Since implants are fragile, insertion into the body requires caution. Nemera has developed several devices to deliver implants with integrated anti-needlestick safety including a safety depot syringe with telescopic plunger rod and a safety retro injector for soft implants. Key product features include:

- Suitable for different implant sizes
- Can accommodate multiple implants, soft implants
- Implants easily loaded
- Integrated safety feature
- Little effort and pressure applied on implant
- Retro-injection feature allows deposit of the implant at a defined depth with multiple implants separated one from the other.

NEMERA CO-DEVELOPMENT

Nemera has positioned and structured itself to become the partner of choice for successful parenteral programme management from concept through to industrialisation.

Nemera offers world-class excellence at each stage of the programme:

- **Concept Generation**. IP Management, patient insights & creative design; concept selection; and a compliant, structured stage gate progress
- **Design & Prototyping**. Human factors studies, DFSS and QbD; detailed design including design for manufacturing; strong programme management & governance; and quality, cost and lead-time
- **Scale Up & Pilot**. Design verification, process de-risking & validation; validated process & samples for clinical trials / stabilities; sourcing & supplier management; and key partnerships for equipment/moulds
- **Regulatory**. Facilitation of filing strategy; detailed design including Design for Manufacturing; long experience with EU & US authorities (FDA 510(k) / DMF / New Drug Applications); and regulatory experts in-house
- **Industrialisation**. Validation according to GMP and FDA requirements; validated commercial batches; and injection moulding and high-speed assembly expertise.

CONTRACT MANUFACTURING OF INJECTION DEVICES

Quality for Patients

More than five million diabetics rely every day on devices manufactured by Nemera. The company manufactures parenteral devices in best-in-class clean rooms. Manufacturing capabilities include injection moulding and complex assembly. Altogether our facilities have the following certifications:

- ISO 9001
- ISO 13485
- ISO 14001
- ISO 15378
- ISO 5001.

We are committed to providing excellence in the quality of our products and services:

- Full traceability, 100% in-line controls
- Production according to 21CFR820/ GMP
- Manufacturing in ISO CLASS 5 to 8 clean rooms
- Datapack available.

Insulin Pens & Auto Injectors

Nemera has proven expertise in managing large-scale industrial projects, manufacturing hundred millions of insulin pens and millions of auto injectors every year. With several decades of experience in manufacturing complex parenteral devices, Nemera offers its unique know-how in this field to its customers, along with premium service.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacturing of drug delivery solutions. It has more than 50 engineers working in development, over 30000 m² of clean-room manufacturing, sales in 47 countries, 750 million+ devices produced yearly and over 1300 employees. Nemera has four plants in Europe and the US at Neuenburg, Germany; La Verpillière, France (Figure 6); Le Tréport, France; and Buffalo Grove, IL, US.

Nemera's portfolio includes devices across the board of drug delivery routes including ear, nose and throat; pulmonary; dermal/transdermal; and ophthalmic. This is in addition to the parenteral offering described here.

Figure 6: Nemera's Innovation Centre at La Verpillière, near Lyon, France.

A RISK MANAGEMENT APPROACH TO PREFILLED SYRINGE SELECTION FOR BIOTECHNOLOGY PRODUCTS

Prefilled syringes are becoming an increasingly attractive option for complex biotechnology products, not least because of the savings in product volume compared to vials. There is now a wide range of options to suit different requirements which can make product selection a challenge. Wendy Saffell-Clemmer, Director of Research at Baxter Biopharma Solutions, looks at what advances are currently being made.

Expectations for growth in the prefilled syringe (PFS) market continue to be strong, and a recent report[1] estimates that the global PFS market could reach a value of US$4.98 billion (£3.9 billion) in 2019. Drivers in the growth of PFS products include both the increase in injectable biologics in the development pipeline and globalisation (specifically, the expansion of PFS products into developing markets).[2]

Prefilled syringes are particularly attractive to the developers of high-value, complex biotechnology products, such as monoclonal antibodies (mAbs) and fusion proteins. In contrast to vials, minimal overfill volume is needed to ensure delivery of the correct dose to the patient.[3] The resulting savings in product volume required per batch may more than offset the increased cost of the PFS components.

The complex requirements of biologic products have driven innovation in PFS. While Type I glass remains the most common material for syringe barrels, new options in plastic syringes are gaining in popularity, including cyclic olefin polymer (COP), cyclic olefin copolymer (COC), polypropylene (PP), and polycarbonate (PC).[3] In Japan today, 50% of syringes are plastic.[4] Polymer syringes can be provided sterile and ready to fill, have the appearance of glass (Figure 1), and are resistant to breakage, making them preferable for highly potent drugs.

With the exception of the West Pharmaceutical Services Crystal Zenith COP syringe, most syringe barrels require the application of silicone oil to allow the plunger stopper to glide smoothly during use. In general, polymer syringes which do require silicone, such as BD's Sterifill™, promote ultra-low silicone levels or, in the case of Schott's TopPac SD®, utilise cross-linked silicone.

> "With options in barrel construction, silicone levels and tungsten levels, PFS selection has become complex."

Reduction of silicone oil in syringe barrels is desirable for biotechnology products because silicone oil has been demonstrated to cause aggregation of a variety of proteins, and studies have demonstrated that the level of aggregation is proportional to the amount of silicone oil present.[5]

During the manufacture of most glass syringe barrels, a tungsten probe is used to form the fluid path in the tip of the syringe, potentially leaving residual tungsten oxide vapour and tungsten particles. Soluble tungsten residue was determined to be the root cause of unusually high levels of aggregation in clinical trial batches of epoetin alfa[6] and in an alpha helical protein formulation.[7]

Ms Wendy Saffell-Clemmer
Director of Research
T: +1 812 355 7105
E: wendy_saffell_clemmer@baxter.com

Baxter Biopharma Solutions
927 S. Curry Pike
Bloomington
IN 47403
United States

www.baxterbiopharmasolutions.com

Syringe manufacturers have responded with PFS systems specifically designed for biotechnology products which have low specifications for tungsten residues, such as BD's Hypak™ for Biotech glass syringe and BD's Sterifill™ COP syringe. The Schott syriQ® InJentle glass staked-needle syringe and West Pharma Crystal Zenith COP staked-needle syringe are both tungsten-free.

With options in barrel construction, silicone levels and tungsten levels, PFS selection has become complex. The use of newer PFS systems can increase costs, so careful evaluation of potential impact on product quality through laboratory studies should be conducted prior to final component selection to balance quality and cost to patients.

The risk management process in the ICH (International Conference on Harmonization) Q9, Quality Risk Management (Figure 2),[8] can be applied to evaluation of drug formulation and PFS compatibility. The first step, risk identification, can be generalised for most peptide, protein and mAb products in a company's pipeline. Suggested incompatibility risks for further consideration include 1) glass delamination, 2) sensitivity to tungsten and 3) aggregation resulting from silicone oil. The second step, risk analysis, can be accomplished with a review of the literature.

Glass delamination, or the flaking of glass particles from the interior surface of the container, has resulted in recalls of parenteral products in recent years.[9] Glass delamination is not evident immediately and is usually observed in stability samples, particularly those at elevated temperatures.[10] Formulation risk factors have been well documented and include a drug product pH ≥8.0, the presence of acetate, citrate and phosphate buffers, the presence of chelating agents such as EDTA, the presence of sodium salts of organic acid, and high concentrations of alkaline salts.[11] Terminal sterilisation is also a risk, but is not applicable to biotechnology products.

The chemical composition of the glass and the production process, particularly formation and annealing, also impact risk of delamination. Factors such as heating rate, maximum temperature, and annealing time and temperature can all result in variations in glass durability.

The production process for PFS differs from vials, reducing the exposure of the product contact areas of the syringe barrel to extreme heat during the forming step. In a study comparing vials with PFS using a variety of formulation conditions, it was concluded that PFS "outperform vials for most test conditions and perform equivalently for the remaining".[12] The presence of citrate or phosphate buffers was the formulation variable most likely to lead to an increase in released elements. No recalls or published reports of delamination in PFS have been reported indicating that it is not a significant risk. However, an assessment of formulation against known delamination risk factors is a best practice during container selection.

Figure 1: (left to right) BD Sterifill™ COP, West Pharma Crystal Zenith COP, BD's Hypak™ Glass, and Schott TopPac® COC syringes.

Figure 2: ICH Q9 risk management process.

Multiple incidences of tungsten-induced protein aggregation have been reported. A study of precipitation of a mAb by tungsten demonstrated rapid coagulation by tungsten polyanions at pH 5.0, but concluded a lower risk for proteins formulated at pH >6.0 since higher pH prevents formation of tungsten polyanions.[13] However, in a study of Epoetin in a buffered solution at pH 7.0 spiked with tungsten pin extract, small amounts of aggregates were detected after storage for six months at 25°C.[6] A study of an alpha helical protein formulation at ~pH 4.0 susceptible to tungsten-induced aggregation determined that the use of vacuum stoppering increases the amount of residual tungsten present in the solution.[7] Vacuum stoppering removed the "air gap" typically present between the barrel funnel area and the product, exposing solution to the "tungsten rich" area of the syringe.

Studies of silicone oil-protein interactions have been conducted using spiked silicone oil in solution as well as by comparing solutions in siliconised syringes to non-siliconised syringes. A comprehensive study of the impact of formulation considerations on silicone oil-induced aggregation has not been completed, but some risk factors can be identified.

Silicone oil-induced aggregation is most likely to occur with high protein solutions, close to their solubility limit. In a study of abatacept,[14] it was hypothesised that relatively high concentration of the protein may have solubilised or emulsified more oil from the surface than would have been the case with a lower concentration. In an anti-SEB mAb study of multiple formulations, the effect was only seen at a pH close to the pI and after shaking.[14] In studies of a model IgG1, the inclusion of 0.01% polysorbate 20 was found to inhibit silicone oil-induced aggregation during agitation. The study authors speculate that the surfactant "competes with the protein molecules for adsorption to the oil-water, air-water, and oil-air-water interfaces".[15] The same study demonstrated that sucrose partially inhibited silicone oil-induced aggregation.

One proposed theory for this effect is that sucrose increased the rate of silicone droplet formation, reducing the possible oil-water interfacial area, but further studies are needed to understand if sucrose has any effect on silicon oil-protein interactions.

Risk analysis for PFS container selection is summarised in Table 1. Following analysis of formulation risk factors, the process moves to risk evaluation. In formulations with multiple risk factors for glass delamination, experimental risk evaluation may not be value-added since extended stability would be required. In this case, or in the case of highly potent drugs where breakage could expose providers to hazards, a copolymer syringe should be considered.

Protein sensitivity to tungsten can be evaluated through simple spiking studies.[16] Risk evaluation for silicone oil-induced aggregation may be conducted by spiking formulations with a silicone oil-

Identified Risk	Factors
Glass Delamination	Citrate, phosphate or acetate buffers pH ≥8.0 Chelating agents (ex. EDTA) Sodium salts of organic acids High concentration of alkaline salts
Tungsten Induced Aggregation	pH ≤7.0 Use of vacuum stoppering
Silicone Oil Induced Aggregation	High protein solutions pH close to pI Lack of surfactant

Table 1: Risk analysis for PFS selection.

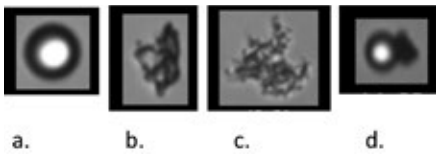

Figure 3: Images of a) silicone oil droplet b) protein aggregate c) protein aggregate d) possible protein aggregate bound to silicone oil captured using flow imaging.

water emulsion and subjecting samples to aggregation. A detailed experimental study is described by Badkar.[17] Many of the studies referenced were published prior to the wide adoption of flow imaging technology. Flow imaging provides both particle counts as well as an assessment of the morphology of a particle. Powerful software allows for the sorting of particles based on their shape. Silicone oil droplets, in particular, may be similar to protein particles and will result in high <10 µm particle counts in all spiked samples. However, silicone oil droplets have a characteristic spherical shape and appearance with a light centre and increasing contrast towards the exterior of the sphere (Figure 3), which allows standard flow imaging software systems to identify and subtract silicone oil particles.[18] Flow imaging can also identify protein aggregates bound to silicone oil droplets.

Following risk evaluation using solution spiking studies, risk reduction can be performed through selection of syringe characteristics such as ultra-low silicone, cross-linked silicone or silicone-free products. A small, accelerated stability study, using hand-filled syringes, is recommended prior to making a final selection. Samples should be stored at standard and accelerated conditions, and exposed to aggregation stress.

> "Evaluation of multiple lots of syringes is strongly recommended."

For biotechnology products, at minimum, flow imaging and product stability-indicating test methods should be used to evaluate the formation of subvisible aggregates and assess product stability. Additionally, the accelerated stability study is an opportunity to ensure that the function of the syringe, specifically the peak glide force, is unchanged by the product and is suitable for patient needs or the requirements of a planned auto-injector system.

Evaluation of multiple lots of syringes is strongly recommended. In internal, non-published studies, significant differences in the number of silicone oil-related particles have been observed using flow imaging in different lots of the same PFS. Extractables/leachables studies should be initiated at the selection of the preferred container closure. The risk management process (Figure 4) concludes with selection of the PFS, acceptance of risk, and development of product test methods and specifications. Continued monitoring through regular product batch testing and a strong supplier relationship for notification and assessment of any syringe manufacturing changes is essential to maintaining product quality.

Figure 4: Risk management process applied to PFS container selection for a biologic product.

The complex requirements of biologic products have driven innovation in prefilled syringe technology, which has resulted in a wide array of options for selection by the product development team. While new syringe options may increase cost for the final product, evaluation of risks of specific formulation instability and component incompatibility should be conducted to balance quality, safety and cost. ICH Q9 Quality Risk Management provides a framework which can be applied to create an efficient process for PFS container selection.

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ABOUT THE AUTHOR

Wendy Saffell-Clemmer is the Director of the Baxter Biopharma Solutions R&D team. The team offers contract development services for small volume liquid (vial and syringe) and lyophilised products which are manufactured for external clients both at Baxter's Bloomington, IN, US and Halle, Germany facilities.

Services include formulation development, lyophilisation cycle development, container compatibility and analytical development for small molecules, peptides, proteins, mAbs, ADCs and vaccines. Additionally the team performs analytical method validation, transfer and lifecycle maintenance for our QC group as well as cleaning validation method development and validation.

She volunteers as a member of the USP Expert Committee for Biological Analysis-General Chapters, the USP Expert Panel for Protein Measurement, and the AAPS Biosimilars Focus Group Steering Committee.

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LUBRICIOUS COATINGS TO REDUCE SILICONE OIL & PARTICLE LEVELS

The market for prefilled syringes continues to grow as does the number of approved biologics delivered in this manner. However, components of the prefilled syringe have the potential to interact with these sensitive drugs rendering them less efficacious or possibly immunogenic. Lubricious coatings that reduce silicone oil droplets and total particle loads may be able to offer a solution to this problem. In this article, Bernd Zeiss from Gerresheimer, and Susan Dounce from Datwyler, outline the results of a study using the combination of a Gx Baked-on RTF® syringe and the OmniflexCP® plunger.

In 2015 more than three billion prefilled syringes (PFS) were sold worldwide, and the market continues to grow. Although anticoagulants and vaccines have dominated in the PFS market, today the number of recombinant proteins stored and administered in prefilled syringes is constantly increasing.

Due to the sensitivity of biologics during storage and the complexity of their mechanisms of action upon administration, primary packaging components used for biologics are faced with the most demanding requirements compared to those used for any other injectable class of drug. The prefilled syringe (including the glass barrel and the elastomeric closure) needs to act as a chemically inert, secure delivery system. The rise of auto injectors and the integration of additional safety features add to the complexity of this syringe system.

For biologics, a major concern is the generation of proteinaceous particles in prefilled syringes. Under certain circumstances, therapeutic proteins can interact with syringe components, in particular the silicone oil that is typically used as a lubricant on both the barrel and plunger. The adsorption/desorption of proteins at aqueous-silicone interfaces can cause non-native structural conformations to arise and protein aggregates to form (Figure 1).[1,2] The nucleation of proteins at silicone-particle interfaces is a known degradation pathway for some biologics and can result in diminished drug efficacy.[3] These phenomena are exacerbated at high silicone concentrations, when an additional aggressor like heat or agitation is involved, and as modern formulations approach the drugs' solubility limits.[4,5]

> "Primary packaging components used for biologics are faced with the most demanding requirements compared to those used for any other injectable class of drug."

The potential risk for protein aggregates to elicit adverse patient reactions has triggered a shift in regulatory requirements related to particles in primary containers. While historically the regulatory focus has been on larger particles which could cause capillary occlusion, new additional scrutiny aims to reduce the immunogenicity risk associated with protein aggregates. It is the expectation of the US FDA that

Bernd Zeiss
Manager Technical Support Medical Systems, Business Development
T: +49 5223 164 309
E: b.zeiss@gerresheimer.com

Gerresheimer Bünde GmbH
Erich-Martens-Strasse 26-32 32257
Bünde
Germany

www.gerresheimer.com

Dr Susan M Dounce
Senior Manager, Business Development & Innovation Injection Systems
T: +1 856 663 2202
E: susan.dounce@datwyler.com

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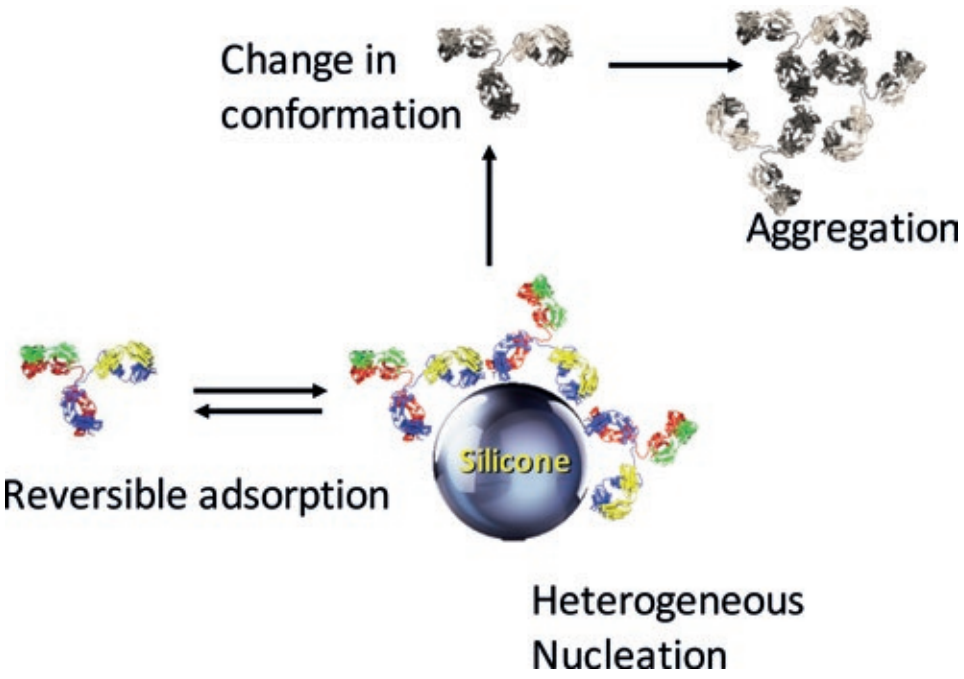


Figure 1: Proteins that are sensitive to silicone oil may undergo heterogeneous nucleation at silicone droplet surfaces or may adsorb / desorb from the droplet which may cause an irreversible change in conformation and an increased risk of protein aggregation.

evidence of a stable production process be provided through measurement and characterisation of particles in therapeutic protein products. Table 1 shows the thresholds for particle levels in therapeutic protein injections (USP<787>), for standard injectables (USP<788> and Pharm Eur 2.9.19), and for ophthalmic solutions (USP <789>). All of these USP and Pharm Eur chapters refer to filled syringes (the combination product). In addition to these pharmacopoeial thresholds for particles ≥10 µm, the FDA Guidance on Immunogenicity Assessment now asks for quantitation and characterisation of particles in the size range of 2-10 µm.

Today, due to the increased scrutiny over particle levels and new regulations around combination products, the manufacturing of primary packaging materials is considered to be an extension of the drug manufacturing process itself. As such, prefilled syringe and elastomeric closures vendors are requested to offer the lowest possible particle loads on the individual components. Both Gerresheimer and Datwyler are addressing these industry needs through innovation in materials, processes and production facilities.

> "Reducing particle loads from syringe plungers is equally as important as reducing particle loads from syringe barrels."

PARTICLE REDUCTION FROM BARRELS AND PLUNGERS

Prefillable syringe manufacturers have found various ways to reduce particle loads. At Gerresheimer this process starts during barrel forming that is controlled by a proprietary camera system, G3, which detects and distinguishes all kinds of both cosmetic and dimensional defects including different types of particles. A dedicated washing process after the barrel forming can already reduce particles from this manufacturing step.

RELEVANT REGULATION		PARTICLE COUNT LIMIT				
		2-10 µm	≥10 µm	≥25 µm	≥50 µm	COMMENTS
USP <787> SbVPs in Therapeutic Protein Injections	**Small volume:** (≤100 mL / container)	N/A	≤6,000 / container	≤600 / container	N/A	Applicable for biologics formulations
						USP <1787>: Orthogonal measurement e.g. MFI recommended
USP <788> Particulate Matter in Injections	**Small volume:** (≤100 mL / container)	N/A	≤600 / container	≤600 / container	N/A	Standard for all injectables
						Measured by light obscuration
USP <789> Particulate Matter in Ophthalmic Solutions		N/A	50 / mL	5 / mL	2 / mL	Measured by light obscuration
FDA Guidance on Immunogenicity Assessment in Therapeutic Protein solutions		Characterisation Only	N/A	N/A	N/A	Particles 2-10 µm to be quantified and characterised

Table 1: Pharmacopoeial and regulatory directives: requirements for particle measurements in filled syringes.

In the adjacent Ready-To-Fill (RTF®) process, particle loads are again minimised by rinsing, upright transport of the syringes and by avoiding glass-to-glass contact. Above all, the use of the proprietary heat-curing process (baked-on RTF®) is advantageous to reduce the number of silicone-oil-based subvisible particles (SbVPs) migrating from the syringe barrel. This proprietary baked-on lubricious silicone coating is highly uniformly distributed, inert and long lasting. The reduction of particle levels due to the Gx Baked-on RTF® curing process is reflected in the new data of this publication. The Gx Baked-on RTF® syringe in combination with a silicone-free plunger allows very low particle loads to be achieved and the needs of the biologic drug delivery to be met.

Reducing particle loads from syringe plungers is equally as important as reducing particle loads from syringe barrels. At Datwyler, this is accomplished through lubricious barrier Omniflex coatings, which do not require siliconisation, and through state-of-the-art clean manufacturing facilities known as FirstLine®.

Datwyler's Omniflex Coated Plungers (OmniflexCP®) utilise a proprietary, flexible fluoropolymer spray-coating technology that is designed to:

1. Be an inert barrier
2. Impart a low coefficient of friction without siliconisation.

The entire plunger surface is covered (in contrast to the partial coverage of most film coatings) and has the benefits of providing a full barrier and eliminating the need for siliconisation of the plunger ribs. The absence of siliconisation eliminates the largest source of subvisible particles and translates into ultra-low subvisible particle loads from the plunger. All Omniflex-coated products are produced in Datwyler's state-of-the-art manufacturing facilities known as FirstLine®.

FirstLine® facilities are designed and operated under a zero defect philosophy. The process flow, gowning protocols, personnel and material flow, and state-of-the-art automation all result in the lowest endotoxin, bioburden, particulate and defect levels available in the industry.

In the following sections an investigation of the optimisation of lubricious coatings on the syringe barrel and the plunger is presented. The aim of this study was to characterise and significantly reduce the overall particle loads and specifically the silicone oil droplet loads in a prefilled syringe system intended for biologic drug delivery.

The combination of the Gx Baked-on RTF® syringe and the OmniflexCP® plunger (Figure 2) is found to provide particle loads that can meet the new stringent pharmacopoeial requirements for therapeutic protein products.

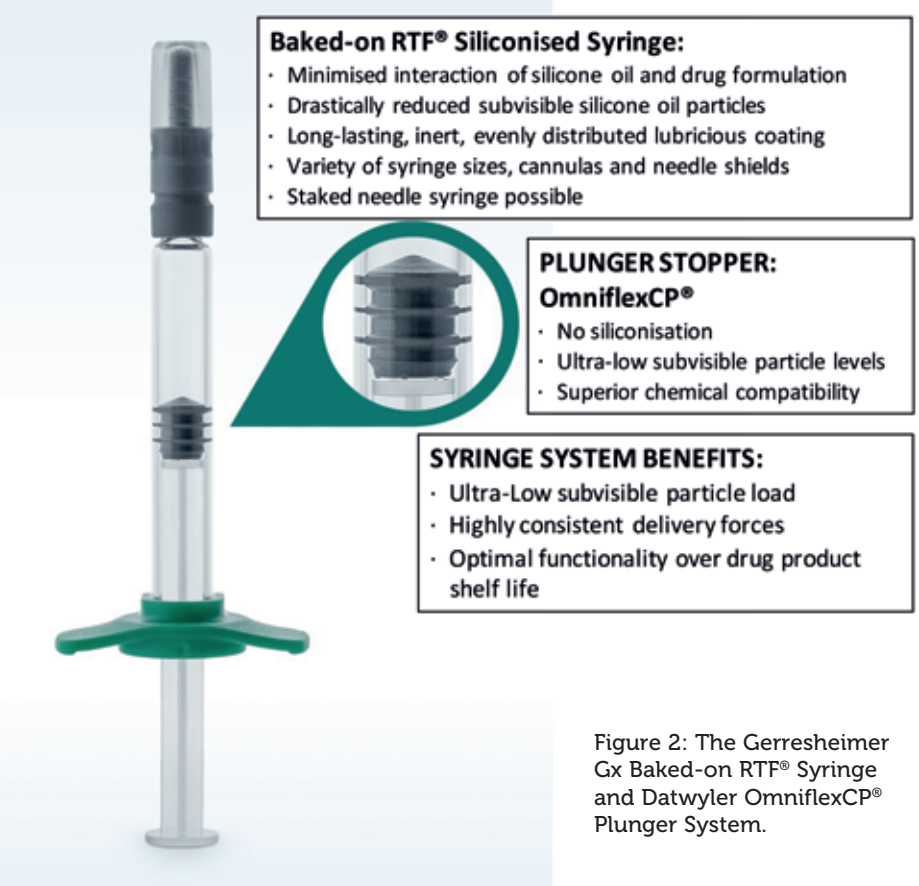


Figure 2: The Gerresheimer Gx Baked-on RTF® Syringe and Datwyler OmniflexCP® Plunger System.

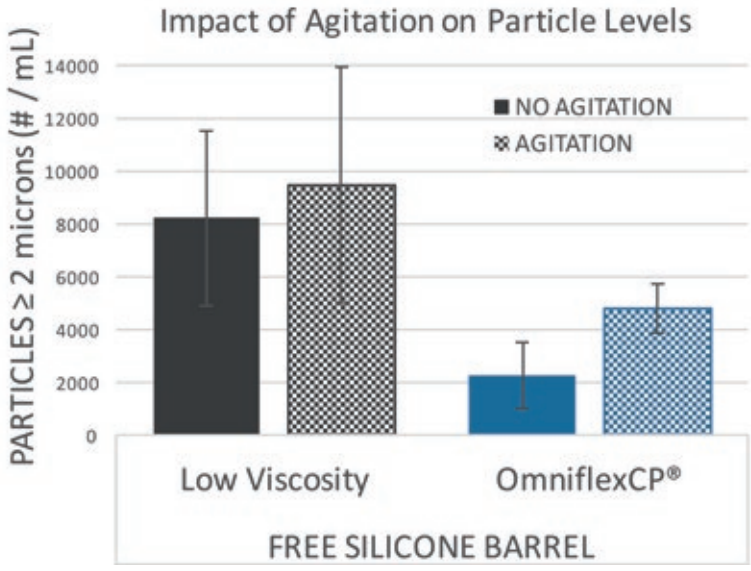


FIGURE 3. The impact of agitation on particle levels in a 1 mL long syringe at the 1 week time point. The syringe barrel has been lubricated with free silicone oil (i.e. not baked-on). The grey bars represent plungers lubricated with low viscosity (350 cSt) silicone oil while the blue bars represent Omniflex-coated (non-siliconised) plungers. Agitation (represented by the checkered bars) was performed for 1 minute on a rotary shaker table at 400 RPM. Particle measurements were made by HIAC Royco light obscuration.

EXPERIMENTAL METHODS

Sample Preparation

1 mL, long syringes with either free silicone (0.5±0.2 mg/syringe) or baked-on silicone (<0.2 mg/syringe) were filled in ambient conditions with 10 mM phosphate buffered saline containing 1 mg/mL polysorbate 80. Plungers were lubricated (~30 µg/cm²) with either low viscosity silicone (Dow Corning DC360, 350 cSt), high viscosity silicone (Bluestar, 30,000 cSt) or were Omniflex coated (no siliconisation).

For the one-week time point, syringes were aged horizontally under ambient conditions. For the three-month time point, syringes were aged horizontally under accelerated conditions (40°C, 75% relative humidity). Syringes that were agitated were placed onto an orbital shaker table (1 min @ 400 RPM) prior to particle level measurements. Time was allowed after agitation and prior to measurement to allow air bubbles to dissipate.

Particle Level Measurements

Particle levels were measured by HIAC Royco light obscuration and by micro-flow imaging (MFI). Due in part to the ostensible intrinsic limitations of light obscuration to count non-spherical and/or transparent particles, particle levels measured by MFI are higher than those measured by HIAC Royco, though qualitative trends are consistent between the techniques.[6]

In both cases, a blank solution was used to clean the instrument and to ascertain the cleanliness of the sampling vessel. Acceptance criteria for the particle levels of the blank solution must be met prior to sample measurement. The contents of the syringes were dispensed into the clean sampling vessel by actuating the plunger in the forward direction.

In the case of MFI, one measurement was made per 1 mL long syringe. In the case of HIAC Royco, which requires greater sample volume, the contents of 15–20 syringes were pooled together for multiple sequential measurements.

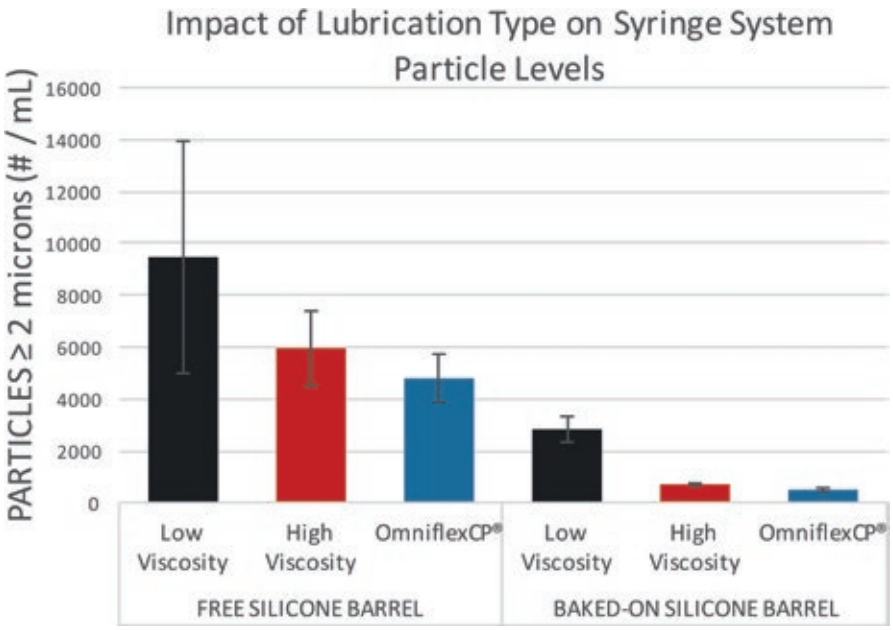


Figure 4: The impact of barrel lubrication type and plunger lubrication type on syringe system particle levels, measured by HIAC Royco light obscuration, after 1 week aging in ambient conditions, with agitation prior to the measurement. The three bars on the left represent a syringe barrel with free silicone while the three bars on the right represent a barrel with baked-on silicone. Grey and red bars show plungers lubricated with low and high viscosity silicone oil respectively. Blue bars represent Omniflex-coated plungers (not siliconised).

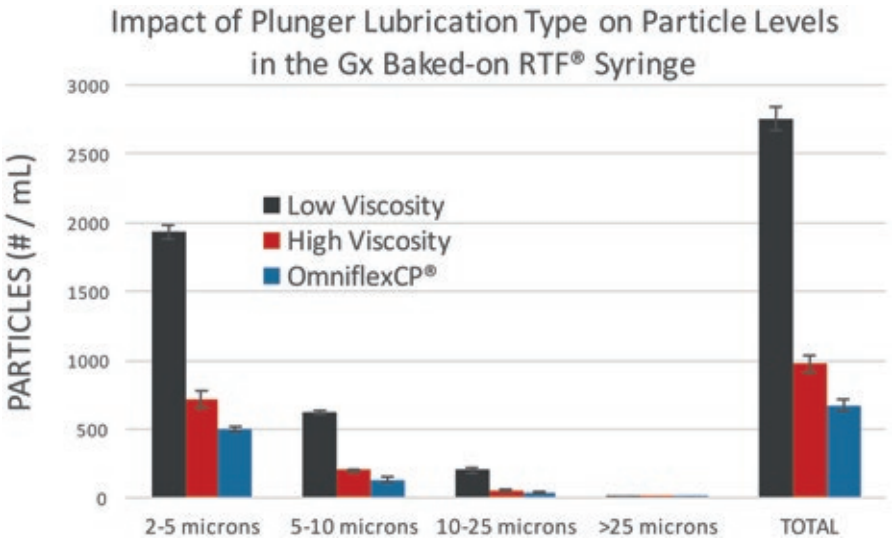


Figure 5: Particle loads by size category as measured by HIAC Royco light obscuration in the Gx Baked-on RTF® syringe with various plungers lubrication types. Syringes were aged for 3 months under accelerated conditions and agitated prior to measurement.

RESULTS

Impact of Agitation

Shaking on a rotary shaker table for one minute prior to sample measurement was intended to mimic the agitation that a prefilled syringe may experience during transport or at the point of care when a patient or healthcare worker handles the syringe and administers the injection. Figure 3 shows the impact of such agitation on the particle levels (≥2 µm) in a free silicone syringe in combination with plungers that are lubricated with low viscosity silicone oil (grey bars) or Omniflex coated (blue bars). The solid bars are samples that have not been agitated while the checkered bars have been agitated. Since a notable increase in particle load is observed with agitation, the data reported hereafter is for agitated samples only.

Impact of Plunger and Barrel Lubrication Type on SbVP Levels

In Figure 4, particle levels (≥2 µm) after one week of ageing in ambient conditions, with agitation prior to testing, were measured by HIAC light obscuration. It is evident that both the barrel lubrication method and the plunger lubrication method impact total particle levels.

The three bars on the left side (free silicone barrel) show significantly higher particle counts as compared with the baked-on silicone barrel (three bars on the right). Interestingly, even in the case of free silicone on the barrel, the plunger lubrication method significantly impacts the system particle counts with the Omniflex lubricious barrier coating (blue bars) providing the lowest possible level of subvisible particles.

The combination of the Gerresheimer Gx Baked-on RTF® syringe with the Datwyler OmniflexCP® plunger provides a 95% reduction in particle levels over a traditional siliconised barrel/plunger system.

Figure 5 (on previous page) shows a closer examination of the Gx baked-on RTF® syringe in combination with different plunger lubrication systems after three months ageing under accelerated conditions as measured by HIAC Royco light obscuration after agitation. In all cases, total particle levels are dominated by particles <10µm and the highest particle levels are observed for plungers lubricated with low viscosity (350 cSt) silicone oil. In the Gx Baked-on RTF® syringe, OmniflexCP® provides a 75% reduction in particle load *versus* a typical siliconised plunger.

Particle Characterisation and Contributions from Silicone Oil

The use of micro-flow imaging allows the nature of the particles to be further characterised through the use of image analysis and morphological filters. Importantly, silicone-oil-based subvisible particles can be distinguished from other particles.

In Table 2, typical images of silicone oil particles and other transparent and opaque non-spherical particles are shown. The silicone oil droplets have characteristics of being highly circular and dark in colour with a white centre. By applying morphological filters to the particle images, the contribution of silicone oil to subvisible particle levels has been ascertained to a reasonable approximation.

Figure 6 shows the total particle levels, measured by MFI, in a traditional syringe system versus the Gx Baked-on RTF® syringe. The left bar represents a system with free silicone on the syringe barrel and a high viscosity siliconised plunger. The right bar represents the Gx Baked-on RTF® syringe in combination with OmniflexCP®. The blue portion of the bars is the contribution from silicone oil droplets while the grey portions correspond to all other particles.

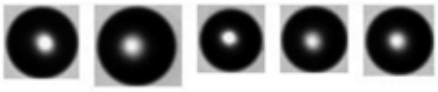
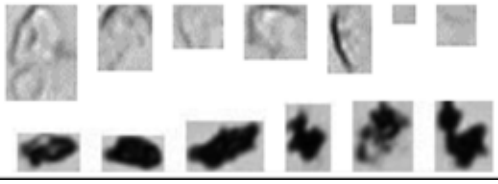
MFI IMAGE ANALYSIS OF PARTICLES IN PREFILLED SYRINGE SOLUTIONS	
SILICONE OIL DROPLETS	
OTHER PARTICLES (i.e. glass, rubber, dust, etc.)	

Table 2: MFI images of silicone oil and non-silicone-oil particles.

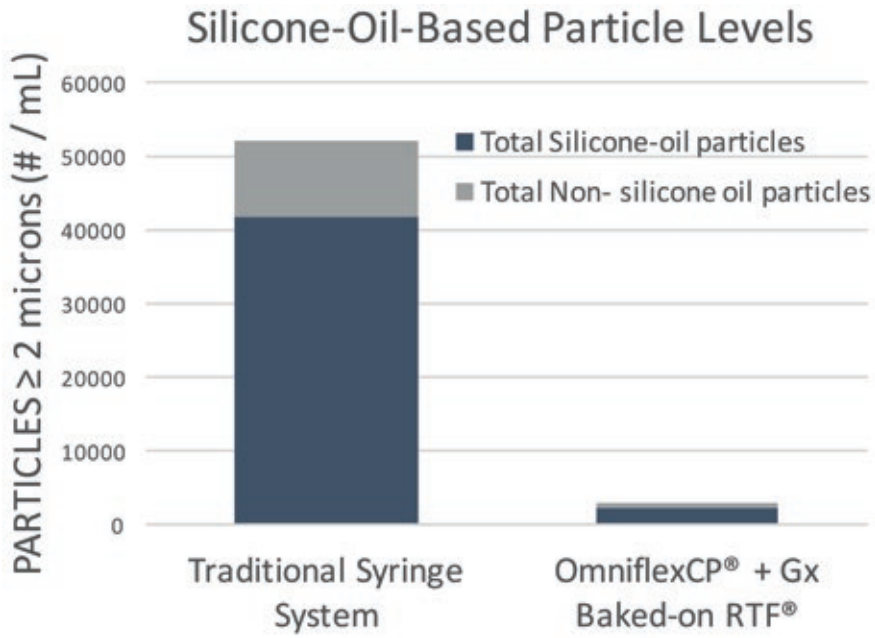


Figure 6: Particle level measurements by MFI in a traditional syringe system (left bar, free silicone on the barrel and a high viscosity siliconised plunger) versus the Gx Baked-on RTF® Syringe with OmniflexCP® (right). Syringes have been aged under accelerated conditions for three months. The blue portion of the bars represent silicone-oil-based particles and the grey portion of the bars represent other particles.

In these MFI measurements made after three months accelerated ageing, the Gx Baked-on RTF® syringe / OmniflexCP® plunger system offers a 95% reduction in particle levels as compared with the traditional syringe system. In the case of the traditional syringe with the high viscosity silicone oil plunger, 80% of the total particle count is due to silicone oil droplets. With the baked-on silicone on the barrel and the lack of free silicone oil migrating from OmniflexCP®, a dramatic reduction in silicone-oil-based particles is realised with the combined Gx baked-on RTF® syringe / OmniflexCP® system.

System Functionality

In addition to the focus on subvisible particles, the overall syringe performance must not be neglected. Low and repeatable break-loose and gliding forces are important syringe features not only for manual PFSs but especially for PFSs used with auto injectors. Although low silicone levels can lead to low particle loads in the syringe, this can conversely lead to higher delivery forces. In a long-term study with different plungers carried out by Gerresheimer, the impact of storage, stoppering method and siliconisation level of Gx RTF® syringes was scrutinised.

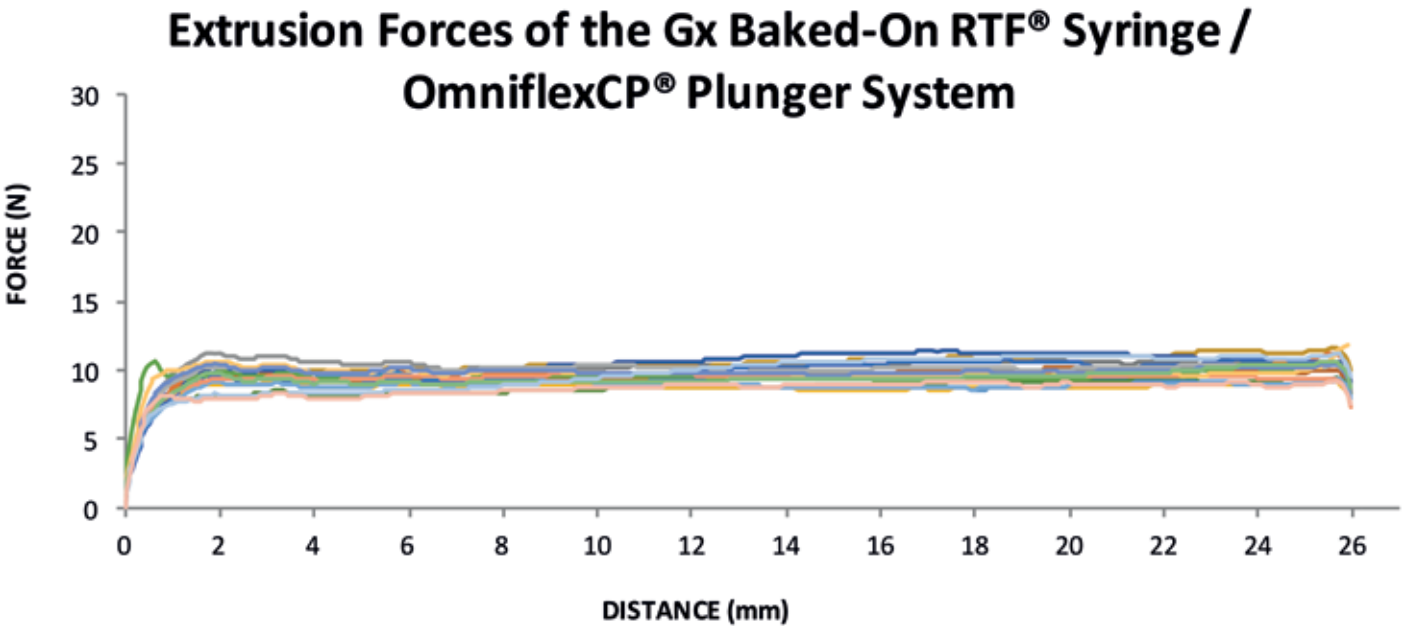


Figure 7: Extrusion forces for the Gx Baked-on RTF® / OmniflexCP® syringe system. The 1 mL, long staked needle syringes (27G) were WFI filled. Plungers were steam sterilised and placed by vacuum placement. The system was aged for one year. Twenty syringe samples were measured at a displacement rate of 380 mm/min..

One of the best results was found with the combination of baked-on siliconised syringes with the OmniflexCP® plunger. Figure 7 shows an extrusion force profile after one year of storage in a 1 mL long baked-on staked needle syringe with OmniflexCP®. Highly consistent delivery forces are observed for this system which makes it ideal for use with auto injectors.

CONCLUSIONS

Since every component's particle levels are significant contributors to the total particle load in a prefilled syringe, a full systems approach is crucial in order to meet the increasingly stringent regulatory expectations for therapeutic proteins. Given the very low particle load and highly consistent delivery forces of the system and the inert fluoropolymer barrier coating on the plunger, the Gx Baked-on RTF® syringe / OmniflexCP® combination is well suited to meet the stringent requirements of biologic drug delivery.

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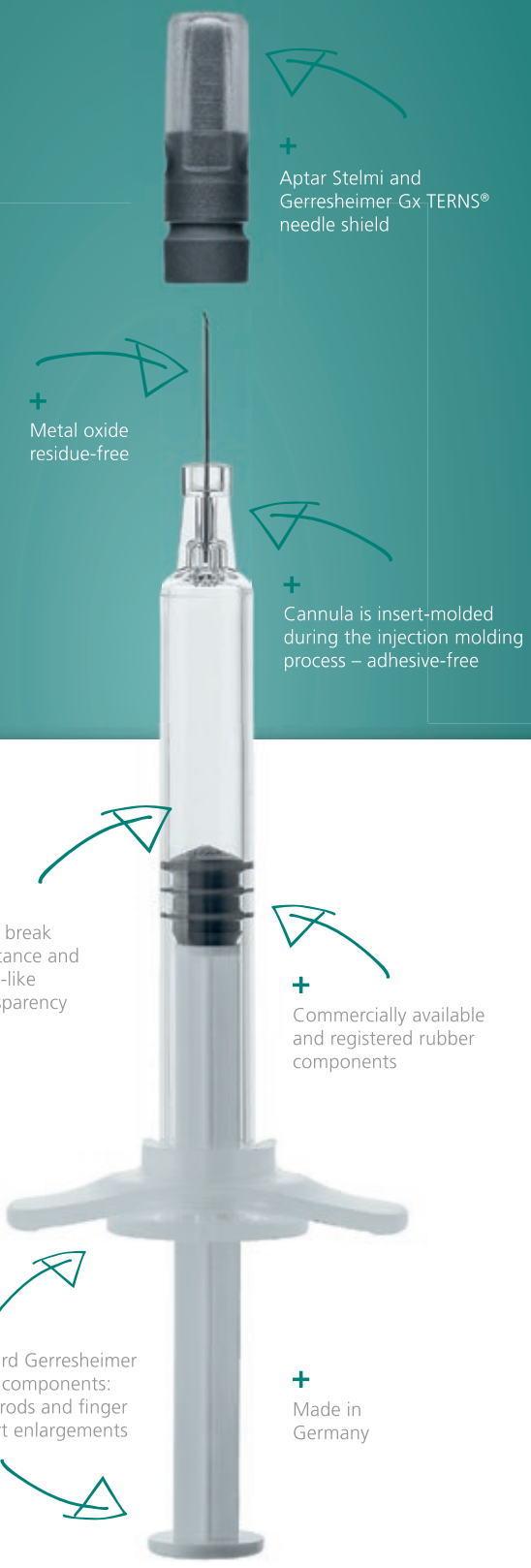

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PRODUCT SHOWCASE: **PremiumCoat®**

Aptar Stelmi

THE 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 components 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."

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 (Figure 2). 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. 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 20 mm coated stopper. A PremiumCoat® 13 mm coated stopper was introduced earlier this year widening our range of coated stoppers.

> "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. As a result, compatibility of the drug and the closure is significantly superior with PremiumCoat® stoppers."

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 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.

Anne Bailly
Product Communication Manager
T: + 33 1 48 63 56 71
E: anne.bailly@aptar.com

Marion Baschet-Vernet
Press Attachée
T: +33 622 170 896
E: mbvernet@gmail.com

Aptar Stelmi
Le Raspail - Paris Nord 2
22 Avenue des Nations - BP 59415
Villepinte
95944 Roissy Charles De Gaulle Cedex
France

www.aptarstelmi.com

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.

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

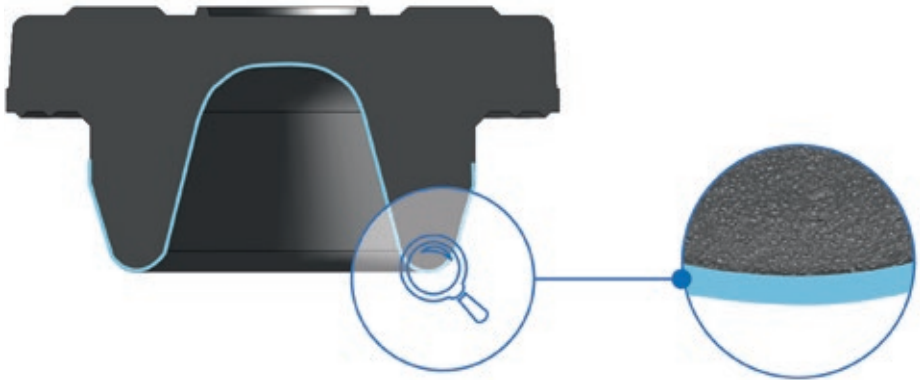

Figure 2: A barrier film covers the drug contact area. (Image courtesy of Aptar Stelmi)

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

PROTECTION, EFFICACY AND SAFETY OF DRUG PRODUCTS

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.

PREMIUM 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.

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.

TERUMO
PHARMACEUTICAL SOLUTIONS

READY-TO-USE PREFILLABLE SYRINGES: STERILISATION EFFECTS ON BIOPHARMACEUTICALS

In this paper, William Dierick, Director, Technology Development, and Koji Nakamura, PhD, Senior Manager, Business Development, both of Terumo Pharmaceutical Solutions, report studies comparing the effects of different sterilisation on the extractables and leachables content of biotherapeutic products in prefilled syringes, make links with free radical production and oxidisation, and PLAJEX™ with i-coating™ plunger stoppers creates a primary drug container that mitigates possible interactions from tungsten, silicone oil and their aggregation.

Pharmaceutical industry growth is buoyed this year by the expectation that 12 new drugs are forecast to reach blockbuster sales by 2020. Within this market, the biotech sector is a large contributor as indicated by the number of biopharmaceuticals within the top-10 drugs by worldwide sales in 2016. R&D in this space is forecast to continue at a high pace with four biotech products in the top-10 of the biggest launches in 2016.[1]

> "New developments have been made in recent years to establish a low-leachable PFS system with a focus on application with therapeutic proteins."

Therapeutic proteins are typically administered by injection and by using prefilled syringes (PFS). However, proteins may be sensitive to heat, oxidation and have the propensity to aggregate.[2-4] Protein aggregation and the elicitation of anti-drug antibodies (ADAs) may have detrimental effects on drug efficacy, pharmacokinetics and safety. There is evidence that protein aggregation may enhance immunogenicity and this can be an important factor in causing adverse events.[5-9] Immunogenicity has been reported with contributing factors related to excipients / formulation and interactions with contact materials of the primary drug container.[10-12]

Protein-aggregation factors derived from storage in PFS may include silicone oil, usually applied to improve the smooth gliding of the rubber plunger along the barrel, and tungsten oxide, a contaminant derived from the syringe glass manufacturing process.[13-16]

In 2014, these concerns led the US FDA to issue a Guidance for Industry: "Immunogenicity Assessment for Therapeutic Protein Products". It states that "interactions between therapeutic protein products and the container closure may negatively affect product quality and immunogenicity. These interactions are more likely with prefilled syringes of therapeutic protein products". In this Guidance, FDA recommends that sponsors should conduct a comprehensive extractables and leachables laboratory assessment using multiple analytical techniques to assess the attributes of the container-closure system that could interact with and degrade protein therapeutic products.[17]

Mr William Dierick
Director, Technology Development
T: +32 16 381 450
E: william.dierick
@terumo-europe.com

Terumo Europe NV
Pharmaceutical Solutions
Interleuvenlaan 40
B-3001 Leuven
Belgium

Dr Koji Nakamura
Senior Manager Business Development
T: 81 3 6742 8392
E: Kouji2_Nakamura@terumo.co.jp

Terumo Corporation
Tokyo Opera City Tower 49F
3-20-2, Nishi-Shinjuku, Shinjuku-ku,
Tokyo 163-1450
Japan

www.terumo-ps.com

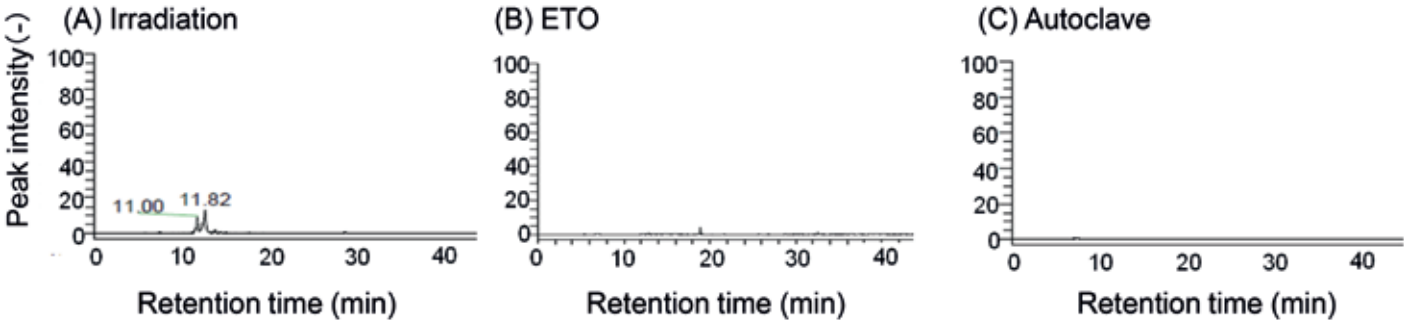

Figure 1: Comparison of extractables for different methods of sterilisation.

With emphasis on the interrelated areas (drug product formulation – container closure system – manufacturing) for therapeutic proteins, the method of sterilisation for prefillable syringes may also become a key factor to mitigate interactions with therapeutic proteins. For sterile ready-to-fill syringes, typical methods of sterilisation include Ethylene Oxide (EtO) gas sterilisation, irradiation (gamma irradiation or e-beam) and steam sterilisation, depending also on the applied materials used in the PFS system.

EXTRACTABLES / RESIDUES FROM DIFFERENT STERILISATION METHODS

New developments have been made in recent years to establish a low-leachable PFS system with a focus on application with therapeutic proteins; particularly PLAJEX™ a cyclo-olefin polymer (COP) PFS with i-coating™ plunger stoppers to eliminate the use of silicone oil as a lubricant of the syringe. These sterile ready-to-use syringes are steam sterilised within the tub/nest presentation.[18-21]

Terumo evaluated the material of PLAJEX™ prefillable syringes and compared the extractables (and residues) upon using different sterilisation methods. Sterilisation of the materials was conducted respectively with steam sterilisation (121°C for 30 min), EtO (EtO concentration 20%), and irradiation (25 kGy).

Extractables were prepared by extractions with water for injection (WFI) at conditions of 121°C for 60 min. The levels of organic compounds in the extractable were determined by liquid chromatography-mass spectrometry (LC-MS) according to methods reported previously.[20]

Figure 1 shows the graphics of relative abundance obtained by LC-MS. Peaks were detected for irradiated samples whereas no peaks were detected for steam sterilisation and EtO sterilisation. In addition, residual EtO was monitored over time by gas chromatography using headspace sampling. Figure 2 shows the

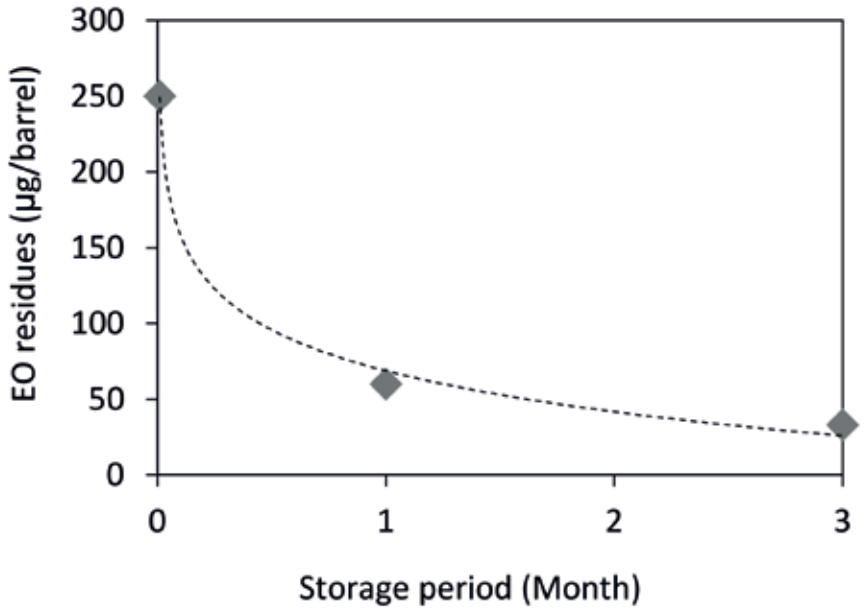

Figure 2: Residual EtO profile on polymer PFS.

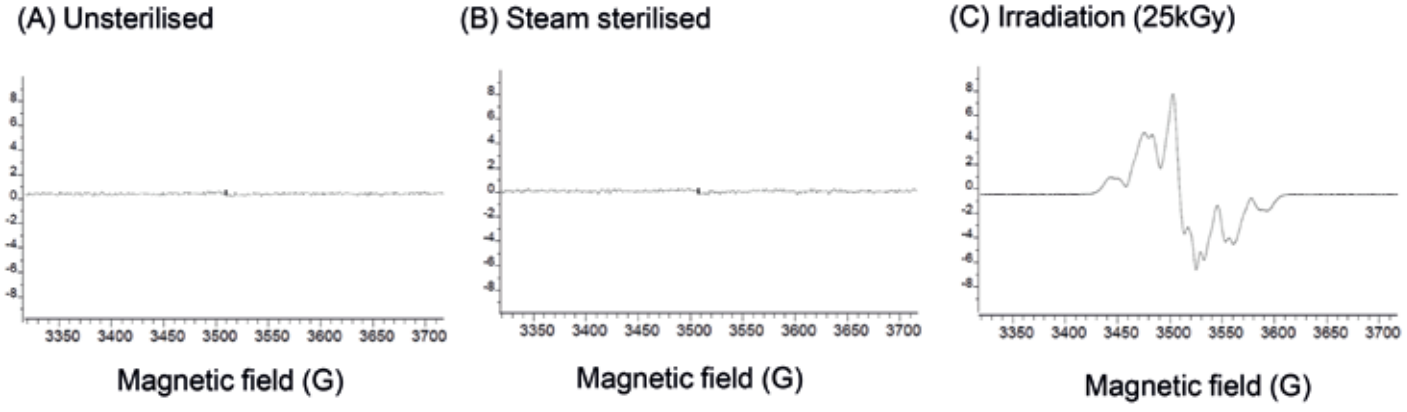

Figure 3: Typical ESR spectra of (A) unsterilised syringe, (B) steam sterilised syringe and (C) syringe irradiated at 25 kGy.

results of residual EtO over time of storage. The potential effect of residual EtO on biopharmaceuticals is not well known and will be subject to our additional research and experiments.

IRRADIATION: RADICAL GENERATION & INFLUENCE ON THERAPEUTIC PROTEINS

Sterilisation by irradiation is a technique commonly applied for polymer-based ready-to-fill syringes. Earlier publications indicated the occurrence of radicals from irradiated polymer-based PFS, affecting the level of protein oxidation as stored in these syringes.[23-26]

The generation of radicals after sterilisation of COP prefillable syringes, by irradiation (25kGy) or by steam sterilisation, was analysed using electron spin resonance (ESR) spectroscopy and the results are shown in Figure 3. There are no significant ESR spectrum changes in autoclaved syringes compared with control (non-sterilised syringe), whereas changes were observed after the syringe was sterilised by irradiation. Quantitative values of the generated radical amounts were calculated based on these spectra as shown in Figure 4.

"We deduce that irradiation of prefillable syringes results in radical generation, resulting not only in syringe polymer oxidation, but also in an extended persistence of radicals."

Additionally, a protein oxidation study was conducted where erythropoietin (EPO) was dissolved in an aqueous solution containing 2 mM Na_2HPO_4 and 0.06 mg/mL polysorbate 80 to obtain a final concentration of EPO with 24,000 IU/mL. Analysis of oxidised methionine in the EPO solution was conducted in using HPLC. The results, shown in Figure 5, demonstrated that oxidation rate increased over time for the protein stored in prefillable syringes sterilised by irradiation. The oxidation rate of proteins stored in steam-sterilised prefillable syringes remains similar to that of non-sterilised syringes. Therefore, protein oxidation may be attributed to

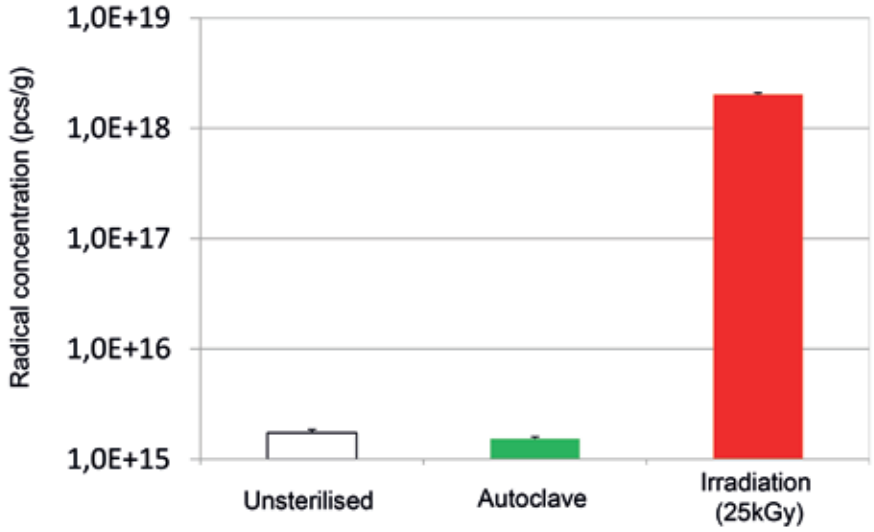

Figure 4: Residual radicals for different methods of sterilisation. Data presented as the mean ±SD (n=3).

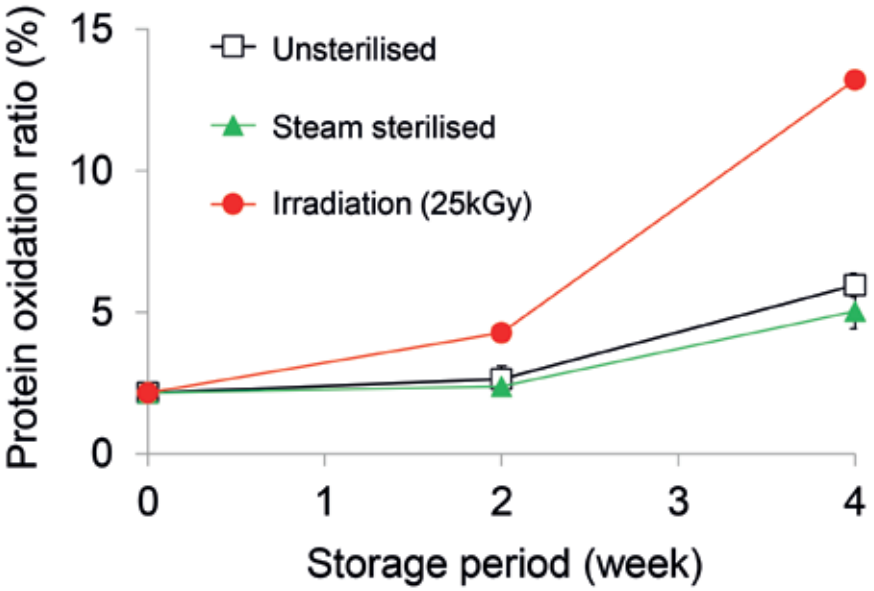

Figure 5: Difference in Oxy-Met production during storage of (square) EPO filled into unsterilised syringe, (triangle) steam-sterilised syringe, and (circle) irradiated syringe at 25 kGy, all at 25°C and 65% RH. Data presented as the mean ±SD (n=3).

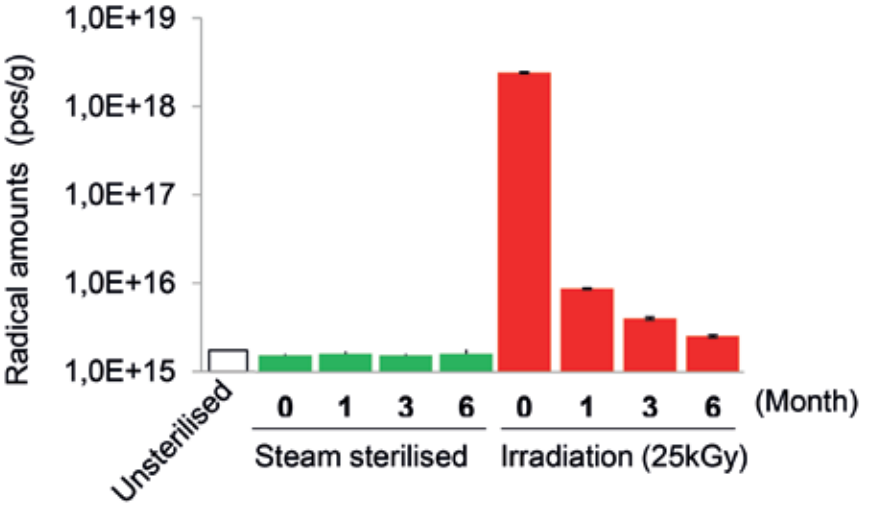

Figure 6: Transition of radical amount after storage of sterilised syringes by steam sterilisation and irradiation at 25 kGy (stored at 25°C and 65% RH).

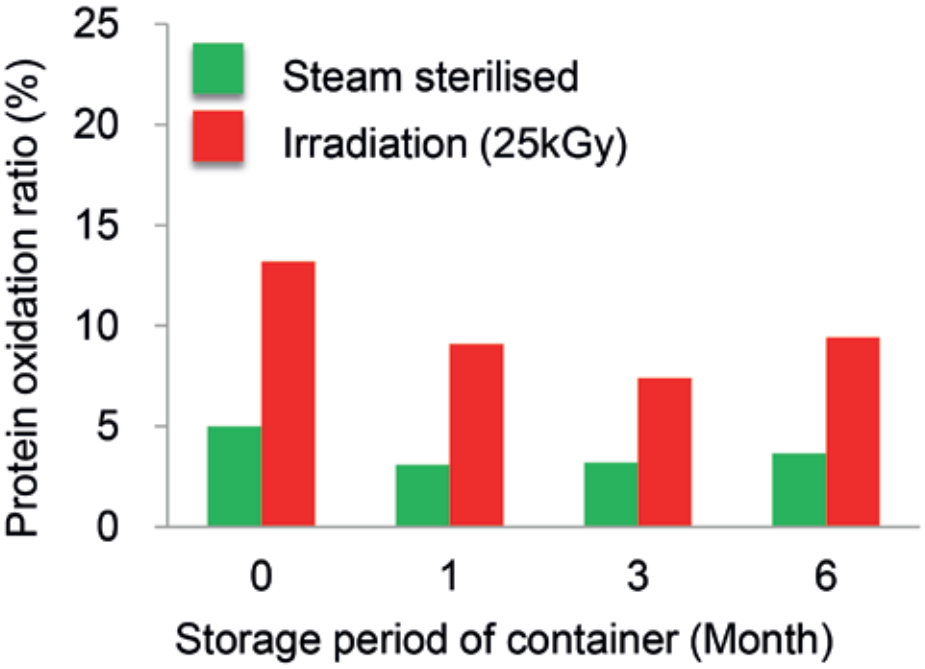

Figure 7: Comparison of protein oxidation after filling protein (EPO) into the sterilised syringe and stored at 25°C and 65% RH.

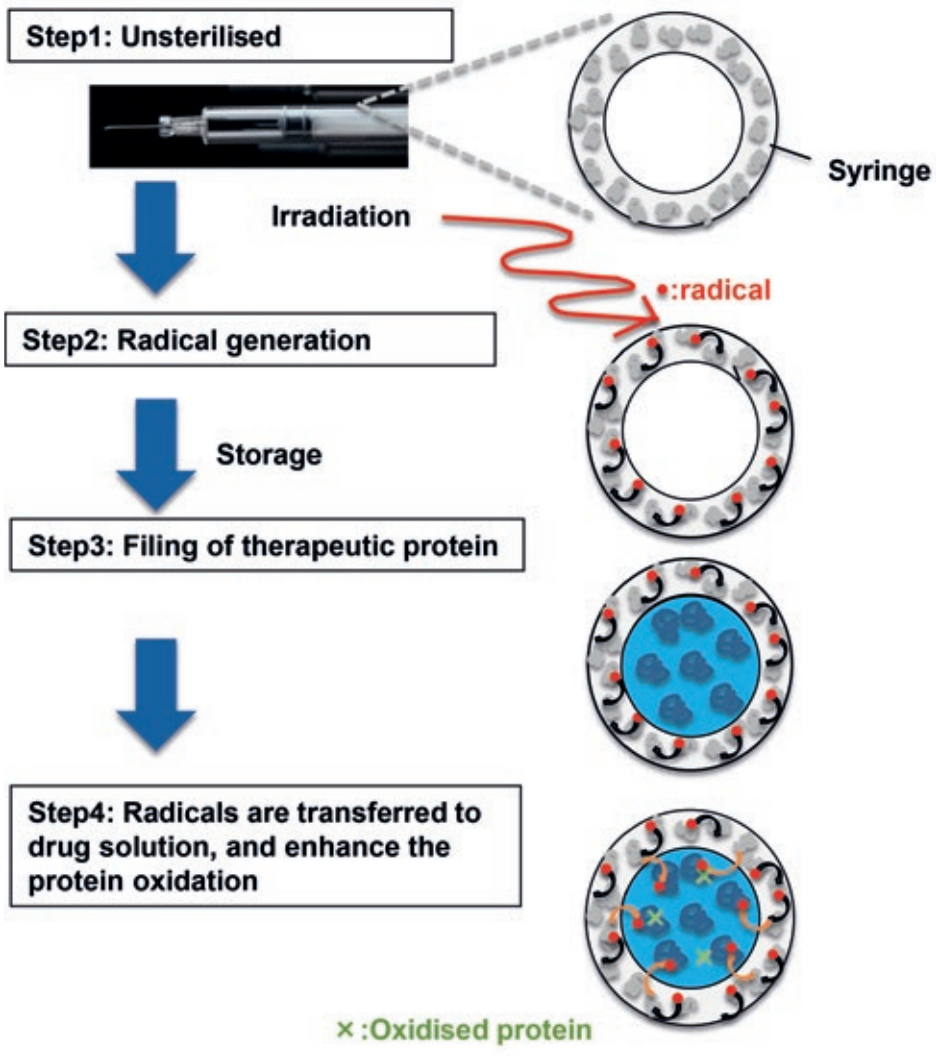

Figure 8. Hypothesis of the protein oxidation mechanism.

the generation of radicals present in the irradiated syringes.

It is generally believed that radicals persist for a very short period and more investigations were made therefore to verify the effects of time elapsing between irradiation and the time of filling of the tested protein solution (EPO solution). Samples were stored at 25°C prior to filling and filled syringes were also stored at 25°C for one month before oxidised methionine was quantified. Figure 6 shows the quantity of detected radicals over time and Figure 7 shows the protein oxidation ratio as measured for those time points. A decrease in oxidation ratio can be noted but the experiments suggest that the effect on the therapeutic proteins may persist over a longer period of storage time after sterilisation. Such effects can be mitigated by applying steam sterilisation for polymer ready-to-use syringes.

According to a report by Reigh *et al*,[27] radicals occur after polymer irradiation, and accelerate the continuous polymer oxidation. In this process, C=O or C-O bonds are produced (auto-oxidation). Development of this auto-oxidation cycle provides radicals to each molecule, resulting in a longer-term persistence of radicals. Our experiments reveal a similar reaction to the aforementioned auto-oxidation. We deduce that irradiation of prefillable syringes results in radical generation, resulting not only in syringe polymer oxidation, but also in an extended persistence of radicals (Figure 8). In our hypothesis, these residual radicals migrate into the biopharmaceutical solution, resulting in an increased oxidation of the protein drug product as was shown in Figure 6.

CONCLUSION

In consideration of the complexity and challenges associated with the development of therapeutic proteins, different regulatory guidance and directions have been developed over the years, emphasising the importance of assessing the possible interactions between biotherapeutics and the container closure system, as it may have detrimental effects on therapeutic protein quality and immunogencitiy.

PLAJEX™ with i-coating™ plunger stoppers creates a primary drug container that mitigates possible interactions from tungsten, silicone oil and aggregation thereof. Using steam sterilisation as the sterilisation method of ready-to-fill COP

syringes may assist in mitigating interactions with the therapeutic protein by reducing the risks of protein oxidation.

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PS12GB-0616VIN-I(06.16)

PRODUCT SHOWCASE: perfeXion™

SCHOTT
glass made of ideas

perfeXion™ is a new quality approach from Schottt, which controls every inch of pharma glass tubing and with its launch the company pushes towards a zero-defect philosophy in pharmaceutical glass tubing production.

"We are taking a major step towards a holistic view of quality in pharma glass production."

In quality control, details matter. When it comes to pharmaceutical primary packaging such as vials, cartridges or syringes (Figure 1), fluctuations in tubing dimensions such as the inner diameter or wall thickness can have a significant impact on the container performance – for instance, the filling or dosing accuracy for high potential drugs. Up until now, manufacturers of glass tubing have usually been monitoring quality parameters on a random sample base. However, Schott has developed a new production quality process. perfeXion™ controls and monitors every inch of the glass tubing that is later converted into a primary packaging container used by pharma companies to store and administer perhaps lifesaving drugs. With this, Schott aims to contribute to patients' safety from the very beginning of the value chain.

Figure 1: Fluctuations in tubing dimensions significantly impacts performance of syringes and other primary drug containers.

Schott officially introduced the perfeXion™ process to the industry with a presentation from Folker Steden, PhD, at CPhI Worldwide in Barcelona, Spain, on 4th October, 2016.

FROM BELIEVING TO KNOWING

"We are taking a major step towards a holistic view of quality in pharma glass production," says Patrick Markschläger, Executive Vice-President at Schott Tubing. "We could see from our existing control mechanisms, which were already extremely tight, that the quality of our glass tubes meets the highest requirements. Now with perfeXion™, we can verify that every inch of the glass tube is accurate."

This is a significant achievement, as Markschläger explains: "Pharma glass is mostly drawn in tubes when it comes from the melt. Schott as well as other quality-oriented converters use these tubes later on to produce vials, syringes, ampoules and cartridges. The challenge lies in monitoring and measuring the curved tubing surface with 100% accuracy, in a high-speed production process." This is achieved by using a combination of line scan and area cameras, laser and IR inspection systems that literally investigate the entire glass tube on-line. The measurement data is then collected and evaluated by a holistic inter-connected IT solution.

"This system recognises even the smallest defective spots in the "endless" glass tube that comes from the melt. It is then able to attribute these spots to a certain position at a single tube once the cooled down glass string is being cut," Markschläger continued. "This sophisticated system enables us to customise the quality level to the specific needs of the industry."

By storing the collected quality information in a database, measurements can be traced back even years later if needed.

Markschläger confirms that Schott has already started implementing perfeXion™ at its main site in Mitterteich, Germany. A company-wide roll-out at its other facilities in Europe, Asia and South America is underway.

With this development, Schott is not only passing another milestone of its future oriented quality roadmap. More importantly, the company's pharma glass known under the brand name SCHOTT FIOLAX® will enable even more sophisticated primary packaging solutions for advanced medical treatment than it already does today.

Each year, the international Schott Group manufactures around 140,000 tons of glass tubing and more than 10 billion pharmaceutical containers such as vials, syringes, ampoules and cartridges.

FIOLAX® and perfeXion™ are registered trademarks of SCHOTT AG.

Contact:
Dr Folker Steden
Director Product Management
& Scientific Services
T: +49 9633 80 253
E: folker.steden@schott.com

Schott AG
Erich Schott Str 14
95666 Mitterteich
Germany

www.schott.com/tubing

By your side
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PFS COMPONENT SELECTION STRATEGIES – RISK MITIGATION, PERFORMANCE, & LARGER VOLUMES DRIVE INNOVATION

With a focus on the company's Novapure® brand, Christa Janssen-Otten, Director, Product Management Prefillable Solutions & Delivery, West Pharmaceutical Services, discusses the application of quality-by-design principles in the development of plungers for prefillable syringes and auto injectors. The selection of optimally designed and developed delivery system components, such as plungers, is presented as an essential part of a pharmaceutical company's risk mitigation strategy.

The market for prefillable systems is still growing. In fact, two-thirds of the world's blockbuster drugs are now delivered via a prefilled syringe system or auto injector, and auto injectors are one of the fastest growing delivery segments. To ensure effective delivery and patient safety, manufacturers need high-quality components that are designed and manufactured to reduce particulates, ensure consistency of delivery and fit the changing needs of higher-volume delivery systems.

As new sensitive pharmaceuticals and biopharmaceuticals are prepared for market, regulatory agencies have asked manufacturers to build quality in from the start and ensure consistent quality throughout the product lifecycle. To make sure drug products maintain safety and efficacy from concept to commercialisation, and to reduce the total cost of ownership, packaging materials must evolve.

Because biologics are typically more viscous, can require larger volume doses, and are often paired with auto injectors and other self-administration systems, they present unique challenges in drug containment and administration. Such new characteristics require high-quality packaging to help maintain drug purity and efficacy, as well as more customised containers and the ability to accommodate larger dose volumes.

> "The plunger is a critical element of the prefillable syringe because it serves as the primary seal for container/closure integrity, maintaining drug purity during shelf life, and its function is central to the delivery of the drug to the patient."

Of course, every product that pharmaceutical companies and their drug delivery partners develop focuses on one priority: patient safety. West leads the industry in risk mitigation in its components, creating best practices that facilitate better quality and ensure regulatory compliance – all for the benefit of patients.

Christa Janssen-Otten
Director, Product Management
Prefillable Solutions & Delivery
T: +49 24 03796332
E: Christa.Jansen-Otten
@westpharma.com

West Pharmaceutical Services, Inc
530 Herman O. West Drive
Exton
PA 19341
United States

www.westpharma.com

Figure 1: NovaPure® components are a crucial part of West's drug delivery systems offering.

NOVAPURE: MITIGATING RISKS WITH QUALITY DESIGN

NovaPure® components (Figure 1) from West are a crucial part of the company's drug delivery systems offering. NovaPure components, including the 1-3 mL and 1 mL long NovaPure plungers and 13 mm and 20 mm NovaPure lyo and serum stoppers, utilise quality-by-design (QbD) principles to help ensure superior quality and function, and addresses the evolving needs of patients who need these injectable biologics in higher doses.

The plunger is a critical element of the prefillable syringe because it serves as the primary seal for container/closure integrity, maintaining drug purity during shelf life, and its function is central to the delivery of the drug to the patient. It is essential to understand and assess the plunger during the QbD process.

Plungers are typically made from butyl rubber and can be coated with a fluoropolymer film that can increase lubricity and serve as a barrier between the drug and the elastomer, reducing the potential for extractactables and leachables. Evolving industry demands for higher-quality components have increased the need for plungers developed using QbD processes.

The ICH Technical Requirements for Registration of Pharmaceuticals for Human Use define QbD as, "A systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management."

With a QbD approach, components are manufactured in a manner that helps to ensure reliability and, most importantly, patient safety. By considering the impact of prefillable syringe systems and their components on a particular drug product early in the development process – and employing QbD strategies to overcome development challenges – manufacturers can minimise potential quality risks and position the product to meet lifecycle needs.

> "As a result of this knowledge, a company can continually monitor and improve its manufacturing process to ensure consistent product quality – and mitigate risks by designing and verifying machinability, testing sterilisation methods, and honing manufacturing methods to reduce particulates in the production environment."

The QbD approach promotes a holistic understanding of the product, its integrated delivery system and the manufacturing process. As a first step in initiating QbD processes, it is critical to understand the unique traits of the product that is to be developed. To this end, a quality target product profile (QTPP), which forms the basis for drug product formulation and process development in a QbD framework, must first be constructed.

The QTPP consists of a series of considerations that will uphold the highest standards. Such standards may include: the desired product performance based on the intended clinical setting, dosage strength and delivery mode, pharmacokinetic characteristics, drug product quality criteria, as well as sterility and the drug's container closure system.

Critical quality attributes (CQAs) and ultimately the critical process parameters (CPPs) for a given product and process, respectively, are developed in support of achieving the QTPP. The information generated to determine the CQAs and CPPs will help to:

- Develop a meaningful control strategy
- Ensure product quality throughout the product lifecycle
- Increase product and process knowledge to support decisions
- Increase transparency and understanding for regulators and industry
- Enhance information needed for identifying and evaluating potential changes
- Monitor and track critical data for continuous improvement.

As a result of this knowledge, a company can continually monitor and improve its manufacturing process to ensure consistent product quality – and mitigate risks by designing and verifying machinability, testing sterilisation methods, and honing manufacturing methods to reduce particulates in the production environment.

DESIGN INTENT

West Pharmaceutical Services developed and commercialised the FluroTec® barrier film laminated NovaPure plungers in

bromobutyl rubber formulation 4023/50 Gray with B2 coating using QbD principles. NovaPure plungers are intended for prefilled delivery systems and designed to reduce particulate, ensure consistency of delivery and fit also the changing needs of higher-volume injectable drug delivery systems.

West NovaPure plungers were developed using a QTPP that ensures dimensional control and consistency, sub-visible and visible particulate control, and low parts per million (ppm) defect attributes. In addition, the break-loose and glide force profile has been optimised to deliver consistent functional performance for auto injector applications across various injection volumes, such as the increasingly common 2.25 mL injectable drug delivery systems.

West developed FluroTec barrier film laminated plungers to minimise risk associated with leachables migrating from the elastomeric plunger in prefilled syringes, which can potentially compromise the quality of the drug and the safety of patients. Such contamination can also impact a drug manufacturer's bottom line via increased costs, lost batches and manufacturing inefficiencies. Further, product recalls can have a negative impact on patient confidence, shareholder value and market share.

The FluroTec film provides a barrier between the drug and elastomer, thus mitigating the risk of interaction over the product's shelf life. In addition to the improved compatibility with the drug formulation, plungers with FluroTec help to ensure container closure integrity in ISO standard glass barrels. Further, FluroTec barrier films in combination with B2-coating provide lubricity without the need for free silicone oil, and reduce stopper clumping during autoclave sterilisation.

Figure 2: West 1 mL Long NovaPure plunger.

NovaPure plungers also have improved control strategies and release specifications and have been optimised through exhaustive studies to ensure the best overall performance. The dimensions of NovaPure plungers not only need to be within specification, but four dimensions are assessed at the release of each lot to ensure a predetermined process capability is achieved.

CCI, BREAK-LOOSE & GLIDE FORCE STUDIES

Container closure integrity (CCI) of the syringe system is critical to ensure the sterility, stability and efficacy of a drug product. Our CCI test – which is ongoing – includes four types of samples:

1. Bulk plungers stored in bags at ambient conditions then filled with water before testing (simulate customer storage before assembly)
2. Bulk plungers stored in bags at 5°C then filled with water before testing (simulate customer cold storage before assembly)
3. Assembled, water-filled syringes stored at ambient conditions (simulate customer product storage)
4. Assembled, water-filled syringes stored at 5°C (simulate customer cold product storage).

The study results up to 12 months show that, in both ambient conditions and 5°C storage, the system remains integral.

Legacy FluroTec plungers were developed for intent to be used for manual injection. As a result, their performance is not optimised for use in auto injector applications. As the market has been evolving from manual to auto injector device applications, a FluroTec barrier film faced plunger with consistent performance became imperative. In order to address that need, NovaPure plungers were developed. To demonstrate the high quality and reliable performance of NovaPure plungers, a co-operative study of break-loose and glide forces was performed alongside legacy FluroTec plungers. The study results showed that, under every test condition, NovaPure

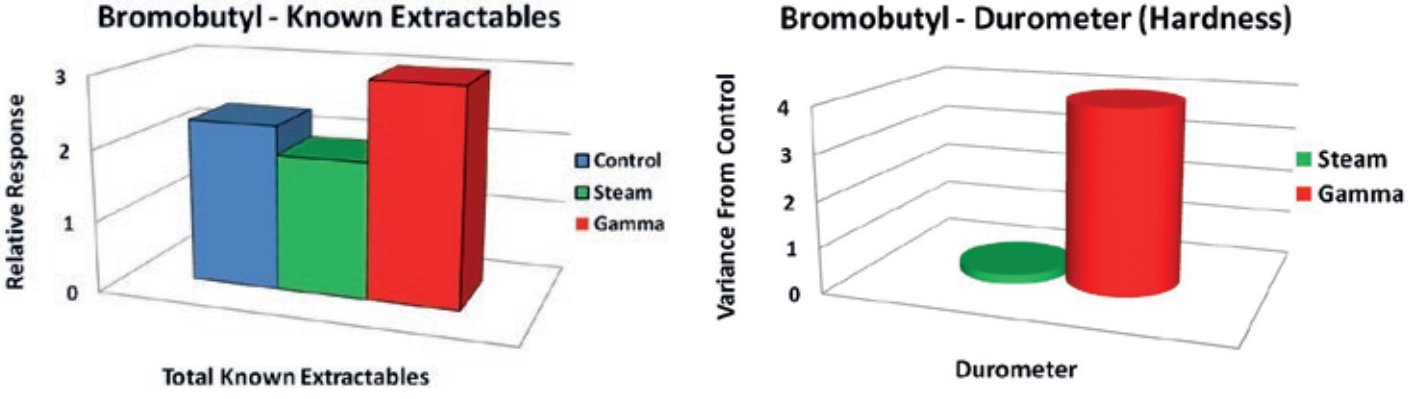

Figure 3: Influence of different sterilisation methods on rubber components. Steam sterilisation: exposure of 122°C for 60 min; Gamma sterilisation: irradiation exposure of 40.7 kGy (target range 36-44 kGy).

plungers had lower break-loose and glide forces, as well as more consistent force profiles, throughout the extrusion within the glass syringe barrel, compared with the legacy FluroTec plungers.

STEAM: PREFERRED STERILISATION METHOD FOR ELASTOMERIC COMPONENTS

The washing and sterilising of parenteral packaging components is required for aseptic pharmaceutical manufacturing in order to ensure the particulate, bioburden, and endotoxin levels are within acceptable limits. The most common methods for sterilising elastomers are gamma irradiation and steam sterilisation.

Some elastomeric components from other manufacturers utilise gamma processing. Because of the complex nature of rubber, the effects of gamma irradiation are immediate, cumulative, more damaging to the polymer, and they continue over time well after the radiation exposure is over. In studies on steam sterilised and gamma-irradiated halobutyl elastomers, gamma-irradiated samples showed higher levels of extractables, mainly degradation products of ingredients and the polymer. These extractables could become leachables in a drug product and cause unpredictable issues for the drug. Additionally, results indicate that gamma processing has a potential for a higher rate of degradation of the elastomeric formulation, ultimately affecting the shelf life of the component.

Steam processed elastomer formulations exhibit less degradation and lower levels of extractables. As such, NovaPure plungers are only available in a steam sterilised format, and we educate our pharma partners on best practices for implementing these processes during the drug packaging process to maintain sterility on their lines, too.

MACHINABILITY IS KEY FOR PHARMA PARTNERS

The machinability of parenteral packaging components – or how components perform and process on a drug manufacturer's filling line – is recognised to have a significant influence on productivity. As such, fill/finish equipment and machining assessments were conducted with the NovaPure plunger to ensure that effective machinability could be achieved on the small, medium and large sized machine lines our customers employ.

The assessments have verified reliable performance of NovaPure plunger on high-speed filling lines. Additionally, NovaPure components were designed with both vent-tube and vacuum filling processes in mind to accommodate the different machines that our partners use. Our exhaustive testing on both types of processing is just one facet of the customer support we provide.

CONCLUSION

A robust and dependable risk management or mitigation strategy is fundamentally critical to the success of a drug manufacturer, and inherently a drug product. Selecting the appropriate parenteral packaging components is one of many factors that should be considered within this strategy.

West developed the NovaPure components using QbD principles specifically to address the industry need for a risk-mitigating, optimally performing plunger for auto injector applications. The design, as well as the dimensional control, of the steam-sterilised and FluroTec laminated NovaPure plungers ensure low part-to-part variability, low and consistent break-loose and glide forces, optimal machinability performance and reliable container closure integrity.

Why employ such rigid risk mitigation in every phase of drug development, including the plungers and other components of a drug delivery system? The process starts and ends with helping our pharmaceutical partners to achieve its most critical goal: providing safe, effective drug products for patients.

West

By your side
for a healthier world™

Performance.
Consistency.
Quality.

High-Quality NovaPure® Plungers Fit Your Needs

The 1mL and 1-3mL NovaPure plungers are manufactured with Quality by Design principles to help ensure efficacy and purity of the drug product. The NovaPure plungers' design incorporates high-quality processes and features, including FluroTec® barrier film, B2 coating, validated wash and sterilization processes, 100% vision verification, and a comprehensive extractable profile. NovaPure plungers are designed to reduce particulate, ensure consistency of delivery and fit the changing needs of higher volume injectable drug delivery systems. By choosing NovaPure syringe plungers, you can help ensure drug product compatibility with components designed specifically for optimized performance and consistency in delivery systems.

VISIT US AT CPHI/INNOPACK IN BARCELONA OCTOBER 4-6, 2016, HALL 2, BOOTH #2M22

West NOVAPURE®
Unrivaled quality...by design

Contact West today to learn more about how NovaPure syringe plungers, offered in multiple sizes, can meet your needs.

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OMPI EZ-FILL® INTEGRATED TIP CAP: PRODUCTIVE SUPPLY CHAIN SYNERGIES BETWEEN OMPI & BALDA

In March 2016, Stevanato Group, specialising in glass pharmaceutical primary packaging, glass converting machines, visual inspection systems, assembling and packaging machines for the pharmaceutical industry, acquired the operating units of Balda Group. The German group specialises in high quality and high precision plastic solutions for the healthcare segment and medical device applications. In this article, Alessandro Artioli, Core Team Leader, and Alessandro Morandotti, EZ-fill Syringes Product Manager, both of Ompi, and Paul Wismer, Business Development Manager at Balda, look at the first example of integration between the two companies: the Ompi EZ-fill® Integrated Tip Cap.

The Ompi EZ-fill® Integrated Tip Cap (ITC) is the first product created by moving from a glass component to the integrated system for pharmaceutical use. Technical studies and tests on torque force and pull force have led to a perfect fit between the glass components of Ompi, and Balda plastic components.

> "What if you can combine the glass/syringe expertise together with injection moulding as well as device technology to provide complete solutions or even solution platforms, to help patients in their daily lives?"

It incorporates a twist-off closure system for Luer lock cone syringes. With an easy twist-off functionality, it provides improved usability for final users without compromising the integrity of the prefilled syringe itself. The ITC is the result of a rubber component (Tip Cap, rubber formulations: 7025, 7028, FM27, FM30) inserted in a rigid plastic cap, screwed onto a Luer lock adaptor and then pre-assembled on the Ompi EZ-fill® Syringe. Its functional performances in terms of torque force and pull force are determined by the Luer lock adaptor, in particular, by the inner hole diameter, as well as the length and thickness of the ribs.

Paul Wismer
Business Development Manager
T: +49 5734 513 2584
E: PWismer@balda-group.com

Balda Healthcare
A Stevanato Group company
Bergkirchener Strasse 228
32549 Bad Oeynhausen
Germany

www.balda-group.com

Alessandro Artioli
Core Team Leader
T: +39 049 9318 611
E: alessandro.artioli
@stevanatogroup.com

Alessandro Morandotti
EZ-fill Syringes Product Manager
T: +39 049 9318 650
E: alessandro.morandotti
@stevanatogroup.com

Nuova Ompi S.r.l.
A Stevanato Group company
Via Molinella 17
35017 Piombino Dese (PD)
Italy

www.ez-fill.com

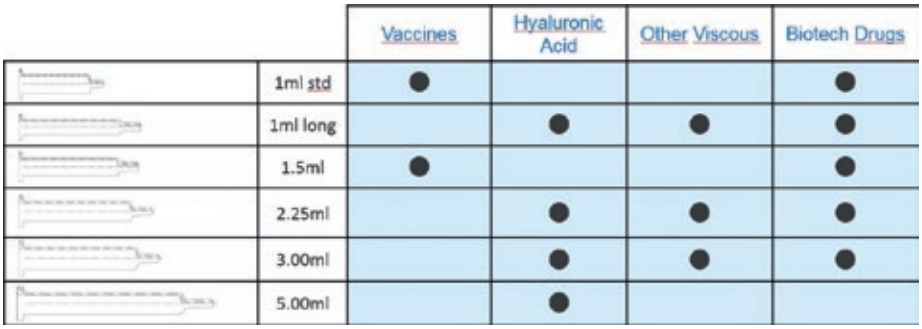

Figure 1: Comparison between Ompi Luer Lock Tip Caps.

Luer Lock Adapter (LLA)	Originalitäts Verschluss Spritze (OVS)	Ompi EZ-fill® Integrated Tip Cap (ITC)
• Original Luer lock option introduced to the market.	• Tamper evident Luer Lock solution offered as an alternative to a twisting system.	• Luer Lock twisting system
• It is still wide-spread for some applications, but above all, it is used in specific countries.	• Less wide-spread than the twisting solution but it was introduced in case the company wants to differentiate from the Ompi EZ-fill® Integrated Tip Cap (ITC)	• Worldwide use due to the intuitive opening movement
• LLA is less common for the vaccines market and it is used for diluent and water liquid products.	• Different applications: diluent, vaccines, HA and Biotech	• Different applications: diluent, vaccines, HA and biotech
• Compatible with existing needle hubs	• Compatible with existing needle hubs	• Compatible with existing needle hubs

Table 1: Ompi EZ-fill Integrated Tip Cap (ITC) typical application.

With its screw functionality, Ompi EZ-fill® ITC is a revolution in the Ompi EZ-fill® Syringes world. Its optimised design on the glass cone has been developed in order to assure the best match possible with our glass prefillable syringes. At the same time our offer provides more options to pharmaceutical companies. As shown in Table 1, Ompi EZ-fill® ITC has been developed for different syringes sizes: 1 mL std, 1 mL long, 1.5 mL, 2.25 mL, 3 mL, 5 mL. In the future, Ompi plans to offer Ompi EZ-fill® ITC in an even wider range of syringe sizes.

The target markets for the Ompi EZ-fill® ITC are: vaccines, hyaluronic acid and biotech drugs. Comparing with other suppliers' tip caps, the absence of ceramic coating on the cone avoids the Ompi EZ-fill® ITC rotation and this is a clear advantage as ceramic coatings create lots of particles. As regards the customisation, Ompi EZ-fill® ITC is available with coloured rigid caps according to customer needs, but the translucent plastic parts will be the standard.

> "Balda is a "one-stop" player in the contract development and manufacturing organisation (CDMO) landscape, providing everything from idea generation to prototyping, to high-volume manufacturing to logistics solutions; and this all throughout the lifecycle of a medical product."

DIFFERENCES BETWEEN LOCK TIP CAPS

There are several differences between Ompi EZ-fill® ITC and the other Ompi Luer lock tip caps, as shown in Figure 1.

Thanks to the collaboration between Ompi and Balda, the Ompi EZ-fill® ITC solution focuses on many different aspects, above all on cone breakage. Thanks to the twisting system and the torque- and de-torque forces, the cone of the syringe doesn't need to be broken any more which means better safety for patients by avoiding the risk of scattering glass pieces into drug.

BALDA'S ROLE IN THE OMPI EZ-FILL ITC PROJECT

What if you can combine glass/syringe expertise together with injection moulding as well as device technology to provide complete solutions or even solution platforms, to help patients in their daily lives? That is exactly what Stevanato had in mind when acquiring the operating units of Balda earlier this year. Balda brings decades of experience with hand-held devices and consumables made of plastic, serving various customers in the healthcare markets.

Balda is a "one-stop" player in the contract development and manufacturing organisation (CDMO) landscape, providing everything from idea generation to prototyping, to high-volume manufacturing to logistics solutions; and this all throughout the lifecycle of a medical product. The core competency is injection moulded polymer plastics, but Balda has surrounded this core with a myriad of other services. Assembly, often fully automated, completes the manufacturing process. This can be done in clean-room conditions as strict as ISO5, thus meeting the demands of many pharmaceutical projects. Balda, with operations in Germany and California, can serve a global base of customers and provide the needed regulatory support for both FDA- and EU-regulated markets. Balda possesses the relevant certifications, such as ISO 13485, in order to serve the high level of quality demanded by international healthcare clients.

However, projects often start in the idea stage. Here Balda conducts an innovation workshop with, and does necessary freedom-to-operate research for, its clients. After completion of this step, actual product development will start, i.e. once the idea (or ideas) exist. Balda then uses modern proven methods in this all-important stage: design-to-cost, design-for-manufacture, design-for-quality and even design-for-disposal to address the ever-increasing demand to reduce the environmental footprint, are all part of the DNA of

Figure 2: Ompi EZ-fill® Integrated Tip Cap (ITC).

Balda. Using 3D or rapid prototyping, the first look and feel of the product can be presented to the client and modifications developed before moving to more rigorous testing or even clinical phases.

Once full industrialisation and production is to start, Balda can deploy its high-precision capabilities on over 200 state-of-the-art injection moulding machines. Based upon over 60 years of experience, Balda is ready to meet the most demanding of specifications of any client project. Whether two- or three-component moulding, over moulding or metal substrates, Balda engineers can come up with the best solution at the highest level of quality. Manufacturing/assembly can be done with 100% control, using modern laser, camera or other electronic monitoring systems. Needless to say, a 100% traceability is designed into the process, which is another critical customer demand that must be met.

Figure 3: Ompi EZ-fill® ITC Nest&Tub.

Finally, a product can only help patients if it gets to the right place at the right time. Warehousing, safety stock holding and distribution to our clients' worldwide logistics hubs, or even directly to their sales chain, are all services Balda provides. Via integration into a customer's enterprise resource planning (ERP) system, quick and error-free management of the logistics process is made easy.

> "Ompi's lead in glass primary packaging for pharmaceutical use and Balda's specialisation in plastics and delivery devices, the synergies between them as well as the integration of the two "know-hows" permit the creation of high-quality, fully integrated products."

Ompi and Balda put together a teamwork of expertise that, working hand-in-hand, provides the best solution for Stevanato Group clients, such as the Ompi EZ-fill® ITC system.

Ompi EZ-fill® ITC is a new component to add to the current offer of EZ-fill® syringes that will play a key role into the expansion of the EZ-fill® line in the market (Figure 2). For this reason, it has its own dedicated nest and tub (Figure 3). However, the process of filling and finishing will not be subject to changes in those lines.

PHASES OF THE INTEGRATED TIP CAP PROCESS

In the EZ-fill® environment, the Ompi EZ-fill® ITC process is the same as for syringes and can be described in the following phases:

- **Incoming materials:** syringes are supplied to the EZ-fill® area (ISO7 and ISO5 under laminar flow).
- **Washing:** in the washing machine using water for injection (WFI).
- **Siliconisation:** syringes are siliconised with a high-performance layer distribution process.
- **Packaging:** the final steps place the syringes into Nest&Tub packaging solutions, which is then sealed with a Tyvek® lid and finally packaged in steribags and case-pack allowing for sterilisation. As much attention is given to the cleanliness of the packaging components as to the production of the glass container itself. Final configuration includes packaging in pallets.
- **Final sterilisation:** filled tubs/tray in steribags are sterilised by Ethylene Oxide (EtO). EtO sterilisation is mainly used to sterilise medical and pharmaceutical products that cannot support conventional high-temperature steam sterilisation. This process is completed by aeration. (Further developments/validation of alternative terminal sterilisation methods are ongoing, as requested from most of the top pharmaceutical companies.)

CONCLUSION

Balda, joining Stevanato Group and closely collaborating with Ompi, is leveraging value for pharmaceutical and healthcare customers. This allows the development of a wider, more integrated and more efficient value proposition. Considering Ompi's lead in glass primary packaging for pharmaceutical use and Balda's specialisation in plastics and delivery devices, the synergies between them as well as the integration of the two "know-hows" permit the creation of high-quality, fully integrated products.

ompi | ez-fill®

Integrated Tip Cap (ITC)

A twist-off closure system for prefilled syringes

ez-fill.com

THE MANDREL CHALLENGE – LABELLING VERY SMALL CONTAINERS

Here, Tamara McCartney, Technical Associate & Senior R&D Leader (North America), and Jos van Noort, Senior Application Manager Pharmaceuticals & Healthcare, explain how the rigorous technical, regulatory and quality requirements of the pharmaceutical industry impact on labelling, including how the very small diameter, curved surface – the mandrel – of a prefilled syringe presents particular labelling challenges.

The way non-oral medication is delivered to patients has changed dramatically over the last 40 years. There are many more types of injection devices, driven by increased demand for injectable biopharmaceuticals. More and more biological medications are now available to treat diseases such as cancer, autoimmune conditions and diabetes. Devices now in common use include ampoules, vials, prefilled syringes, auto injectors and pen systems. Prefilled syringes deliver benefits that include dosage accuracy, reduced drug waste and the assured sterility that improve patient safety.

> "There are very significant hurdles to overcome when attaching a label reliably to prefilled syringes."

As with any medicine, reliable identification of a prefilled syringe is paramount. Patients, pharmacists and doctors need to have complete confidence that a device contains the right drug, for the right person, with a label that shows a clear description of contents, instructions for use and expiration date.

This is not such a straightforward requirement as it might initially seem. There are very significant hurdles to overcome when attaching a label reliably to prefilled syringes. Such syringes are very small containers, with difficult surfaces for adhesion, and often with the presence of an anti-adherent coating on the surface (like traces of silicone). A standard stationery label of the kind used in offices falls far short of the performance required.

THE LABELLING CHALLENGE

Several criteria must be met when labelling a prefilled syringe:

- Production efficiency must be optimal
- Labels must remain firmly adhered to a container with a very small diameter
- The adhesive has to be compatible with 'low surface energy' materials, notably some plastics (COC/COP)
- Information must remain legible for extended periods of time
- Labels must withstand environmental variations, such as temperature and moisture changes
- Nothing in the label should interact either with the syringe material or the syringe contents.

Sterilisation-friendly products are also required for some applications, with labels that are able to withstand heat, steam and chemicals. As far as possible, the label

Tamara McCartney
Technical Associate &
Senior R&D Leader (North America)
E: tamara.mccartney
@averydennison.com

Jos van Noort
Senior Application
Manager Pharmaceuticals
& Healthcare (Europe)
E: jos.van.noort
@eu.averydennison.com

Avery Dennison Materials Group Europe
Willem Einthovenstraat 11
2342 BH Oegstgeest
The Netherlands

www.averydennison.com

should also be easy to process, so that costs are controlled.

Some of the criteria listed above act in opposition to each other. For example, an arbitrarily strong adhesive could be used to ensure permanent adhesion to a syringe. However, such an adhesive might not meet the need for migration resistance of label components into the syringe – and a label that contaminates the drug it is labelling is of no use. An adhesive also has to be practical for production purposes, enabling high speed manufacture and trouble-free end use. To take another example, a label using a highly aggressive but overly thick layer of adhesive, which 'oozes' and contaminates production equipment, would be slow and costly to produce.

Perhaps the most difficult single labelling challenge is posed by the very small diameter or "mandrel" of a prefilled syringe. Mandrel performance can be viewed as a tug-of-war between two forces. A retractive force arises from the stiff, adhesive-coated facestock (or label). In opposition to the retractive force is the adhesion force provided by the label's adhesive. The label will lift at the edges if the retractive force is greater than the adhesion force.

Factors that need to be taken into account when designing a label material for good mandrel performance therefore include the modulus and thickness of both facestock and adhesive, and the radius of the mandrel. Materials such as polypropylene (PP), cyclo-olefin polymer (COP) or cyclo-olefin co-polymer (COC), with low surface energy, make good mandrel performance more difficult to achieve because adhesives are not strongly attracted to such surfaces.

The surface energy of a substrate has an impact on the so-called wetting of an adhesive to the surface. Favourable wetting characteristics mean an adhesive can flow out onto a surface, which has an impact on both initial tack and final adhesion. A low-surface-energy substrate typically reduces the wetting properties of an adhesive. Good wetting characteristics are achieved at the expense of the modulus properties an adhesive needs to perform well in mandrel applications.

> "Pharmaceutical labelling is also subject to very strict qualification, and so drug manufacturers want to avoid changes to adhesive formulation whenever possible."

In order to understand mandrel performance and other factors, it is worth briefly reviewing how self-adhesive (or pressure sensitive) labels are made and used.

PRESSURE-SENSITIVE LABELLING

A basic pressure-sensitive labelling laminate contains the facestock, which can be made of film or paper, an adhesive layer, a release liner (to hold the label until ready for dispensing) and a silicone-release coating that facilitates separation of the label from the release liner (Figure 1).

A laminate of this kind is made in large rolls by a label manufacturer, and subsequently turned into sheets or rolls of labels by a label converter – a specialist printing firm. Individual labels are then dispensed from their release liner, either manually or automatically, onto containers. Productivity is important throughout this chain. Labelling materials should convert as quickly and cleanly as possible, and offer good printing and dispensing characteristics.

Adhesive technology is pivotal in label design. A balance has to be struck between an adhesive's ability to adhere to a container and its ability to release from the liner during dispensing. For pharmaceutical applications, migration properties are also crucial – with no contamination of the container's contents from adhesive, facestock or ink.

Three adhesive systems are commonly used in pressure-sensitive label manufacture:

- Solvent-based processes dissolve the adhesive ingredients in a solvent before application to a web of material, after which the solvent dries out.
- Hot-melt adhesives use thermoplastic rubbers, compounded with tackifying resins, antioxidants and oils – coated onto the web at elevated temperatures.
- The emulsion process uses adhesive ingredients that have been emulsified in water.

Adhesive formulations further include rubber-based, acrylic and modified acrylic adhesives, using non-latex rubbers, acrylic polymers and acrylic polymers with additional components respectively.

Solvent acrylic-based adhesives have been the pharmaceutical industry standard for years, but developments by the chemical industry have resulted in new emulsion acrylic polymers, and adhesive properties that match pharmaceutical industry requirements very closely.

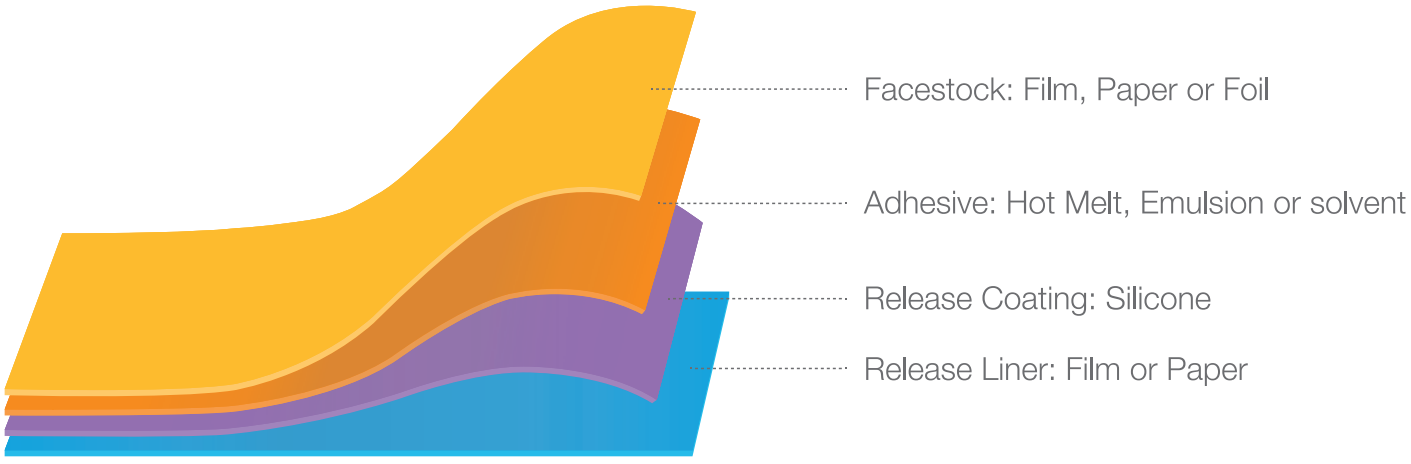

Figure 1: The basic pressure-sensitive label laminate.

For example, S717P is a tackified acrylic emulsion adhesive developed by Avery Dennison for pharmaceutical applications. When combined with low stiffness paper or filmic facestocks, it gives the mandrel performance and low migration properties needed for prefilled syringe labelling.

AVERY DENNISON S717P ADHESIVE

S717P offers a range of benefits for pharmaceutical labelling. The most significant benefit for prefilled syringe applications is far lower levels of edge lift, all the way down to diameters of 7 mm. Figure 2 shows how the adhesive holds the label firmly in place on a 1 mL PP syringe.

The Avery Dennison Research Centre in Europe, located in Oegstgeest, the Netherlands, uses an extensive set of equipment to test new developments such as S717P in a way that reflects real-world conditions as closely as possible, using international FINAT, DIN or ISO test protocols. Different aspects of adhesive performance are assessed using FINAT Test Methods (FTMs) 1, 2, 9 and 13. For example, the test method used for adhesion and loop tack (FTM 9) is shown in Figure 3.

Relevant tests are performed on various kinds of substrates, and on objects that range from standard panels to syringes and vials. Substrates are also subjected to different treatments when appropriate,

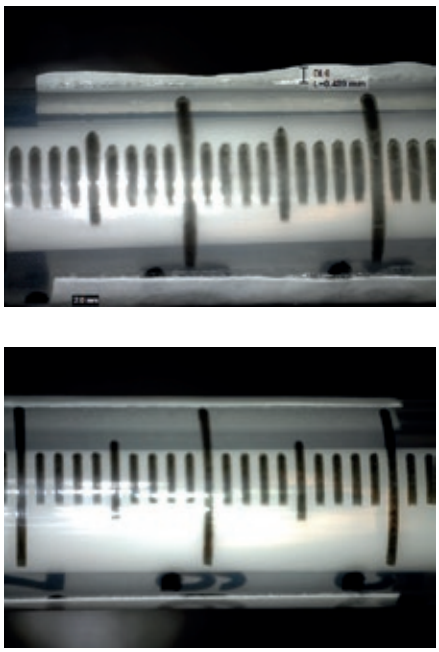

Figure 2: Comparitive edge-lift performances for (top) a conventional adhesive and (bottom) S717P.

for example by cooling down and allowing condensation to develop. Applied labels are also stored under varying conditions, and tests are conducted using equipment familiar in the pharmaceutical segment, such as fridges (down to -85°C), climate chambers and a steam sterilisation machine.

A microscope with a measurement system determines any resulting label lift to a high degree of accuracy (following FTM24). Figure 4 shows an example of the results from an FTM24 test, comparing S717P mandrel hold performance with a commonly used commercial adhesive, on 1 mL, 2 mL and 5 mL PP syringes. In each case, S717P delivers far lower levels of edge lift.

Good performance across a range of criteria is needed for a production-ready label, and Table 1 shows the performance improvements (or parity) delivered by S717P.

Next to the choice of adhesive, selecting the most appropriate facestock is also important. It is not uncommon to see standard laser printer papers being used on syringes by end users. Unfortunately, a paper of this kind has to be stiff enough to survive passage through a laser printer, and the result is significant label lift when it is used on a small diameter container. Figure 5 shows mandrel hold for different facestocks, illustrating the significant improvements seen when using a more flexible material.

ADDITIONAL PHARMA DEDICATED PRODUCT FEATURES

Pharmaceutical labelling is also subject to very strict qualification, and so drug manufacturers want to avoid changes to adhesive formulation whenever possible. This safeguards production continuity and avoids additional testing costs. The "P"

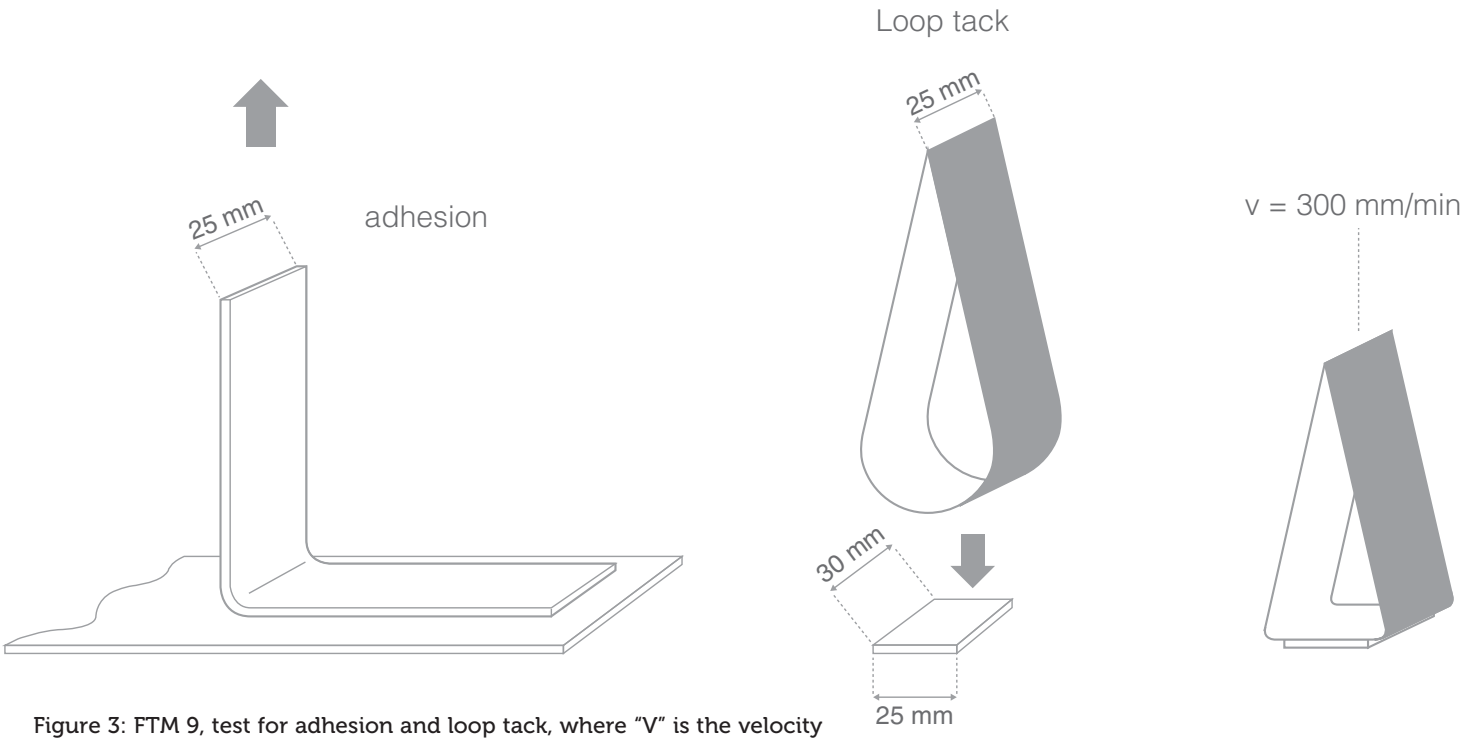

Figure 3: FTM 9, test for adhesion and loop tack, where "V" is the velocity of the tensile tester as it descends onto and then pulls up the test sample.

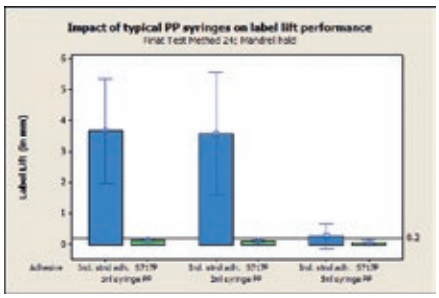

Figure 4: Mandrel hold on PP syringes: S717P versus commercial adhesive.

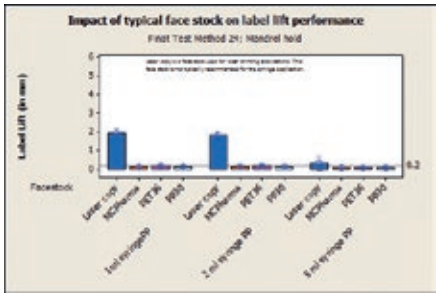

Figure 5: Mandrel hold for different facestocks.

suffix (for "Pharma") on S717P confirms that S717P adhesive benefits from Avery Dennison's change management control. It is planned to retain the proprietary adhesive in the portfolio for at least five years, and if for any reason this is not possible then change notification will be sent out a year in advance. To support the qualification of S717P, a complete set of certificates (among others, migration and toxicology) is available together with the option of conducting customised analytical tests in our central laboratory.

CONCLUSION

The unique labelling requirements of prefilled syringes, with their small diameters and difficult labelling substrates, mean that a very high performance labelling material is needed. S717P adhesive provides excellent adhesion and low migration. It offers label converters and end users a convenient and reliable way to label prefilled syringes, vials and other packaging with all of the information required to safeguard patients. With its S717P innovation, Avery Dennison has solved the mandrel challenge and created a label suitable for small pharma containers made from many different types of material.

ABOUT THE AUTHORS

Jos van Noort is a Senior Application Manager at Avery Dennison Materials Group Europe. He first worked on new polymer chemistry at Royal Shell in the Netherlands, before moving to the R&D department at Avery Dennison to work in analytical chemistry and product development. Mr van Noort now leads pharma label innovations.

Tamara McCartney is a Senior R&D Leader at Avery Dennison Materials Group North America. She has worked on new product development at Avery Dennison for 24 years, specialising in pressure-sensitive adhesive technology across many different market segments and applications including pharmaceutical; variable information; beer & beverage; and removable label innovation. Ms McCartney also holds a Project Management Professional (PMP) certification.

Application		S717P	Typical Industrial Standard Adhesive
Adhesion	Room temperature	+	+
	Moist substrates	0/+	0
	LSE substrate	+	0
	Cold substrates (< 5°C)	0	0
Mandrel	Syringes/vials (Glass)	++	+
	Syringes/vials (HDPE/PP)	++	0
	Treated surface glass vials	++	0
Sterilisation	Syringes (PP/Glass)	++	+
	Vials (PP/Glass)	++	+
Extractables	EtOH (10%, 95%)	++	+
Application	Service temperature	-60°C to >135°C	-50°C to 120°C
	Minimum application temp	10°C	10°C

Table 1: S717P adhesive characteristics. "0" = average performance and "+" = above average.

A labelling solution for demanding pharma applications

THE PHARMA LABELLING CHALLENGE

Label 'lift' is a major challenge for pharma applications such as plastic, treated glass syringes and vials. Low surfaces energy and/or small container diameters place enormous demands on the label adhesive – and changes to manufacturing designed to raise productivity can mean that an existing labelling solution no longer performs adequately.

As a pharma labelling solution, the adhesive S717 offers excellent performance on difficult containers and a rapid re-certification process. S717 is part of the pharma dedicated range that offers a robust change management control to make sure that components do not change and notification times are in place if a change has to be made.

ADDING COLOUR & FUNCTIONALITY TO PLASTICS USED IN MEDICAL DEVICES

In this piece, Stephen J Duckworth, Global Head of Healthcare Polymer Solutions, Clariant Plastics and Coatings, explains how – with an emphasis on the importance of complying with stringent and changing pharmaceutical regulations – advanced additives in plastics used to make drug delivery devices can significantly enhance the product. Colour is an important example yet, beyond colour, additives for special textures, additives that aid product identification and tackle counterfeiting, and functional additives – imparting lubrication, stabilisation, radio-opacity (shows up on x-rays) or antibacterial properties – are all described.

"The market has changed so that devices no longer are used exclusively by physicians in a clinical setting, but often by the patient him or herself at home or on the go. Increasingly, treatments are self-administered where compliance to a regular regime is important."

Regulations, change control, unique device identifier (UDI) marking, counterfeiting prevention and marketing … there is much more to manufacturing medical devices than simply a functional design and a competent injection moulder. Today's device manufacturers face a bewildering array of issues and challenges. Fortunately, there are ways to simplify things and, in the process, simplify manufacturing and improve the marketability of products.

The medical device industry continues to use plastics with high-performance properties and cutting-edge aesthetics in ever-increasing amounts. These materials must deliver certain performance characteristics, including resistance to sterilisation, chemicals and lipids. They must also meet standards for biocompatibility and toxicity, where even slight changes in the ingredients used could have an impact on leachables and affect the acceptability of the finished device.

For these reasons, regulatory authorities such as the US FDA, EU EMA and other relevant authorities around the world require detailed information on the material components and formulation, manufacturing processes, and extensive supporting data with respect to physical and mechanical properties, biocompatibility and toxicity. Once these materials are properly documented, device manufacturers can use them in their designs and products with the confidence that they will meet regulatory and application requirements. However, the documentation is a point-of-time submission and is material- and formulation-specific. Any material or formulation change over the life-time of the product, and at any point in a sometimes highly complex supply chain, can invalidate previous approvals and, therefore, change control becomes a formidable challenge.

It becomes essential, then, for device manufacturers to select materials that not only meet the necessary criteria, but also are supplied with the appropriate documentation and are sourced from a supplier with the good manufacturing practices and defined procedures to ensure continued compliance over time.

ADDING "SHELF APPEAL"

At the same time, in today's market, success depends on much more than just compliant materials and change-control procedures. Device developers face a growing dilemma – how to make their products not only functional and compliant, but also more distinctive, more user-friendly and more aesthetically appealing to the patient. Indeed, the market has changed so that

Stephen J Duckworth
Head of Global Segment
Healthcare Polymer Solutions
T: +41 61 469 61 71
E: steve.duckworth@clariant.com

Clariant Plastics and Coatings AG
Rothausstrasse 61
CH4132 Muttenz
Switzerland

www.clariant.com/mevopur

Figure 1: Colour can be used in medical devices for safety identification and to make them more attractive to users.

devices are no longer used exclusively by physicians in a clinical setting, but often by the patient him or herself at home or on the go. Increasingly, treatments are self-administered where compliance to a regular regime is important, and where product branding influences consumer decisions about over the counter (OTC) products. Healthcare designers could learn a few things from the personal care packaging (PCP) and consumer goods sectors and use colour more effectively. They should understand that there are now more options to use colours that support the regulatory compliance needs.

The science of semiotics suggests that colour, just like any sign or symbol, can have a direct effect on emotions and that each one of us responds to the stimulus of colour in a certain way. People tend to be attracted by some colours and repelled or disturbed by others. The differences may arise from deep-seated personality traits, life experiences, basic desires and even subconscious mental processes.

Colour can signal certain subtle differences in familiar scenes, giving us information about what we see. A lush green forest impresses us with its health and vitality, but when the same forest view is tinged with yellow, we see it as unhealthy, even if nothing else has changed. In other situations, a person's response to colour may be conditioned by their culture or national origin. In many parts of the world, red inspires strong feelings of excitement or danger. However, in China, red is all about power, prestige, and happiness, while Koreans are unique in the world in associating red with innovation.

These differences in perception and response are important when it comes to branding and differentiation. They can also be used to boost the success of a medical device by reinforcing the value of a particular brand or by helping patients feel more comfortable about using it. That can potentially go a long way towards treatment compliance.

As diseases such as asthma, COPD and diabetes become more common, and self-administered medication via inhaler or auto injector is becoming the norm, patient compliance becomes extremely important. Yet, US studies indicate only 28% patient-adherence to treatment programmes. The cost of wasted medication and follow-on treatment is estimated in the billions of dollars and companies are looking for ways to make their devices more attractive and easier to use, creating standard device platforms that can be customised with colour and special effects.

Just about any colour imaginable can be developed for medical devices and there is a huge palette of "standard" colours with documented compliance to regulatory standards available and change control policies already in place (Figure 1).

Figure 2: Components and bottle closure that take advantage of pearlescence effect. Ingredients in these new materials conform to medical and pharmaceutical norms.

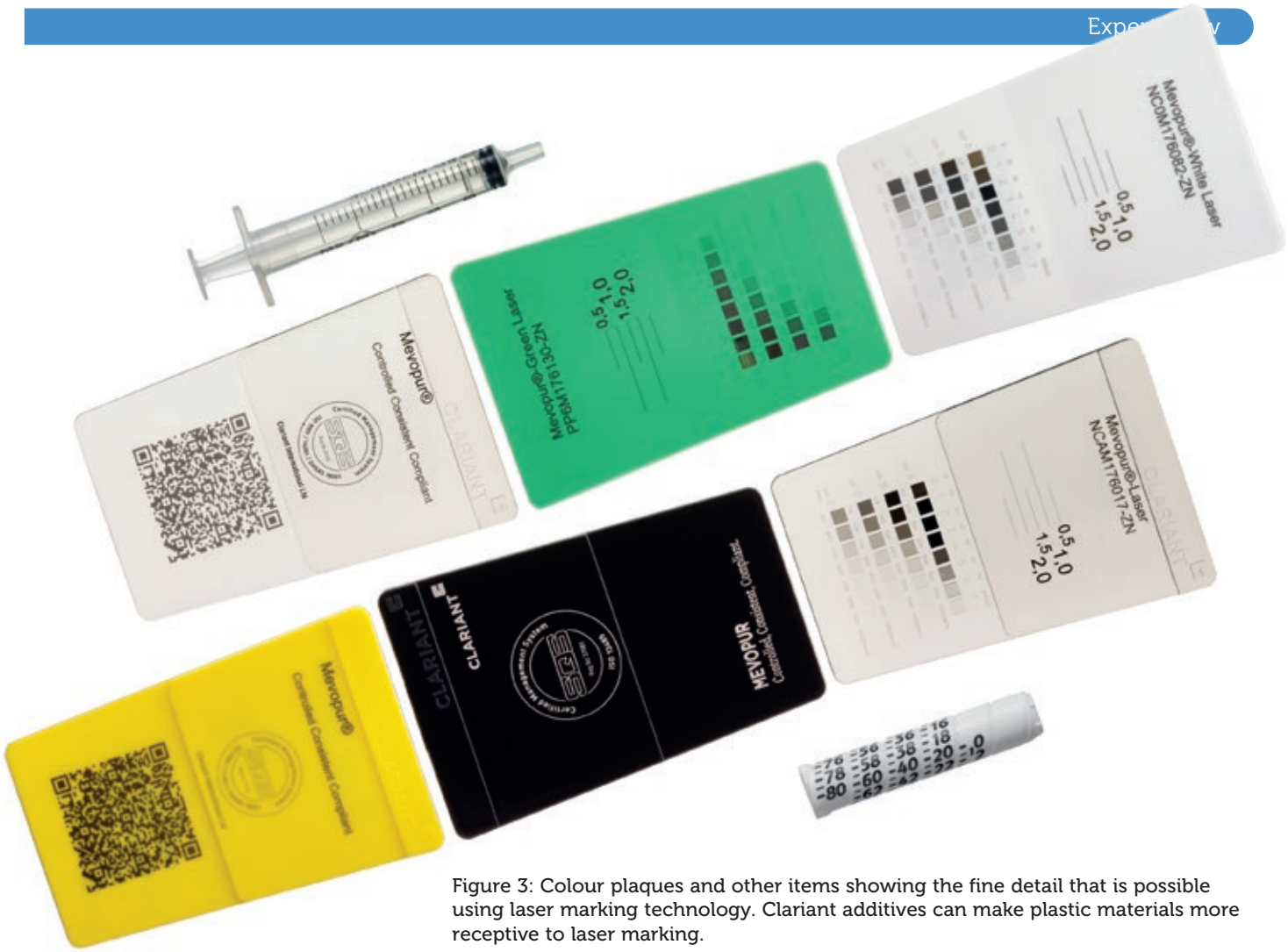

Figure 3: Colour plaques and other items showing the fine detail that is possible using laser marking technology. Clariant additives can make plastic materials more receptive to laser marking.

The same applies to special effects, which have been used for many years to enhance the look and market appeal of personal-care and consumer goods. When added to plastics, these special effect pigments create a singular impression like pearlescence (on previous page Figure 2), sparkle or a metallic look. Testing has been completed to confirm that the ingredients in these new materials conform to medical and pharmaceutical norms.

MORE THAN COLOUR

Colour and special-effect pigments are not the only materials being used to add value and consumer appeal to medical devices. A growing number of functional additives – pre-evaluated using biological evaluation standards ISO10993 / USP23 parts 87 and 88 – are also becoming available to manufacturers.

These include:

- **Lubricants**… reduce the surface friction between plastic components such dial-gauge / actuators for auto-injectors. They make it easier for medical personnel and patients to use these devices.
- **Stabilisers**… provide protection for certain polymers against loss of mechanical properties caused by gamma or e-beam sterilisation. These same stabilisers can sometimes help reduce yellowing caused by sterilisation.
- **Nucleating agents.** When different colours are added to plastics the finished product dimensions can vary even if everything else remains the same. Nucleating agents, which affect how some plastics harden during processing, can help prevent warping due to differential shrinkage. In addition, they can help speed up the process cycle or reduce weight of the component, reducing costs.

Other available functional additives include transparency-enhancing clarifying agents, antimicrobials to limit bacterial activity on devices, anti-stats and radiopaque fillers that make plastic materials more visible to X-rays.

> "When fully implemented in 2020, UDI must be placed on the device label, device packages and, if the device is intended to be used more than once and reprocessed between uses, on the device itself. The permanent label must include the UDI in human- and machine-readable form."

PRODUCT IDENTIFICATION

Lasers offer a permanent, non-contact marking solution that can survive repeated sterilisation. It opens opportunities for precise and small marking in nearly inaccessible areas, which can be extremely important as unique device identification (UDI) programmes are being rolled out in both the US and Europe over the next few years. When fully implemented in 2020, UDI must be placed on the device label, device packages and, if the device is intended to be used more than once and reprocessed between uses, on the device itself. The permanent label must include the

UDI in human- and machine-readable form.

Laser marking is ideal for direct part marking because it is fast and economical and allows variable data printing for serialisation and on small parts. However many plastics are transparent to the laser energy, and very little marking occurs. Laser-friendly additives, now available with the biological evaluation and supporting regulatory documentation required for medical devices and pharmaceutical packaging applications, make plastic materials more receptive to laser marking (see Figure 3), which offers device makers many advantages over printing or labelling.

"The covert approach involves the use of taggants – unique ingredients that are incorporated into plastic components to provide immediate and incontrovertible proof of the genuine article."

UDI helps protect patient safety by providing traceability, but is only one weapon against the growing problem of counterfeiting, which impacts both consumable medical devices (insulin pens, inhalers, diagnostic tools, syringes, etc) as well as high-value drugs. Worldwide sales of counterfeit medicines could top US$75 billion (£57 billion) this year, a 90% rise in five years, according to an estimate published by the US Center for Medicine in the Public Interest. According to the WHO, more than 8% of the medical devices in circulation are counterfeit. Clearly, counterfeit medical devices pose a significant liability to their manufacturers and a risk of injury, permanent disability, or even death to both patients and healthcare providers.

One of the most effective ways to address counterfeiting/ brand protection problems is to use multiple level security involving use of covert (hidden) and visible coding on both outside packaging and the device itself. In plastics the covert approach involves the use of taggants – unique ingredients that are incorporated into plastic components to provide immediate and incontrovertible proof of the genuine article (Figure 4). This technology, however, poses a few problems when it comes to its use in medical devices. Most importantly, taggants represent another ingredient in the plastic material and, like all colours and additives, they are subject to compliance and change-control regulations. However, solutions have been developed to address such challenges.

For example, an alliance between Clariant and SICPA SA (Lausanne, Switzerland) announced in September 2016, overcomes several critical roadblocks to successful implementation of taggant technology in medical devices. The companies have launched PLASTIWARD™, a robust integrated protection system for plastic pharmaceutical packaging and medical devices. Specifically, in partnership with SICPA, Clariant is able to provide taggants that meet regulatory requirements for medical and pharmaceutical products, in a form that is easily included in the manufacturing process. SICPA is able to provide needs assessment, a proven means to actively track tagged devices from factory to end-use, as well as data-gathering and ongoing performance monitoring. Data gathered from instantaneous authentication using a handheld detector can be uploaded and aggregated on a secure inspection platform from SICPA that facilitates real-time monitoring at global, regional or local levels.

MINIMISING RISK

As noted, device designers and developers have a host of new options to add colour and performance to components made of plastics, so long as they understand the regulatory complexities involved. There is almost always a risk associated with a simple and otherwise routine change in the supplier of a pigment or additive, even if the chemical type did not change. The key is in understanding where risk comes from and dealing with this in the early stages of design.

Approximately 10 years ago, Clariant Masterbatches recognised the issues facing the supply chain to the healthcare industry and reorganised its approach to the medical device and pharmaceutical packaging markets to help its customers rationalise their approach to risk. This involved creating a network of three global manufacturing plants (one each in the US, Europe, and Asia) and managing them under the ISO13485 quality system with change control protocols. This is important because, firstly, production of a medical device may be required in different regions or be transferred and, secondly, back-up supply is normally a requirement.

Then came standardisation of raw materials in terms of chemistry and supplier. This process involved the technical, product stewardship and supply chain functions that assess each raw material not only on performance characteristics, but on regulatory criteria such as RoHS, Reach, BSE/TSE and so on, and whether the supply was available in each of the three sites. Each plant uses the same defined raw material ingredients, the same formula, and the same key product quality parameters. The measurements not only include typical tests such as colour and physical properties, but also ISO10993 part 18 extraction, biological evaluation (ISO10993 and USP parts 87, 88) and comparison with a chemical "fingerprint"' of a reference product.

CONCLUSION

Whether the issue is regulatory compliance, change control, UDI, counterfeiting prevention, patient acceptance or marketing; or whether the material involved is polyethylene, polycarbonate or polyetheretherketone, there are solutions readily available to help manufacturers get a better product to market more quickly. Once some of the uncertainty that is part of the global material sourcing process has been eliminated, manufacturers can concentrate on making devices that are more functional, more attractive and, thus, more effective at giving patients around the world greater access to better and safer treatment.

Figure 4: A simple handheld device recognises covert taggants incorporated into plastic materials as anti-counterfeiting and brand-protection measures.

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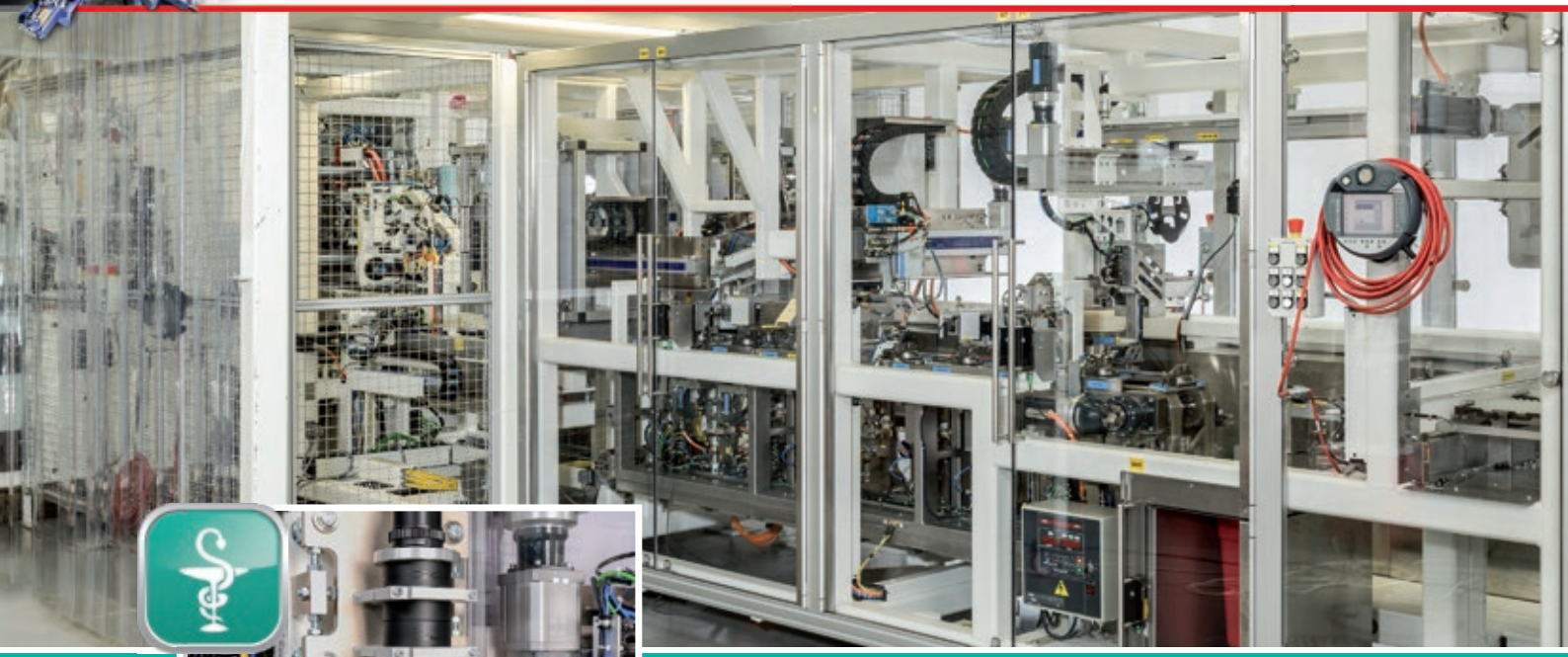

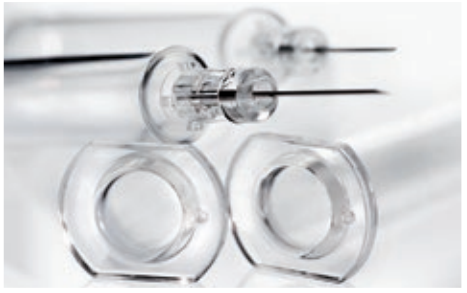

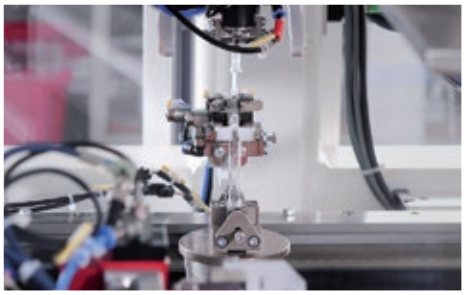

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CARTON PACKAGING SYSTEMS FOR PARENTERALS

Set against the background of prefilled syringe and injection devices such as auto injectors as increasingly attractive presentations for both new and established parenteral pharmaceuticals, Christoph Hammer, Chief Executive Officer, Dividella, explores how innovative carton packaging solutions can enhance these presentations whilst meeting the stringent requirements of product protection.

Biotech products are rapidly becoming more important because of their extraordinary pharmaceutical potential. The active ingredients of biotech products are often too unstable to be incorporated into solid pharmaceutical products (tablets or powders). Well over 90% of these products are therefore packaged as liquids in syringes, injection devices, vials or ampoules.

Since the products are distinctly more expensive than other pharmaceuticals, they must be packed as securely as possible. Moreover, often the products have to be transported in a precisely defined temperature environment. Cold chain logistics are needed to ensure that a product is transported at the correct temperature from manufacture through transport, and storage to administration.

Many pharmaceutical companies produce and market a wide range of products worldwide. The different demand in the respective market and product segments therefore requires a highly flexible packaging system which can handle a wide range of different items and, at the same time, provide optimal product protection. It is also essential to guarantee efficient, low-cost packaging of small, medium and large lot sizes. Other requirements of a modern packaging system include item and code checks (vision systems), inspection systems, track and trace, printing and checking of variable data, the shortest possible machine set-up times and compliance with GMP standards.

> "In the case of a syringe pack, for example, the syringes are inserted in front of and behind the barrel of a syringe in such a way that the product itself virtually "floats" and is connected to the actual box only by the two flutes. In this way multiple products can be packaged close to each other without touching."

PREFILLED SYRINGES & INJECTION DEVICES

Prefilled syringes and injection devices have gained wide acceptance, driven by various factors including lifecycle benefits that can be identified as follows:

- The prefilled syringe or injection device is easy for healthcare professionals to handle
- The risks of spillage, contamination and ampoule cuts are reduced or eliminated. Furthermore, the potential risks of misidentification or dosage error are greatly reduced
- The potential risk of needlestick injury, associated with all methods of injection, is greatly reduced by the addition of a safety needle device to the syringe

Mr Christoph Hammer
Chief Executive Officer
T: +41 81 750 3366
E: info@dividella.ch

Dividella AG
Werdenstrasse 76
9472 Grabs
Switzerland

www.dividella.ch

- The availability of such devices enables compliance with current and envisaged legislation
- Self-administration by patients on long-term therapies is practical
- For the pharmacist, requirements for storage, preparation and disposal are simplified
- For the pharmaceutical manufacturer, the prefilled syringe and injection device offer advantages in both marketing and distribution
- For the prefilled syringe and injection device there is no overfilling required, as it is filled with less drug substance per dose than a vial or ampoule, hence leading to significant cost savings.

Prefilled syringes and injection devices are being used increasingly frequently, so that application of liquid pharmaceutical products at the doctor's surgery, by nursing personnel or by patients at home, can be more simply and reliably handled. In the simplest case, it is necessary only to remove the needle protection prior to injecting the drug. There is no longer any need to break off the heads of ampoules, with the possible ensuing injuries, or for troublesome handling of vials or syringes.

THE REQUIREMENTS OF THE PACKAGE

All packages must safeguard the product throughout its route from manufacture to final point of use. The package must also convey sufficient information to ensure that the product is used correctly. Each package provides the vital link between manufacturer and consumer; it is an essential component of the product itself.

The prefilled syringe and injection device are examples of a high-value product that must be safeguarded throughout a long shelf-life and yet be readily and accurately used whenever required. The proper selection of the package and the attention to its design will promote the benefits of the product in addition to fulfilling these fundamental functions. The syringe or device is not viable without a secondary package.

The package must enable rapid access to each of the products it contains, and must remain intact until the last of the syringes or devices has been removed, if that last product is to be safeguarded. The printing of the package will clearly present essential product information. Further features may confirm that the syringe or device is untouched until required for use.

A re-closable package can be retained for subsequent use without difficulty. If the package contains a course of treatment for a single patient, features to assist dosage compliance are appropriate. If the contents are to be used over an extended period, opening features that release only one product at a time can assist the user. Examples are shown in Figure 1.

> "A reduction in pack volume of 50% cut the expensive cold-chain shipping and storage costs in half."

LOGISTICS OF DISTRIBUTION

Costs are affected by the volume of the package itself. Where the product must be held in a temperature-controlled environment, it is particularly important to adopt a package of minimum volume relative to its contents. Minimising package volume also benefits storage immediately prior to use; for example in a hospital pharmacy.

The immense cost pressure within the medical sector encourages the increasing trend towards self-medication. The branch of liquid pharmaceuticals is also drawn into this development with the use of prefilled syringes and injection devices on the increase. They are not only easy and safe to handle by the patients themselves, but are also favoured by both doctors and hospitals. The potential dangers involved with breaking the ampoule are therefore avoided. Another important factor for this development is found in the low logistical costs which, thanks to optimal packaging solutions, are easily accomplished.

THE PARTITION CONCEPT

This space saving is achieved thanks to Dividella's special design concept. Since the whole box is made of flat cardboard, customised partitions, specially adapted to the products, can easily be glued inside the box (see Figure 2). The product is placed crosswise in relation to these flutes. In the case of a syringe pack, for example, the syringes are inserted in front of and behind the barrel of a syringe in such a way that the product itself virtually "floats" and is connected to the actual box only by the two flutes. In this way multiple products can be packaged close to each other without touching. Since the products do not touch the base or the lid of the box, they are highly impact-resistant and the firmly anchored products cannot break even if they are dropped onto the floor. This flute concept is highly versatile, so the layout within a box can easily be adapted to individual customers' needs. In so-called combi packs, not only the syringes but also the accompanying vials and accessories, such as needles, filters and the like can be inserted at fixed points.

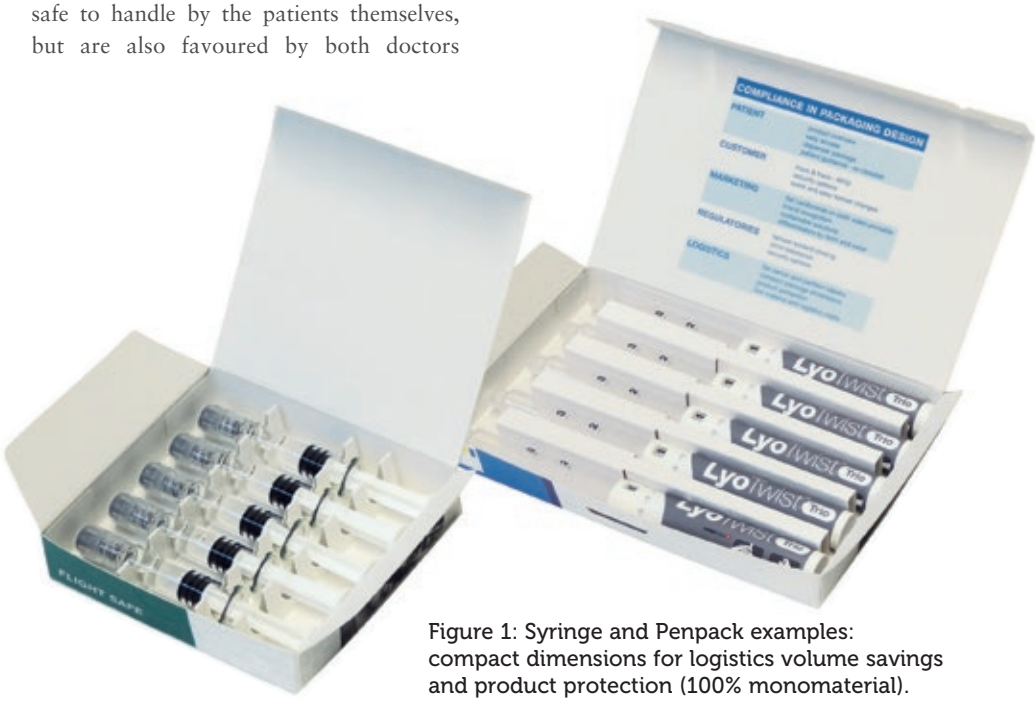

Figure 1: Syringe and Penpack examples: compact dimensions for logistics volume savings and product protection (100% monomaterial).

VOLUME SAVINGS OF UP TO 50 %

Dividella folding boxes are pure mono-material packaging, i.e. the folding box is made from 100% cardboard material. This distinguishes it from other conventional Top-Load packs. For customers in the pharmaceutical industry, this means that by using only one packaging material the space required and the transport costs can be significantly reduced. Dividella reports volume savings of 25% to 50% compared with traditional blister packs. These figures are important in that many of these highly sensitive drugs are cold-chain products. In other words, they must be cooled continuously from production until they are used by the patient. The less space these products take up the better. This includes space in the refrigerator in which general practitioners keeps their sensitive vaccines, for example.

WORLD STAR PACKAGING AWARD

The Dividella NeoTOP Syringe pack designed for Sanofi Pasteur (Figure 3) received the World Star Packaging and Sustainability Award. A reduction in pack volume of 50% cut the expensive cold-chain shipping and storage costs in half. Major benefits were obtained by replacing pre-made plastic trays & lid material with a 100% paperboard material, consisting of a carton and partition. The new package uses a specially designed paper partition that precisely fixes each syringe in a nest. There is no glass-to-glass contact, thus preventing cracks and breakage. The plunger movement is limited by the tight tolerances between the syringe and inner walls of the pack.

Figure 3: Sanofi Pasteur Dividella Syringe Pack, WorldStar award winner.

Figure 2: Highly versatile partition concept, so the layout within a carton can easily be adapted to individual customers' needs.

TAMPER-EVIDENCE & ANTI-COUNTERFEITING

The pharmaceutical industry has been concerned with guaranteeing originality for many years. The NeoTOP packstyle allows the integration of a number of protection features – conforming to directive 2011/62/EU. We solved the problem quite simply by applying a spot of hot-melt in the right place. If the box has been opened, this is immediately apparent to the user – and it involves virtually no extra machine costs and has no effect at all on performance. This solution can be applied for the box, placing a glue spot on one or all the three flaps of the carton before the fully automated, in-line closing.

With smart package design, we not only apply tamper evidence for the outer carton but also for the individual products in the pack as well. As an alternative for the tamper-evident (TE) glue spot we can also apply a TE label in-line, after the closing process. The unique Dividella NeoTOP pack style is hard to manufacture without our machinery and thus can itself also be considered as a level of brand protection.

ANTI-COUNTERFEITING AS LIFE INSURANCE

Biotechnology products in particular require considerable effort to produce and are therefore expensive to manufacture. However, the risk of these products being counterfeited or manipulated is unfortunately omnipresent and has already become a major issue on some continents. If a counterfeit product is used for cancer therapy, or even for antibiotic therapy, the consequences for the patient could be fatal.

Concepts relating to guaranteeing originality and counterfeit protecting have been developed, which can also be implemented in the short term on existing packaging solutions. An invisible code for the pack, and product and information on usage, ensure the necessary security – and also permit effective track and trace.

SMALL BATCHES

Dividella's small batch machines are a one-up machine, which means that no more than one magazine needs to be filled and cleared per packaging component. The machines have small and simple format parts, and digital read-outs for a safe format changeover. The carton-vacuum transfer allows the machine to be fully accessible, so products can be inserted manually or with a flexible robotic feeding system. Dividella also offers a variety of other features from white-line printing to personalised production (see Figure 4). For very small lot sizes, clinical trials or product launches, Dividella's sister company, Rondo (Allschwil, Switzerland) offers a carton-erecting service, using Dividella machines. This way, a customer can start using NeoTOP cartons without having to invest in a machine.

Figure 4: Personalised production for small lot sizes, clinical trials or product launches.

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..and profit from volume savings of up to 50 %

Dividella packaging solutions - 100% recyclable cardboard material. By using only one packaging material the space required and the transport costs can be significantly reduced.
Dividella TOPLoading cartoners report volume savings of 25% to 50% compared with traditional blister packs. Customised partitions, specially adapted to the products, are easily glued inside the carton and multiple products can be packaged close to each other without touching. Since the products do not touch the base or the lid of the box, they are highly impact-resistant and the firmly anchored products cannot break even if they are dropped onto the floor.

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ZAHORANSKY
PERFECTLY DIFFERENT

DRUG DELIVERY SYSTEM BY ZAHORANSKY WITH OWN AUTOMATIC NEEDLE FEEDING & AUTOMATED PRODUCTION OF READY-TO-FILL PREFILLABLE SYRINGES

In this article, Harry Pruner, Freelance Journalist, Pruner Marketing Services, describes the automated assembly equipment offered by ZAHORANSKY AG for the production of ready-to-fill, prefillable syringes.

As a supplier of automation equipment for drug delivery systems, ZAHORANSKY provides the Z.BLIZZARD (Figure 1) system for the glueless production of staked needle syringes (Figure 2). It combines complete needle isolation, the injection mould and the downstream automation into a single unit.

The Z.BLIZZARD system for the production of staked needle syringes is an integrated automation solution in a modular design, allowing the isolation and glueless overmoulding of cannulas. The Z.BLIZZARD system features both the Needle Feeding System (Z.NFS) as shown in Figure 3, and the injection moulding machine with mould (Figure 4) to produce hybrid components.

The integrated Z.NFS is also modular in structure, with the effect that different design variations of cannulas can be processed within the specification. The Z.NFS is capable of handling needles, cannulas and lancet devices in various lengths and diameters. Optionally, even needles and cannulas with ground or shaped sections can so be aligned automatically and then carried to downstream processing.

ZAHORANSKY offers needle isolation systems (Figure 5) capable of singularising between four and currently 32 needles or cannulas with as much as 12 cycles per minute. Diameters range from 0.2 mm upwards, lengths of as much as 40 mm are handled properly. There are plans for more model sizes to enlarge the delivery range.

Z.NFS SYSTEM, IDEAL NEEDLE ISOLATION FOR MEDIUM BATCH SIZES

The market already offers a number of different solutions for needle isolation, but many of these systems have been designed for producing very large unit quantities. With its new Z.NFS unit, ZAHORANSKY closes the downward gap for delivering as many as 400 cannulas per minute, covering the general tendency in the industry toward smaller batch sizes and higher redundancies and toward multiple units for smaller volumes.

The new Z.NFS system allows the quick conversion to similar products or the flexible production in the event of breakdowns without causing delivery delays or keeping stocks high as a safeguard. The new Z.NFS system has been designed such that it can be used smoothly for inserting needles in automation equipment, moulds or injection moulding machines.

FIVE STEPS TO NEEDLE ISOLATION

Generally speaking, the full function sequence of the isolation process right

Contact:
Berthold Schopferer
Business Development,
System Technology
T: +49 761 88509 33
F: +49 761 88509 46
E: berthold.schopferer
@zahoransky.com

Zahoransky
Hanferstrasse 21
79108 Freiburg
Germany

www.zahoransky.com

Figure 1: The Z.BLIZZARD system for the glueless production of staked-needle syringes.

through to overmoulding can be divided into five steps. The first step involves mounting the filled magazine, followed by splitting off and separating the needles from the magazine by gripping or vacuum pickup. The next step is the visual check for "all needles available". Finally, the needles are fed for overmoulding or further processing using a gripper head with a linear robot or an alternative automation component of the injection moulding machine or a downstream automation device.

The five steps in detail are:

1. Filling Needle Magazines

There are several options for filling the compact and transport-safe magazines. Either customers themselves fill the magazine or they have it filled by their needle supplier. The magazine is used internally or externally as a reusable transport unit, with the design of the magazine guaranteeing the safe transport of the needles to the point of processing.

Keeping a second ready-filled magazine in stock in the Z.NFS unit is another advantage, allowing the fast mechanical or manual changeover. The ideal variant – virtually without any downtimes – is ZAHORANSKY's optional automatic magazine changing device where as many as two ready-filled magazines are installed additionally in the Z.NFS system that are changed automatically. This has the added advantage that the operator does not touch the needles, with the effect that contact contamination by personnel is largely ruled out.

2. Needle Isolation

To isolate the needles, a so-called partition slide equipped with the desired number of notches matching the design and size of the needles passes underneath the loaded magazine by means of a left-right movement, placing a needle in every notch. This movement is servo-electrical and can therefore be controlled with SPC device.

Once the final position is reached, the needles are either taken by mechanical grippers or released for vacuuming through stainless steel tubes. The isolation process is now repeated by the partition slide moving in the opposite direction until it is located in front of the second vacuuming or gripper station. Isolation from the magazine follows the first-in-first-out principle (FIFO) which ensures the best possible batch processing of the needles. This would be a substantial advantage if the batch needed to be tracked at some point in time later. Production in medical category 1 and 2, but also in category 3 is possible.

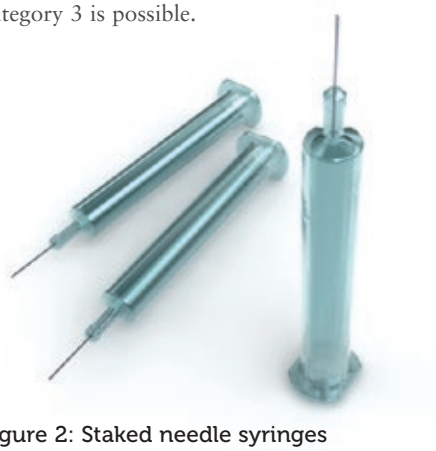


Figure 2: Staked needle syringes produced by the Z.BLIZZARD system.

3. Visual Completion Check

Sensors mounted to the left and right of the feeder magazine check the needles in transit to ensure that they are complete. While moving in the direction of the final position, it also checks if the required number of needles is available. Once the partition slide moves back, a check is made to ensure that all the needles have been duly removed for further processing.

4. Transporting Isolated Needles

There are two equivalent options for carrying to the syringes' cavities – rearward suction or mechanically gripping the separated cannulas.

The needles separated by the partition slide are vacuumed off at the same time. To do so, a transfer station with the tubes leading to the gripper head or the transfer unit docks against the separated needles. For the vacuuming process, a gripper head docks at the other end of the tube, triggers a suction impulse and sucks up the needles without damaging the tips or the grinded section. The resulting vacuum positions the needles against the corresponding stop in the gripper head. The cannulas are gripped directly at the partition slide, with one gripper head located at each end position of the partition slide removing the cannulas and taking these to the transfer position required for further processing, from where they are taken off aligned in the proper position. Every part making contact with the product is subject to the stringent US FDA and GMP regulations and is corrosion-resistant and designed compatible with the product.

5. Handover of Loaded Gripper Head into the Injection Mould

Before insertion, checks are carried out at various points to make sure that the following injection moulding process proceeds without any rejects. In line with the number of cavities in the injection mould, the cannulas are aligned and transferred to a handling system which first checks whether they are in place and in the correct position.

A two-axes linear unit hands over the cannulas placed on a holding plate into the mould cavities on the ejector side. There, they are already exactly positioned matching the mould inserts. Parallel to the insertion phase in the mould half on the closing side, the already injected parts are at the same time removed on the nozzle side mould half via a six-axes robot. This

substantially reduces the cycle time, as feed-in and removal take place at the same time.

The injection mould used is a ZAHORANSKY-patented Stack Mould System. The special features of this patented system are the two parting lines, allowing cannulas to be inserted and to remove ready overmolded cannulas at the same time.

Injection is performed by a Ewikon (Frankenberg, Germany) Hot Runner System with needle valve gate. The material used is a high-grade technical polymer, mostly cyclo-olefin copolymer (COC) or cyclo-olefin polymer (COP).

The cavity inserts are heated, while the rest of the mould is cooled normally. To do so, the inserts are thermally separated from the mould in order to minimise the energy loss and quickly accomplish a thermal equilibrium in the system.

EASY PRODUCTION CHANGEOVER

The engineers also focused on easy, quick and cost-effective refitting during a production changeover. During a product change, essential components of the Z.NFS system can be used again for a later use. Especially in the production of smaller and medium batch sizes, this flexibility offers substantial cost benefits compared with rigid systems designed only for a single product.

SUMMARY AND OUTLOOK

Additional external automation equipment makes the system even more convenient. After the isolated cannulas are handed over to a gripper head, the needles are delivered either to an injection moulding machine for direct machining or to another automation equipment item.

A system for bending the needles for higher retention forces, beading the blunt end for better piercing strength, or aligning the grinded cannula tips, for example, are conceivable downstream processing steps.

Depending on application, the machined needles are servo-motor removed, fed in and placed back in position either by a six-axes robot or a linear handling unit. If the needles are carried into the injection mould directly for overmolding, a linear axis is used. Before being transported further into the downstream unit – in most cases an injection moulding machine – the needles are normally checked for completeness. If the insertion gripper is not completely filled, the machine operator or the previously specified procedures in the system control unit decide whether the missing needle should be replenished or whether the complete content of the gripper head should be discarded. Another option involves an intermediate station to make the fully automated orientation of the polished needles.

Laser devices check both the feed-in of the needles and the overmoulded needles for completeness. The finished syringe bodies can then be siliconised in an integrated follow-up station to improve the sliding property of the needles.

Other operational steps could possibly include placing a protective cap on top or a subsequent X-ray test to ensure that the integrity of the tip of the syringe is guaranteed and that the overmoulded zone complies with requirements. This step is followed by automatic packaging in standard or customer-specific trays, ensuring that particle contamination caused by hand contact is prevented or at least minimised throughout the whole of the process chain.

Figure 3: The Z.NFS – ZAHORANSKY Needle Feeding System.

Figure 4: Cannula mounted in b-side of injection mould.

Figure 5: Detailed view of needle isolation.

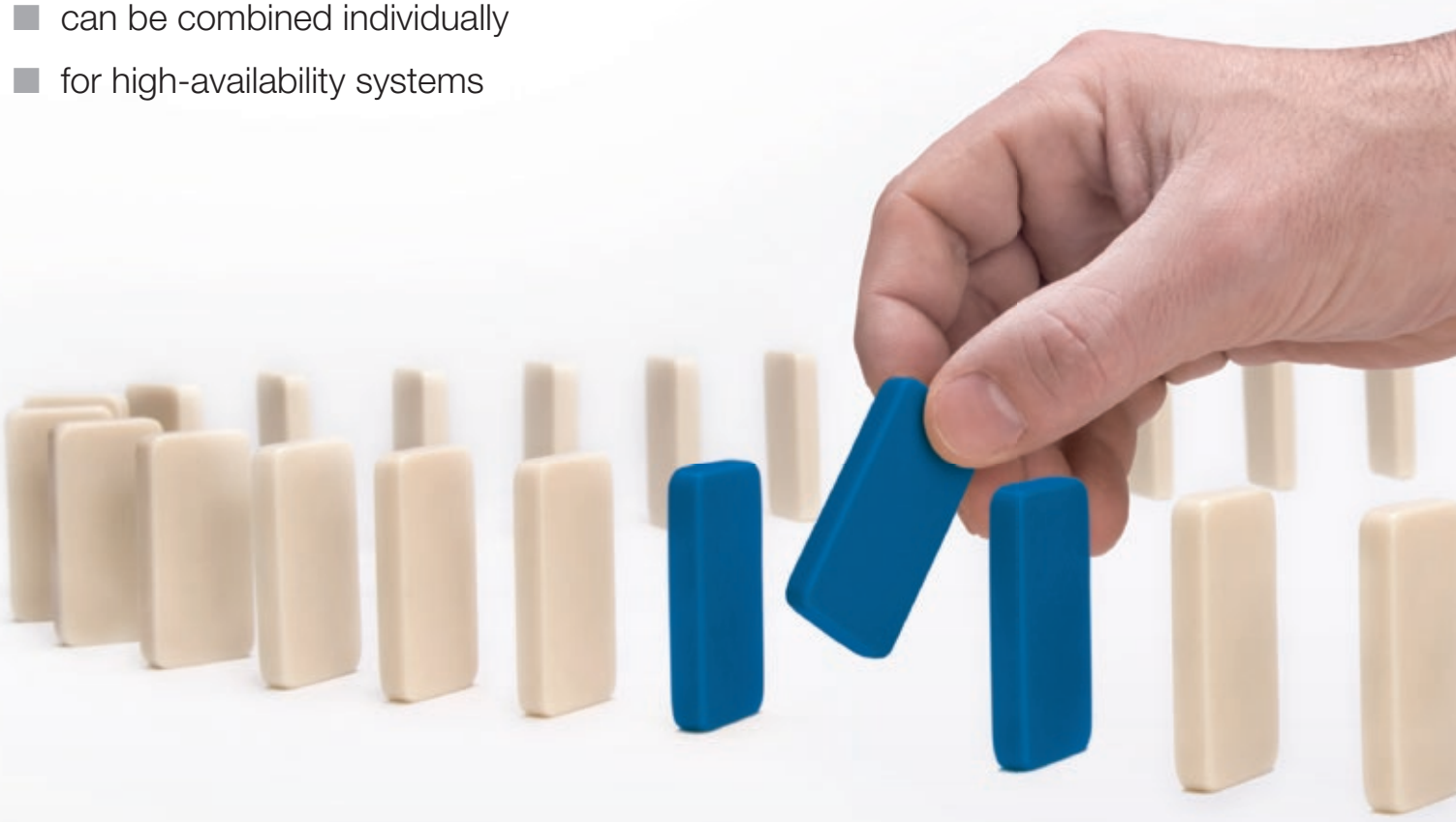
ABOUT THE COMPANY

ZAHORANSKY AG is a full-range supplier in machinery and production lines, sophisticated, innovative injection moulds and automation equipment. The company operates with over 700 associates at production sites in Germany, Spain, China, India and the US.

System Technology offers across-system solutions for the injection-related automation. These systems are based on injection moulds by ZAHORANSKY Automation & Molds GmbH and on established systems from different modules of automation. Intelligent and injection-related automation solutions can be composed with these modules. ZAHORANSKY Automation & Molds GmbH serves the areas Industrial Automation and Medical Devices, with pre-configured solutions provided for medical engineering. Z.BLIZZARD, for example, is an integral solution for making ready- to-fill prefillable syringes as primary medical packaging.

Automation solutions from the **toolkit**

- System modules for automating manufacturing processes around injection molding
- can be combined individually
- for high-availability systems



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