P06 A COLLABORATION THAT SAYS YOU'RE IN SAFE HANDS

P16 THE ADD-ON APPROACH TO CONNECTIVITY

P40 SPRING DEVELOPMENT FOR MEDICAL DEVICES

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ONdrugDELIVERY

6 - 13 Terumo's Plajex™ and Nemera's Safe'n'Sound®: a Collaboration That Says You're in Safe Hands
William Dierick, Director Technology Development
Terumo
Pascal Dugand, Technology Product Manager, and
Adrien Tisserand, Golbal Category Manager – Parenteral
Nemera

16 - 19 The Add-On Approach to Connectivity
William Cirillo, Head of Product Development
Innovation Zed
Christian Keller, Director for Engineering Solutions
SHL Group

22 - 25 Unisafe™: a Patient-Centric Approach to Optimise Confidence in Medical Device Design
Alex Fong
Owen Mumford

26 - 27 Company Profile: Noble

30 - 32 Newguard™: Safer Prefilled Syringes & Fewer Changes
Jean Vuillecard, Product Innovation Manager,
Philippe Lesaulnier, Business Development Manager, and
Eric Dessertenne, Head of Business Development
Biocorp

34 - 36 Drugdeliverysystem for Standard 1 mL Long Prefilled Syringes
Hans Peter Manser, Business Director, and
Ludwig D. Weibel, Chief Executive Officer
Weibel CDS

38 - 39 Product Showcase: PremiumCoat™

40 - 43 Expert View: Spring Development for Medical Devices
Neil Fletcher, Technical Manager
Advanex

45 - 46 Product Update: Schott's adaptiQ® and Vials DC

48 - 50 More Product Effeciency by Fully Automated Production Processes
Berthold Schopferer, Business Development Manager
Zahoransky

52 - 53 Company Profile: Avery Dennison

56 - 58 Packaging & Machinery Engineered to Go Hand-in-Hand
Christoph Hammer, Chief Executive Officer
Dividella

Nemera

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TERUMO'S PLAJEX™ AND NEMERA'S SAFE'N'SOUND®: A COLLABORATION THAT SAYS YOU'RE IN SAFE HANDS

Nemera and Terumo have established compatibility between Terumo's PLAJEX™ COP prefillable syringes and Nemera's Safe'n'Sound® passive safety add-on platform. Here, William Dierick, Director Technology Development, Terumo; and Pascal Dugand, Technology Product Manager Device Development and Adrien Tisserand, Global Category Manager, Parenteral, both of Nemera, describe the collaboration focusing specifically on two of the main functions, resistance to drops, and residual volume after delivery of the intended dose and activation of the sharps protection device.

We are in an exciting new era of drug development. The relentless R&D efforts made by the pharmaceutical industry and the advances in both science and technology could facilitate many innovations making treatments widely available and accessible to patients. Such efforts have already contributed to considerable improvements in patient well-being alongside life expectancy, which has also increased dramatically compared with the past century.[1]

Parenteral drug delivery is one of the largest segments of the drug delivery market and accounts for approximately 30% of the market share. This is a result of various factors, including the increase of new biotherapeutics in the market place. Thanks to advancements in biotechnology, monoclonal antibody drug development makes a major contribution in this market, providing improved therapies for various disorders, such as autoimmune and cardiovascular indications, infectious diseases, cancer and inflammation. The emergence of these new biological products and the introduction of new biosimilars demands more attention for the development of advanced drug delivery technologies for these sensitive biological products.[2-3]

According to market analysts, the global market for prefilled syringes (PFS) will grow at a steady pace. PFS consumption has more than tripled over the past decade due to the increasing number of drugs in this format. To date, more than 3.5 billion PFS are being produced each year and that number is expected to grow by approximately 10% on an annual basis.[4]

Therapeutic proteins are typically administered by injection using PFS. However, these proteins may be sensitive to heat and oxidation and they have the tendency to aggregate. Protein aggregation and the elicitation of anti-drug antibodies (ADAs)

> "To serve the needs of our clients to the very highest degree, Terumo and Nemera have collaborated to create a compatibility between Terumo's PLAJEX™ prefillable syringes with Nemera's Safe'n'Sound® platform of add-on passive sharps injury protection devices for PFS."

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may have a detrimental effect on drug efficacy, pharmacokinetics and safety for the patient.[5]

In order to meet the growing regulatory demands and to produce a PFS as an appropriate primary drug container for use with these biotherapeutics, Terumo developed a polymer-based PFS. By using the advancements in polymer science Terumo has expanded its technological development and innovation in this area.

> "PLAJEX™ 1 mL Long with staked needle offers an opportunity to mitigate potential interactions with the biological drug product."

More than 16 years ago, Terumo launched a polymer PFS for its own branded products and has continued to develop this application for many different drug products, including applications for biotherapeutics.[6]

Terumo has set up an integrated manufacturing process for all steps of manufacturing, including:

- Integrated moulding operations and robotised transfer
- Automation and subsequent assembly steps
- Fill & closure
  - Aseptic filling (biotherapeutics)
  - Terminal sterilisation (small molecules)
- Secondary packaging operations.

Assembly and integration of add-on safety devices (sharps injury protection devices) and auto-injectors is also an option that is on offer from Terumo's CMO services.[7]

Based on this vast experience, in 2012, Terumo launched a sterile ready-to-fill prefillable syringe called PLAJEX™. A combination of Zeonex® cyclo olefin polymer (COP) for the syringe barrel with a chlorobutyl rubber (CIIR) plunger stopper and its proprietary coating (i-coating™) is used for the creation of a PFS system without the use of silicone oil lubrication inside the syringe.[8-9]

The PLAJEX™ 1 mL Long with staked needle (27G TW x ½" or 29G TW x ½") offers an opportunity to mitigate potential interactions with the biological drug product for numerous reasons:[9-10]

- No internal syringe lubrication with silicone oil minimises the occurrence of protein aggregation
- Low sub-visible particles (SbVPs)
- Insert-moulding for bonding the stainless steel needle without the use of glue; no tungsten issues
- Tub/nest Syringe component sterilised by steam sterilisation, avoiding protein oxidation by the occurrence of free radicals (from irradiation sterilisation)
- Selected materials for minimising extractables and leachables.

By combining the i-coating™ plunger stopper, several functional properties provide further advantages for syringe applications:[8-9]

- Securing container closure integrity
- The absence of a break-loose peak force to initiate plunger movement; break-loose and gliding forces (BLGF) are consistent and predictable and do not deteriorate over time.

Polymer prefillable syringes produced from COP also offer physical properties that serve the application and integration for advanced parenteral drug delivery technologies, such as auto-injectors for self-injection and for use with add-on devices for protecting the user and healthcare provider from the risk of needlestick injuries. These features include:

- High transparency
- Resistance to breakage
- Narrow dimensional tolerance of the moulded parts.

To serve the needs of our clients to the very highest degree, Terumo and Nemera have collaborated to create a compatibility between Terumo's PLAJEX™ prefillable syringes with Nemera's Safe'n'Sound® platform of add-on passive sharps injury protection devices for PFS. Under this collaboration, Nemera together with Terumo have defined a development plan to confirm compatibility of Safe'n'Sound® with PLAJEX™ prefillable syringes as illustrated in Figure 1.

This development plan was defined around three main activities: (1) adaption of the sharps injury protection device to PLAJEX™ characteristics; (2) verification of the performances through a design verification plan; and (3) validation of the performances through a simulated clinical user study.

Figure 1: Nemera's Safe'n'Sound® combined with Terumo's PLAJEX™ COP prefillable syringe.

Safe'n'Sound® is a customisable platform of add-on passive sharps injury protection devices for PFS, which not only aims to prevent needlestick injuries but also to ease usage, facilitating the injection process. As a passive sharps injury protection device, no extra gesture is required by the user with Safe'n'Sound® compared with a naked syringe. The sharps injury protection feature activates automatically after completion of the entire dose, simplifying use. User interface has been integrated since the beginning in the design and development of the device, integrating many ergonomic features: a large thumb pad surface to smooth the injection; large built-in finger flange to facilitate handling; a round shape for easy and comfortable handling; a spring located at the syringe flange position to provide good visibility

Figure 2: Safe'n'Sound® before syringe assembly, drop test without syringe.

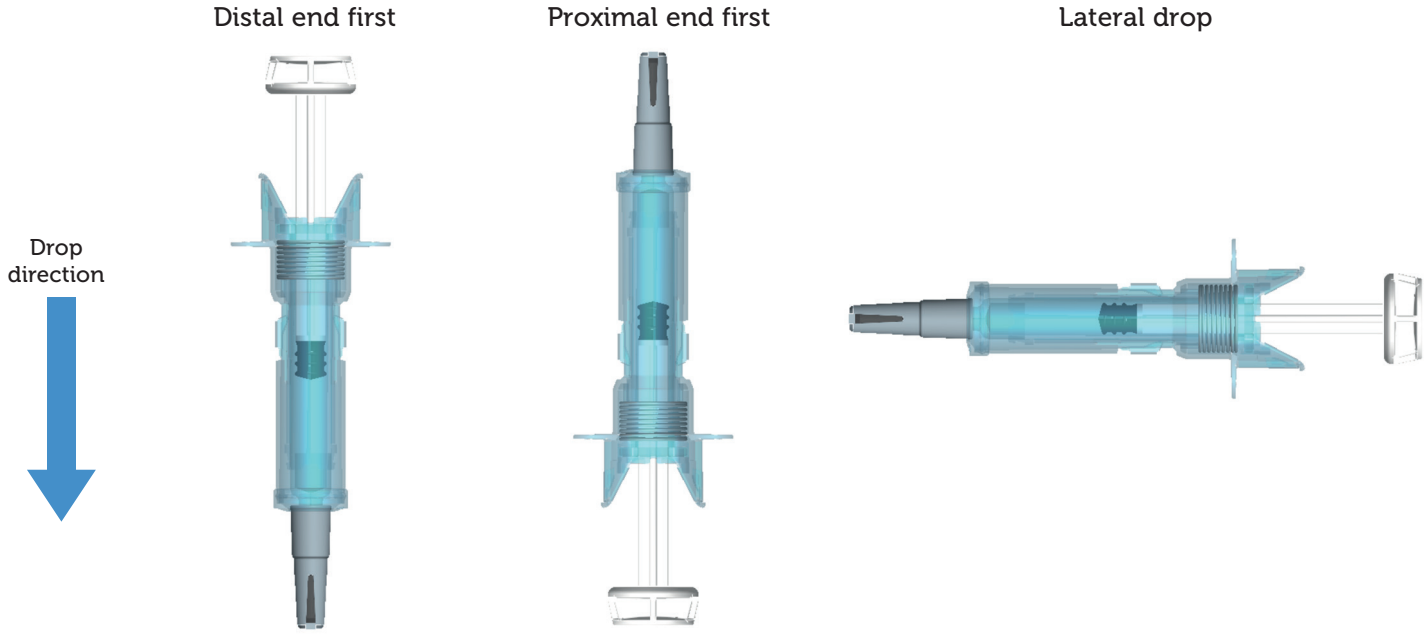

Figure 3: Safe'n'Sound® with WFI filled PFS, drop test before use.

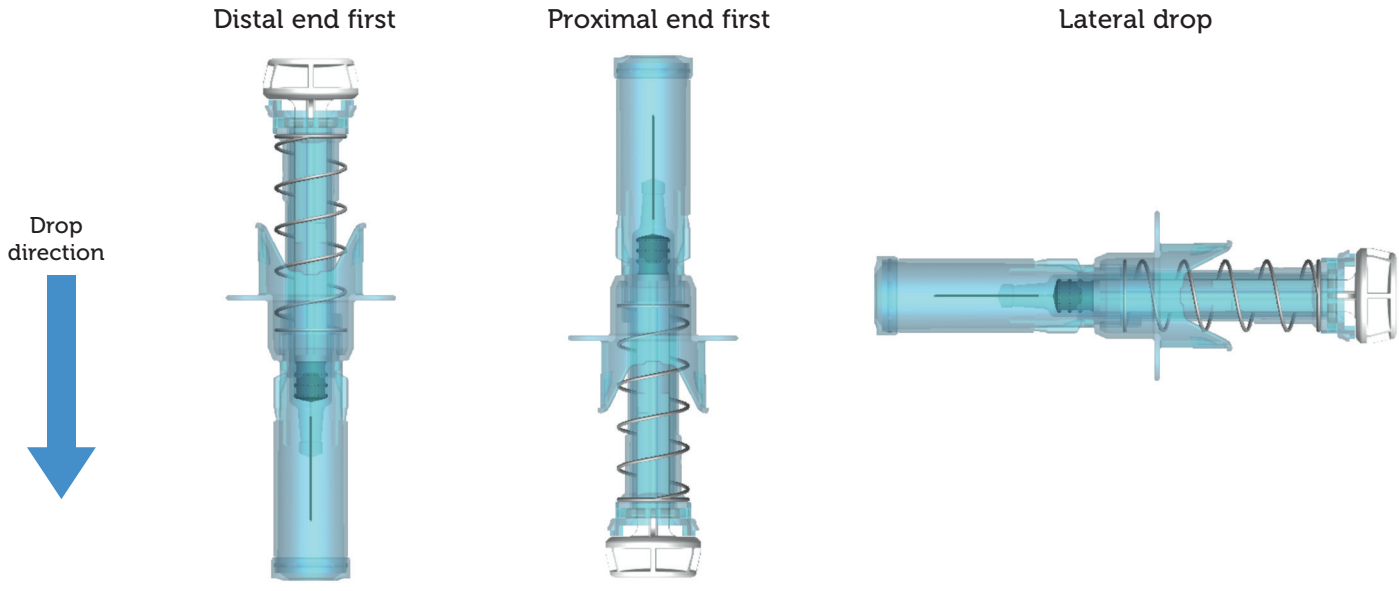

Figure 4: Safe'n'Sound® with PFS, drop test after dose delivery and activation.

"Of the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ without EFF and the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ with EFF, zero failures were observed."

of the tip and front side of the syringe for easy inspection of the drug even with low filling volume drugs. Optional add-on ergonomic extended finger flanges have also been developed to improve handling, gripping and comfort for the user.

Safe'n'Sound®, based on high molecular weight polycarbonate, is a fully transparent device, very resistant to breakage. PLAJEX™ COP prefillable syringes are in accordance with ISO 11040-6 and present distinct design features. For example, the flange geometry is more pronounced with the edges accurately defined and having narrow tolerances, based on injection moulding process capabilities. These features of PLAJEX™ COP provide strong performance and interaction with the Safe'n'Sound® add-on device, such as interlocking and avoidance of inadvertent dislocation. Therefore, Safe'n'Sound® device matching was conducted to create device compatibility with PLAJEX™ 1 mL Long-staked-needle PFS.

Nemera developed a specific sleeve (the inner part of the sharps injury protection device in which the syringe is snapped-in) and a specific plunger rod was prepared to be compatible with PLAJEX™ syringes and the i-coating™ plunger stopper. All performances associated to the syringe specific design and those new components were checked during the design verification plan.[11]

DEVICE PERFORMANCE BEFORE AND AFTER DROP

Resistance to accidental shocks is key not only from a patient perspective but also a cost point of view. A high resitance to shocks and vibrations may improve patient safety by avoiding dangerous dislocation of the add-on device. Moreover, it allows bulk packing of the safety device (lowering the transportation costs) and a more efficient process on the assembly line for higher productivity. In addition, once assembled together with the syringe, it eliminates the potential loss of expensive drugs through accidental activation.

In developing the design verification plan, and to determine performance testing criteria, reference was made to ISO 11608-1:2014, "Needle-based injection systems for medical use. Requirements and test methods, Part 1: Needle-based injection systems". Where a PFS by itself is not regarded as needle-based injection systems (NIS), it was considered to be a sound rational to refer to preconditioning and free fall testing requirements of this standard as it represented a potentially very effective means of really challenging and confirming the robustness of the design of the needle injury protection feature, assessing the operation and functionality of the accessory as mounted onto the PFS.

Safe'n'Sound® was developed with the aim of achieving a high drop resistance.

DESIGN VERIFICATION: DROP RESISTANCE

To assess the drop resistance of the Safe'n'Sound® device with PLAJEX™ syringes, free-falling drop tests were performed following three different drop directions (as shown in Figures 2-4). Tests were conducted following Nemera internal protocols on: 30 units of Safe'n'Sound® without syringe (Figure 2); 30 units of Safe'n'Sound® with PFS filled with water for injection (WFI) before use (Figure 3); and 30 units of Safe'n'Sound® after dose delivery and activation (Figure 4).

Drop tests were performed on the devices at room temperature before and after accelerated ageing conditions, and also after cycling conditions described hereafter.

Ageing conditions:

- 77 days at 65°C before syringe assembly
- 77 days at 65°C before syringe assembly + 60 days at 65°C after syringe assembly.

Cycling conditions:

- Four days at -40°C and four days at +70°C
- The devices were left to cool down to room temperature (20°C) before being tested.

The acceptance criteria were defined as per ISO 11608-1. Failure is considered as syringe unloading/dislocation, breakage and/or device activation. An overview of the results of the testings with the different conditions are shown in Figure 5 and Figure 6.

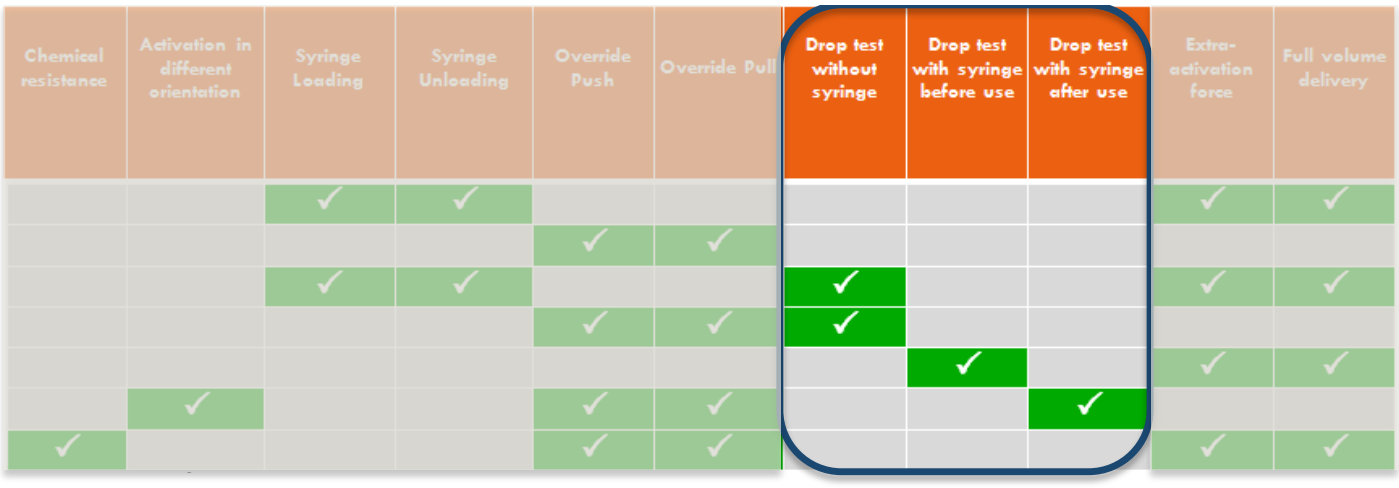

Figure 5: Test result overview, without preconditioning.

Group	Test conditions	Activation in different orientations	Syringe Loading	Syringe Unloading	Override Push	Override Pull	Transport	Drop test without syringe	Drop test with syringe before use	Drop test with syringe after use	Extra-activation force	Full volume delivery
8a	Transport (single carton)		✓		✓	✓	✓			✓	✓	
8b	Transport (pallet)		✓		✓	✓	✓			✓	✓	
9	77 days 65°C										✓	✓
10	77 +60 days 65°C		✓	✓							✓	✓
11	77 +60 days 65°C				✓	✓						
12	77 days 65°C		✓					✓			✓	
13	77 +60 days 65°C								✓		✓	
14	77 +60 days 65°C	✓			✓	✓				✓		
15	Cycling				✓	✓		✓	✓		✓	
16	Cycling	✓	✓	✓								✓
17	Operating 40°C										✓	
18	Operating 5°C										✓	

Figure 6: Test result overview, after preconditioning (drop, ageing, transport, cycling).

Chemical resistance	Activation in different orientation	Syringe Loading	Syringe Unloading	Override Push	Override Pull	Drop test without syringe	Drop test with syringe before use	Drop test with syringe after use	Extra-activation force	Residual volum
		✓	✓						✓	✓
				✓	✓					
		✓	✓			✓			✓	✓
				✓	✓	✓				
							✓		✓	✓
	✓			✓	✓			✓		
✓				✓	✓				✓	✓

Figure 7: Test result overview for residual volume, without preconditioning.

Group	Test conditions	Activation in different orientations	Syringe Loading	Syringe Unloading	Override Push	Override Pull	Transport	Drop test without syringe	Drop test with syringe before use	Drop test with syringe after use	Extra-activation force	Residual volum
8a	Transport (single carton)		✓		✓	✓	✓			✓	✓	
8b	Transport (pallet)		✓		✓	✓	✓			✓	✓	
9	77 days 65°C										✓	✓
10	77 +60 days 65°C		✓	✓							✓	✓
11	77 +60 days 65°C				✓	✓						
12	77 days 65°C		✓					✓			✓	
13	77 +60 days 65°C								✓		✓	
14	77 +60 days 65°C	✓			✓	✓				✓		
15	Cycling				✓	✓		✓	✓		✓	
16	Cycling	✓	✓	✓								✓
17	Operating 40°C										✓	
18	Operating 5°C										✓	

Figure 8: Test result overview for residual volume, after preconditioning (ageing, cycling).

"Safe'n'Sound® / PLAJEX™ with EFF was considered to be an effective needlestick protection device, without use problems, which allows an injection to be performed using a one hand technique, and which does not need extensive training for correct manipulation."

Out of the 72 devices tested in every configuration, all devices passed the test successfully. No inadvertent device activation nor syringe unloading has been observed in any of the conditions described above. No breakage was noted on the PLAJEX™ PFS nor the Safe'n'Sound® device. These results confirm the robustness and compatibility of the Safe'n'Sound® device in combination with PLAJEX™ PFS.

DESIGN VERIFICATION: RESIDUAL VOLUME

Residual volume is considered as the volume of drug left in the syringe after completion of the injection of the intended dose. In order to confirm the compatibity of Safe'n'Sound® with PLAJEX™ syringes, tests were performed according to Nemera's internal protocols on devices at room temperature before and after accelerated ageing conditions, as well as after cycling conditions.

Ageing conditions:

- 77 days at 65°C before syringe assembly
- 77 days at 65°C before syringe assembly +60 days at 65°C after syringe assembly.

Cycling conditions:

- Four days at -40°C and four days at +70°C
- The devices were left to cool down to room temperature (20°C) before being tested.

The acceptance criteria were defined as residual volume should be ≤70 µL according to ISO 7886-1:1993, "Sterile hypodermic syringes for single use, Part 1: Syringes for manual use", as well as being equivalent to the syringe without Safe'n'Sound® device. An overview of the results is shown in Figures 7 and 8.

72 devices were tested by each condition. All devices passed the test successfully. It is important to note that the results presented a very low residual dose, an important aspect for use with valuable biopharmaceuticals. Indeed, average values registered went from 1-4 µL. It has been demonstrated that the residual volume remains the same whatever the device pre-conditioning.

In order to confirm the compatibility of Safe'n'Sound® with PLAJEX™ syringes, once the design adjustment and design verification plan have been successfully executed, a simulated clinical user study was performed to validate the functionality of the device.

SIMULATED CLINICAL USER STUDY VALIDATION

A simulated clinical user study[12] was designed to evaluate the safety of use of Safe'n'Sound® PLAJEX™ version with and without an extended finger flange (EFF) in the prevention of needle stick injuries. The primary objective was to evaluate the number of injuries or non-activation of the safety feature reported by the evaluators for each device. Success was defined as a complete activation of the safety feature following injection without a needlestick injury, whereas failure was defined as a non-complete activation of the safety feature following injection.

The study was designed in accordance with ISO 23908:2011, "Sharps injury protection: Requirements and test methods. Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling", and US FDA Guidance for Industry and FDA Staff, "Medical Devices with Sharps Injury Prevention Features, Section 10, Simulated Clinical Use Testing".

In accordance with the FDA recommendations, 1000 safety devices (n=1000) of each configuration (with and without EFF) were tested. Acceptance criteria were defined in accordance with ISO 23908 and the FDA Guidance.

The study was performed in the US by a total of 60 evaluators. The evaluators were composed of 30 non-healthcare professionals (NHCP) and 30 healthcare profesionals (HCP). Of the 2000 injections performed with Safe'n'Sound® PLAJEX™ version with / without EFF, 1320 were performed by a HCP and 680 by a NHCP. The order of testing was determined randomly among evaluators so as not to favour one version over another.

To mimic real clinical conditions of device use, HCPs performed injections with gloves and NHCPs without gloves. Injections were performed using an appropriate patient's substitute and with Safe'n'Sound® / PLAJEX™ PFS filled with WFI.

The analysis of the injury onset and success of manipulations showed the following results:

- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ without EFF performed by a HCP
- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ without EFF performed by a NHCP
- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ with EFF performed by a HCP
- zero injuries and zero failures of the Safe'n'Sound® / PLAJEX™ with EFF performed by a NHCP.

Of the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ without EFF and the 1000 simulated injections performed with Safe'n'Sound® / PLAJEX™ with EFF, zero failures were observed. According to the tables given in the FDA guidance, these observations have determined that the primary objective of the simulated clinical user study was achieved for Safe'n'Sound® / PLAJEX™, both with and without EFF.

This study not only confirmed the performance of the two versions of the sharps injury protection device but also gave the opportunity to capture feedback from the evaluators on several aspects of the safety device. Figure 9 shows a summary (results expressed in percentage) of the ratings from all the evaluators on the Safe'n'Sound® / PLAJEX™ version with EFF.

From this survey, evaluators confirmed the performance of the device and its ease of use. Safe'n'Sound® / PLAJEX™ with EFF was considered to be an effective needlestick protection device, without use problems, which allows an injection to be performed using a one-hand technique, and which does not need extensive training for correct manipulation.

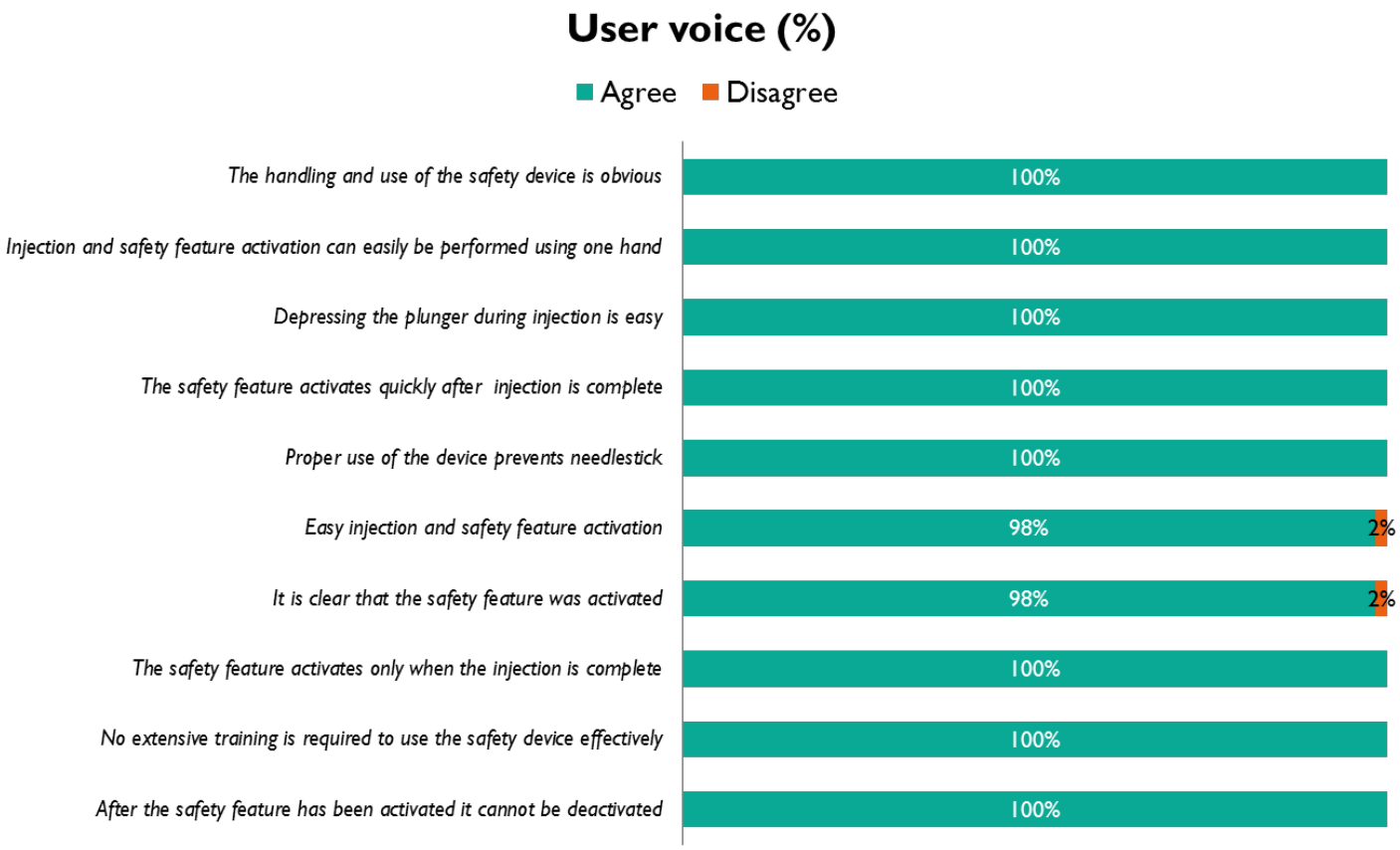

Figure 9: summary of evaluators rating one of the tested Safe'n'Sound®/PLAJEX™ device.

CONCLUSION

In this article, the compatibility of the PLAJEX™ prefillable syringes with Safe'n'Sound® passive sharps injury protection device has been highlighted. Nemera and Terumo have leveraged their polymer science know-how and competences to serve the needs of their clients and provide a unique offering for the delivery of biopharmaceuticals products.

Safe'n'Sound® combined with PLAJEX™ is a fully compatible offer which has been verified technically and validated by users. Among the key advantages, this compatibility offers the biopharmaceutical industry a passive sharps injury protection device with robustness and resistance to shocks and vibrations, minimising the risk of potential needlestick injuries and loss of expensive and lifesaving drugs. Furthermore, a very low residual volume is obtained thanks to Safe'n'Sound® functioning and specific PLAJEX™ design and performance characteristics. The ergonomics and functionality were confirmed and appreciated by users during the simulated clinical user study.

In conclusion, Safe'n'Sound® compatibility has been established and validated with PLAJEX™ COP prefillable syringes and Safe'n'Sound® / PLAJEX™ is prepared and ready for commercial supply.

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ABOUT TERUMO

Tokyo-based Terumo Corporation is one of the world's leading medical device manufacturers

with over US$5 billion in sales and operations in more than 160 nations. Founded in 1921, the company develops, manufactures and distributes world-class medical devices including products for use in cardiothoracic surgery, interventional procedures and transfusion medicine; the company also manufactures a broad array of syringe and hypodermic needle products for hospital and physician office use. Terumo contributes to society by providing valued products and services to the health care market and by responding to the needs of health care providers and the people they serve. Terumo Corporation's shares are listed on the first section of the Tokyo Stock Exchange (No. 4543, Reuters symbol <4543.T>, or Bloomberg 4543: JP) and is a component of the Nikkei 225, Japan's leading stock index.

ABOUT THE AUTHORS

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Adrien Tisserand, Global Category Manager at Nemera, is in charge of the parenteral range of proprietary products including Safe'n'Sound®. Mr Tisserand joined the company in 2013. In his previous career he worked for Janssen in the strategic marketing division. He holds: a Bachelor in International Business from HUBS, UK, a Masters in Marketing from URJC, Madrid, Spain, and a Masters from Kedge Business School, France.

Pascal Dugand, Technology Product Manager, Nemera, graduated as a polymer engineer from EAHP in Strasbourg, France. He holds a Masters in polymer mechanics and joined Plastic Omnium in 1990 where he started to work in development and innovation. In 2004, the medical division of Plastic Omnium was acquired by Rexam and more recently the four drug delivery devices plants, including the Innovation Centre, became Nemera. Today, Mr Dugand is an experienced medical device developer engineer specialised in the development of parenteral delivery devices. He developed for Nemera own IP products including Safe'n'Sound and Safelia auoinjector as well as working on several customer injectable product development projects.

ABOUT NEMERA

More than five million diabetics rely everyday on parenteral devices manufactured by Nemera.

With over 1,300 people and four plants across two continents, Nemera is a world leader in the design, development and manufacturing of drug delivery solutions for pharmaceutical, biotechnology & generics industries. Nemera's expertise covers several modes of delivery: Parenteral, Nasal, Buccal, Auricular, Ophthalmic, Pulmonary, Dermal and Transdermal.

Nemera leverages decades of manufacturing and development experience in the parenteral devicesegment (passive safety devices auto-injectors, pens, and implanters), from full development to pure contract manufacturing, through customised solutions. Nemera applies the same quality-oriented process to the development of proprietary devices and to customised solutions under contract with laboratories.

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THE ADD-ON APPROACH TO CONNECTIVITY

Digitalisation is playing an increasing role in the way healthcare is delivered, particularly in terms of compliance with treatment. However, the lengthy time taken in getting digital delivery devices to market can mean that patients are being denied the benefits of these advances. One solution is the use of simple add-on platforms that can work with an existing device. William Cirillo, Head of Product Development at Innovation Zed, and Christian Keller, Director for Engineering Solutions at SHL Group, describe one such platform developed by their companies.

Digital health is an umbrella term that covers a lot of different applications of technology in the health industry. From wearable sensors and electronic health records to health apps, connected and digital solutions are becoming more accepted. With almost three-quarters of the world's population having access to mobile technology, usage is increasing among all age groups; already up to 75% of people in the UK are going online for health information.[1,2]

WHY DIGITAL HEALTH?

Digitalisation of healthcare is happening and connected solutions will continue to play an increasing role for patients, healthcare providers, payers and pharmaceutical companies. These advances are supported not just by the availability of technology. A new generation of patients has grown up and they approach their own and their families' healthcare differently today. They want to be informed, engaged and in control of their treatment process more than any previous generation.[3] From the point of view of governments and insurers, longer life expectancy and increasing prevalence of chronic diseases mean that healthcare costs are growing unsustainably. According to the OECD, health spending has been rising faster than economic growth in the developed world and will reach 14% of GDP by 2060 unless reforms are implemented.[4] Wider implementation of digital technologies can save healthcare systems 7-11% of spending by improving hospital efficiency and encouraging home care and self-management.[5] One major area in which new technology can be used to curb costs is outcome-based healthcare. To ensure that therapies benefit patients and reward outcomes, it is crucial for health agencies to be able to monitor adherence; and connected technologies are an excellent solution for this.

> "To ensure that therapies benefit patients and reward outcomes, it is crucial for health agencies to be able to monitor adherence; and connected technologies are an excellent solution for this."

ADHERENCE TRACKING AND CONDITION MANAGEMENT

The World Health Organization agrees that "increasing adherence may have a greater effect on health than improvements in specific medical therapy".[6]

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Yet an average compliance rate is only 50% in the developed world and even lower in the developing.[1] Non-compliance is damaging for everyone. Patients have their health deteriorating; doctors and pharmaceutical companies cannot properly assess the effectiveness of the treatment; and both pharma and payers suffer avoidable costs.

The pharma industry understands the importance of digital solutions in dealing with this challenge. This is evidenced by the fact that the number of unique proprietary health apps by pharmaceutical companies has grown by 63% in 2013-2014.[2] Sensors and smart technologies are being introduced for various stages and indications, including:

- Monitoring real-time patient experience in clinical trials in order to improve adherence to COPD treatment[7]
- Branded drug apps to help manage the treatment of type-2 diabetes[8]
- Comprehensive cloud-based device/software solutions for sleep and respiratory patients.[9]

THE ENYA PLATFORM

Now that data from already introduced tools is becoming available, it is clear that they can bring about real improvements in outcomes and are highly accepted by patients and healthcare professionals.[2] However, introducing connectivity for combination products is often a lengthy process complicated by regulatory hurdles, costs and time-to-market considerations. Therefore, while pharma companies are still considering, or are in the process of developing, a delivery device with integrated connectivity, a gap appears between patients' expectations and available solutions. One way to narrow this gap is to use an add-on platform that can work with an existing device.

SHL, in partnership with Innovation Zed, has developed such a solution for pen injectors – the ENYA Platform. It allows connectivity to be added to any multiple dose injection pen in a fast and easy way without any modifications to the existing device (Figure 1). The cross-platform solution can track injections "on the go" and connect via Bluetooth to a custom-made or third-party condition management application.

The beauty of ENYA is that it is completely injection device independent. Therefore, a pharma company can connect an existing product for any indication within a 12-month timeline. There is no need to recertify the injection device, no extra regulation and no change to the manufacturing process.

As the industry is focusing more on patient-centricity, the add-on platform provides an excellent opportunity to improve user experience without changing the injection process that they are accustomed to. The data captured by the add-on device can be used to help patients manage their therapy and, with their consent, it can be shared with caregivers, doctors, payers and pharma companies.

Figure 1: The ENYA platform can work with existing devices.

BENEFITS OF THE ADD-ON APPROACH

What are the key benefits of the add-on approach? For pharma companies, it is an opportunity to present an innovative offer at lower cost and faster time to market. In addition, as the platform is completely customisable and entails incremental functionality for different markets and indications, the ENYA Platform can be effectively used to differentiate across devices and conditions.

For patients, it is the peace of mind. They don't have to worry anymore about remembering or manually inputting their injection data. The connectivity empowers them to interact directly with various stakeholders in real time, providing what many advocacy groups are emphasising – confidence, engagement and feeling in control of their health. And, of course, with improved adherence their long- and short-term health outcomes will improve.

For healthcare professionals, the recording of injection behaviour "on the go", eliminates conjecture by lending factual evidence to the data. This enhances the professional's ability to have more meaningful interactions with their patients with a view to improving therapies and achieving better health outcomes.

For health agencies and payers, these improvements in health outcomes will significantly lower their chronic condition-related spending. Moreover, the availability of real-time evidenced data on adherence and outcomes will make reimbursement decisions more informed. It will also reduce emergency admissions and make hospital visits more effective.

Figure 2: Patients can continue using their chosen insulin pens.

Figure 3: The connected device is designed to integrate with any diabetes management system.

CASE IN POINT – INSULCHECK

An example of the ENYA Platform that has already proven itself on the market is InsulCheck – an add-on device for insulin pens. With over 100 million diabetic insulin pen users globally, it provides a powerful solution that does not require them to change their injection habits in any way. InsulCheck works with any existing pen through the customised sleeve interface (Figure 2). The connected device records injection behaviour and sends this data to the patient's mobile device, where it can be integrated into diabetes management algorithms (Figure 3). Research shows that using the InsulCheck device provides better clinical outcomes. A study by Minnock[10] has shown that the effects of using the device included improved HbA1c readings (average long-term blood sugar level indicator), fewer hypoglycaemic events (blood glucose below 3.9 mM) and fewer hyperglycaemic events (blood glucose over 11.1 mM).

What does it mean for patients using the device? If they know exactly the details of their previous injection, they will avoid dose miscalculations and miss fewer injections. That means they will suffer fewer hypoglycaemic events, have greater control of their glucose levels and minimise the time spent in hyperglycaemic states. Less injection mistakes also mean less hospital emergency admissions to treat the short and long-term problems connected to hypoglycaemic events. In short, it means that diabetes patients are able to lead a safer life without worrying constantly about missed injections – they are in control of their treatment.

All of which helps to reduce HbA1c readings and the long-term complications of diabetes. According to the research,[11] reducing HbA1c levels by just 1% will:

- Decrease risk of heart failure by 16%
- Decrease risk of heart attack by 14%
- Decrease the risk of stroke by 12%
- Decrease risk of diabetes-related death by 21%
- Decrease risk of amputation by 43%
- Decrease risk of small blood vessel disease by 37%
- Decrease risk of death from all causes by 14%.

Using InsulCheck device over a one-year period can improve HbA1c by more than 1.0%. Thus, by using this simple device that does not require any extra steps during the regular process of injections, people living with diabetes will enjoy greatly improved health outcomes. At the same time, it will help their clinicians to adjust and modify their treatment based on consistent data monitoring and reduced number of complications resulting from non-adherence. Finally, it will significantly reduce the healthcare costs of hypo- and hyperglycaemic events and other diabetes-related conditions.

> "...a simple add-on solution recording and transmitting the data about injection time and dose can create long-term health benefits, lower the costs of health care and introduce a new interface with the patient."

BEYOND THE INJECTION

In conclusion, a simple add-on solution recording and transmitting the data about injection behaviour can create long-term health benefits, lower the costs of health care and introduce a new interface with the patient. The resulting increased adherence leads to better outcomes. Pharma companies can achieve better positioning in their markets as they differentiate their offer and manage an improved product lifespan.

But compliance tracking is about more than just injection; it is about a range of behaviours. Therefore, it is important to look deeper into the therapy practices. Drug temperature tracking, needle withdrawal duration, training tips, preparation confirmation – all of this information can be vital to condition management. Thanks to the variety of customisation and functionality options available, the ENYA Platform can accommodate a variety of requirements from pharma and biotech industries.

SHL's vast experience in developing, designing and manufacturing injection devices for a number of major pharma customers means that the ENYA platform has the support of SHL's broad knowledge base and comprehensive capabilities. Combining longstanding

reliability and visionary innovation, SHL and Innovation Zed offer a flexible, robust and risk-proof approach to adding connectivity and jump-starting your entrance into the digital health era.

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ABOUT THE AUTHORS

Christian Keller is working for SHL Group in Taiwan, where he leads an engineering team which is dedicated to creating new customer value in health and medical applications through the latest developments in IoT, connectivity and digital health. SHL is one of the world's largest solution providers in design, development and manufacturing of advanced drug delivery systems. Mr Keller graduated in 2005 from prestigious Swiss Federal Institute of Technology in Zurich (ETHZ) with a Master's degree in Electrical Engineering, and since then has been working in different engineering and project management positions. He has been involved in product developments from early-stage concepts to design for manufacturing and production.

William Cirillo is the co-founder and Head of Product Development of Innovation Zed, a company focusing on research and development in the area of connected solutions and services in drug adherence and condition management. A diverse technical background and experience enables Mr Cirillo to work on developing new and interesting products in many different areas to help make people's lives better. Graduating from the University of South Australia with a Bachelor of Applied Sciences degree in Physics in 1986, Mr Cirillo has been working in various engineering and scientific fields for 30 years, with areas of expertise ranging from manufacturing to pure research and from hardware to software.

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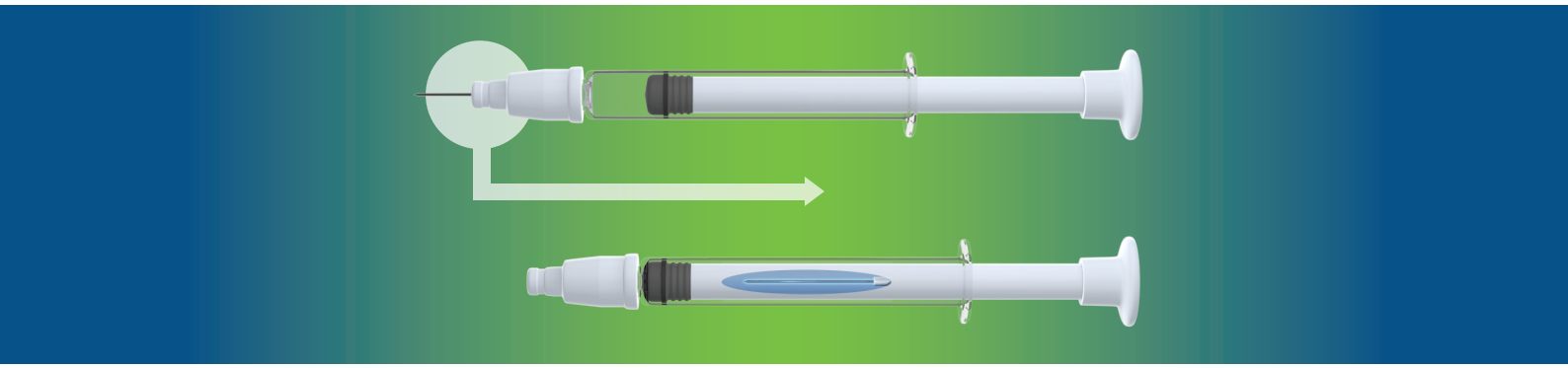

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UNISAFE™: A PATIENT-CENTRIC APPROACH TO OPTIMISE CONFIDENCE IN MEDICAL DEVICE DESIGN

Here, Alex Fong, MBA, Research and Insights Manager at Owen Mumford, provides an overview and update on needlestick injury, its prevention and the market for needle safety devices, and introduces Unisafe™, Owen Mumford's springless, passive safety device designed to work with existing prefillable syringes.

The global healthcare system is experiencing growing pressure, affecting every segment from costings and financial requirements, through to the quality and safety of treatments made available. The world's population is expected to rise to 9.7 billion by 2050, according to the United Nations Department of Economic and Social Affairs,[1] with an impending demand for medical services and treatment higher than ever before. With the requirement for treatment at an all-time high, it is imperative to empower patients with the correct tools and awareness that will enable them to execute their treatment correctly.

A GROWING POPULATION, DEMANDING SAFETY

Injections have become one of the most common healthcare procedures across the world, with over 16 billion treatments via injection taking place each year.[2] Injections come in a variety of forms, but self-injection of medication (into subcutaneous or intramuscular layers) is one of the more frequently used methods.

Due to the invasive nature of the treatment, injections are not universally safe. Needlestick injuries (NSIs) can arise from the injection process itself and can occur during the use, dissembling of or disposal of needles. For healthcare workers, the risk of cross contamination or transmission of blood or bodily fluid from patients infected with HIV, or hepatitis B or C, for instance, also remains a concern. In 2003, the WHO estimated that each year up to three million needlestick injuries occur in healthcare workers,[3] whilst up to a half of all occupational needlestick injuries remain unreported.[4]

Today, the risk of injury to both end-user and healthcare worker has escalated in line with the market demand for treatments via injection. The severity of the issue has been recognised in the US, and more recently Europe through the European Health and Safety (Sharps Instruments in Healthcare) Regulations 2013, an EU directive with a framework agreement on the prevention of sharps injuries.[5]

Patients and workers alike who access this method of treatment must be protected against the risks of using and disposing of needles. According to The Premier Safety Institute (Charlotte, NC, US), 40% of injuries occur during treatment, whilst another 40% occur after use and before disposal of the needle.[6] Injuries of this kind remain one of the most serious hazards faced by healthcare workers. Most needlestick injuries can be avoided with the use of a safety-engineered device which may protract

> "There are huge advances in innovation and technology in relation to the design of safety devices with government regulations and end-user demand contributing two strong driving factors."

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a needle before and after use, ensuring that the end-user remains protected.

Compared with traditional devices, safety injection devices reduce the risk of needlestick injuries by offering optimal protection to the healthcare provider or patient. These safety-oriented devices have emerged as one of the most popular and preferred delivery methods for injections. The US CDC estimates that using safer medical devices could indeed prevent anywhere between 60-80% of sharps injuries in hospitals.[7] Safety injection devices including safety syringes and safety needles are designed to enhance the safety of drug administration and reduce risk of injury.

For prefilled safety devices, the market is set to triple by 2020, from US$250 billion (£205 billion) to $797 billion, and between 2017 and 2018 alone the sales forecast is set to see its largest increase of 34% annual growth.[8]

Pharmaceutical companies and healthcare providers alike are facing a great change in market demand, with patient safety and confidence at the heart of effective treatment delivery. Regulations in recent years have also demanded this and safety injection devices have emerged as one of the key focus areas for device solutions. Not only do these enhance the patient experience and promote wider adoption of treatment (due to a safer and more effective experience) but they also encourage long-term economic benefits to an already overloaded healthcare system by allowing the patient to treat themselves effectively.

There are huge advances in innovation and technology in relation to the design of safety devices with government regulations and end-user demand contributing two strong driving factors behind device development amongst medical device teams.

RESPONDING TO MARKET DEMANDS

Owen Mumford, has responded to the increasing requirement for a safer, more effective syringe device. A thorough understanding of long-term treatment and injecting, partnered with world class research, design expertise and engineering capabilities has led Owen Mumford to a strong and close working relationship with pharmaceutical partners.

The current market place is largely composed of retractable and non-retractable safety syringes which are activated through a spring component. This has previously led to challenges, including accidental activation where a device may activate in transit or accidental under-dosing, where it may be challenging for the user to visually confirm the full dose has been delivered (for instance, if a spring is placed at the front of the syringe barrel, obstructing the view.)

Figure 1: Unisafe™, the springless, passive safety device designed to work with existing, prefillable syringes, avoids disruption to an end-user's treatment routine whilst ensuring that there is no need to change any existing injection components.

Scenarios such as these can impact the efficacy of the treatment – the patient may not receive the correct dosage, the device may be under-populated and there may be discomfort experienced in using the device, alongside the risk of injury. All of these factors create a barrier to continued treatment.

Owen Mumford focused on designing a passive safety device that would overcome these issues. The first option was to start with an existing and proven prefilled syringe and build a spring driven safety mechanism around it, but this could introduce other compromises to device performance. A second was to design a completely new safety syringe to make a brand new solution. However, this would necessitate the use of an unproven primary container that was considered unattractive in the industry. Owen Mumford needed to create a device which would remain effective whilst reducing potential barriers to treatment (painful administration, bulky design, uncomfortable use) whilst also offering suitability for ISO prefilled vendors.

PATIENT-CENTRIC DESIGN IMPACT

The device had to respond to the need of the patient first, whilst allowing for a greater patient responsibility and accountability. By following a patient-centric approach, the device design had to be both intuitive and easy to use for patients and offer additional safety for healthcare workers.

Owen Mumford thus developed a springless, passive safety device designed to work with existing, prefillable syringes. Unisafe™ (see Figure 1) is designed to increase patient confidence when injecting, eliminating the possible risks and challenges of traditional sprung syringes whilst also reducing potential barriers to sustained treatment. The device works just like a normal syringe, ensuring a lack of disruption to an end-user's treatment routine. Change, and the unknown, can both be barriers to treatment, and so Unisafe™ has been developed to ensure there is no need to change any existing injection components. For healthcare providers, the device can be used across an array of injectable formulations which require a syringe, reducing the financial implications of having to purchase multiple devices.

After conducting early formative studies on the design, Owen Mumford continued to develop the concept and further enhance usability. The finger flanges are now smoother, creating a more integrated look and feel, and the plunger head has been made larger for easier handling.

The design and usability of Unisafe™ has recently been the focus of a study conducted with an independent research house.[9] The study comprised nurses (50) and patients (57), accessing and administering injections across various rheumatology, oncology, respiratory, cardiology and gastroenterology indications. In traditional safety syringes, a lack of visibility or confidence that a treatment has been executed fully and correctly can cause anxiety for the end-user.

In response to this, Unisafe™ provides an unobscured prefilled syringe barrel allowing the user to view the drug and labelling

without having to spin the barrel, reducing the risk of under-dosing. In the study, 94% of nurses agreed it was easy to view medication in UniSafe™ before delivering the dose, whilst 89% of patients stated UniSafe™ made it is easy to know that the entire dose had been delivered.

Intuitiveness and ease of use are essential components of patient-centric product design. Working in the same way as a normal syringe and thus preventing any complication, Unisafe™ only requires the end-user to: remove the needle shield, inject the needle into the injection site, then depress the plunger. Needlestick injuries can happen in the first few moments after needle withdrawal and so Owen Mumford responded to this by ensuring the needle is shielded right away.

The device has a passive needle-retraction mechanism, meaning the user does not need to take any additional steps to shield the needle after use. This in turn reduces the risks associated with needle reuse and contamination. In addition, the device has been built with a strong grip, promoting confidence that the end-user or healthcare provider can administer the treatment safety. For 88% of nurses questioned and more than 75% of patients, grip was a key factor in the design of Unisafe™, particularly in raising confidence that the device would not slip during administration.

Some patients with chronic diseases can suffer from impaired dexterity, making it difficult to perform an injection. Mindful that this could produce a barrier to treatment, Unisafe™, has been designed with a larger, ergonomic plunger head and a smoother, more integrated finger flange for a more comfortable and integrated look and feel. This ensures the end-user can use the device confidently and intuitively, regardless of hand size, dexterity or condition. The device is thus suitable for all patient types and, in the study, 82% of nurses agreed their patients would find Unisafe™ intuitive to use, whilst 83% of patients agreed they would feel more confident using the device.

CHANGING MARKET NEEDS REQUIRE CONSTANT REVIEW

Patient-centric design is always changing and Owen Mumford is working closely with pharmaceutical partners to adapt products to meet the growing demand for injectable treatments.

The safety syringe market is set to expand at 9.7% CAGR following a rise in health and safety awareness[10] in 2013-2019. Manufacturers utilising a patient-centric design are responding to this, changing in line with market evolution and customer demand. The demand and development of injectable devices is a constant feedback loop between end-user and manufacturer, and development is vital to both encourage adherence to treatment regimes and help patients effectively self-manage their condition.

With up to 16 billion injections occurring every year, there is a demand for manufacturers to provide devices that are intuitive, safe and easy to use, for both patients and healthcare providers.

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ABOUT THE COMPANY

Owen Mumford is a major medical device manufacturer that develops pioneering products for its own Owen Mumford brand and custom device solutions for the world's major pharmaceutical and diagnostic companies. Owen Mumford's goal is to improve quality of life, encourage adherence to treatment and reduce healthcare costs. Making a world of difference, to a world of people.

With a history of world firsts in device solutions, Owen Mumford offers proven design, development and delivery services from a broad base of proven self-injection and blood sampling platform devices and intellectual property.

In business for over 60 years, Owen Mumford remains privately owned with a focus on long-term investment to deliver sustainable business growth. With a strong internal research and development capability, Owen Mumford's goal is to develop solutions that address today's healthcare demands. Through advanced research involving end users and healthcare professionals, and extensive design and manufacturing capabilities, Owen Mumford produces class-leading medical devices that are used globally, exporting over 85% of its products to more than 60 countries worldwide.

Selected as one of The World Economic Forum's Global Growth Companies, Owen Mumford is a trusted partner to many of the world's biggest medical device, diagnostic and pharmaceutical companies and works with international organisations to support customers at a local level and provide consistent and dedicated support.

THE AUTHOR

Alex Fong is a Research and Insights Manager at Owen Mumford. He holds an MBA and has worked in the market research industry for ten years, on both client and agency side. His current role manages market analyses, understanding the consumer and the end-user.

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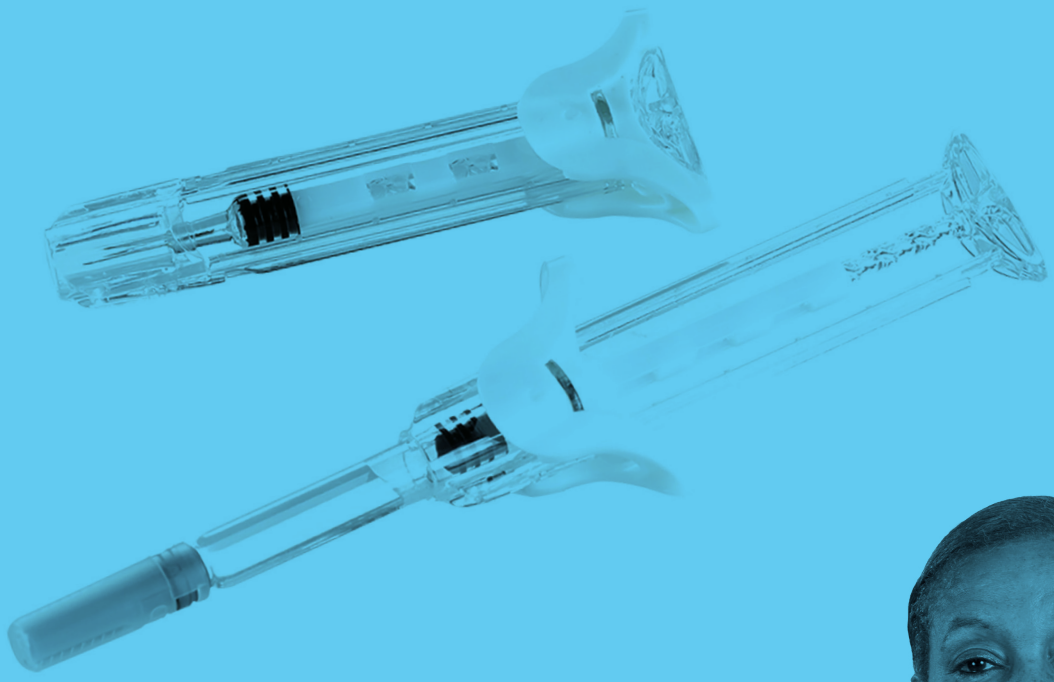

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OWEN MUMFORD

PUTTING **LIFE** INTO **TECHNOLOGY**

ONdrugDELIVERY

ONdrugDelivery 2017/18 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
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
January 2018	Ophthalmic Drug Delivery	November 20th
February 2018	Prefilled Syringes	December 22nd
March 2018	Skin Drug Delivery: Dermal, Transdermal & Microneedles	January 22nd

Device training happens here.

There's life beyond chronic conditions. Distractions, anxiety and understanding correct administration technique can all affect compliance. Studies suggest 61% of patients don't completely read the IFU[1] and 12% of patients have proficient health literacy.[2]

Will your patients correctly administer their drug delivery device?

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Onboarding and Device Training

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Reference: 1. Noble. (2015, November). The link between device training and patient compliance. Poster session presented at PDA – Universe of Prefilled Syringes 2015, Vienna, Austria. 2. Kessels, R. P. (2003, May). Patients' Memory for Medical Information. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539473/

COMPANY PROFILE: NOBLE®

Noble®, the leader in onboarding and device training, is a full-service, 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 designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes. Cross-disciplinary designers and engineers provide fully customised solutions from the first concept sketch through production, in both regulated and non-regulated environments. Noble uses ISO 9001 and ISO 13485 supply chains and manufacturing facilities.

As the number of patients required to self-administer medication increases, so does the need for patient-centric training and education, including training devices such as autoinjectors, prefilled syringes, wearable injectors and respiratory platforms.

CONNECTING PATIENT ONBOARDING WITH THE PATIENT JOURNEY

The first 30-, 60- and 90-days, commonly referred to as onboarding, are the most important regarding patient adherence. This is the time when a patient is expected to self-administer medication based upon prescribed regimen. While a patient's first exposure to a drug delivery device typically consists of training with a healthcare professional onsite at a medical facility, a patient will most often perform their medication administration alone outside of a healthcare facility and healthcare provider supervision. Yet:

- 45% of patients avoid injections due to anxiety[1]
- 93% of patients use their inhaler incorrectly[2]
- 40-80% of information provided by a HCP is forgotten immediately[3]

INJECTION AND RESPIRATORY DEVICE TRAINING

As the number of patients required to self-administer medication increases, so does the need for patient-centric training and education including training devices such as autoinjectors, prefilled syringes, wearable injectors and respiratory platforms.

Noble has developed a wide variety of patient-centric onboarding products to help patients administer correctly and improve adherence and patient outcomes. Noble's offerings range from mechanical training devices to smart error-correcting training platforms, assistive devices and even patient support including travel packs and training instructions for use (IFU).

In the modern era of patient-centric care, products that are able to provide superior onboarding and patient experiences will be well positioned and benefit by reducing patient errors, while improving patient satisfaction and outcomes.

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These devices have been designed to mimic actual commercial drug delivery devices while being a low-cost re-usable solution to onboard users safely and effectively.

- Off-the-shelf and customised solutions, including proprietary technologies
- Technologies range from resettable mechanical to smart features, such as sensors, audio and error-correcting
- Trainers designed to emulate actual device characteristics such as:
  - Shape and design
  - Needle insertion simulation
  - Forces: cap, unlock, actuation, breakout and glide
  - Sound replication
  - Plunger replication
  - Post injection safety

RESPIRATORY PRODUCT FEATURES – MDI & DPI TRAINERS:

- Off-the-shelf and customisable solutions, including proprietary technologies
- Technologies range from resettable mechanical to smart features, such as sensors, audio and error-correcting
- Trainers designed to emulate actual device characteristics
  - Shape and design
  - Inhalation forces
  - Sequence

CHOOSE NOBLE

As the number of patients being required to self-administer medication via drug delivery devices continues to grow, training and education will remain a critical success determinant of a patient's ability use these devices to safely and effectively and adhere to therapy. Novel training technologies such as mechanical and smart, error-correcting autoinjectors, prefilled syringes and pulmonary delivery devices, angle aid tools, auditory packaging and other multisensory solutions help empower patients to lead healthier lives.

In the modern era of patient-centric care, products that are able to provide superior onboarding and patient experiences will be well positioned and benefit by reducing patient errors, while improving patient satisfaction and outcomes.Noble's focus is to bring value to our clients, driving innovation in onboarding and device training.

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NEWGUARD™: SAFER PREFILLED SYRINGES & FEWER CHANGES

Given the rising number of guidelines to reduce risks of needlestick injuries, pharmaceutical companies have been searching for systems to ensure safe syringe use. Despite great innovations, adopting new safety systems has always been a trade-off between safety and the cost of implementing new processes. Now, Biocorp can offer Newguard™, a new passive safety system integrated on prefilled syringes without such compromises being required. Jean Vuillecard, Product Innovation Manager, Philippe Lesaulnier, Business Development Manger, and Eric Dessertenne, Head of Business Development, of Biocorp, explain more.

THE CHALLENGE OF INTEGRATING SAFETY SYSTEMS TO PFS

The frequent exposure to needles increases the risk of needlestick injuries. Given the rising number of reported incidents among healthcare workers, guidelines and best practices have been issued to avoid unnecessary handling and use of needles by encouraging the use of devices with safety features, and to promote education and safe work practices.

> "Biocorp has been developing a passive safety system requiring no change for pharma companies."

Hence, delivery systems – reducing the steps involved in drug administration and needle handling – have been preferred by the industry. Indeed, in addition to better cost-effectiveness, the switch from vials to prefilled syringes (PFS) brings comfort to end users in terms of safety and user-friendliness.

This growing trend has been followed by an increase in the number of safety devices preventing injuries. 'Clip-on' safety systems were added on PFS after the filling process in order to avoid any major regulatory changes. Although add-on systems bring increased safety to the syringes, they require additional assembly steps at the end of traditional PFS filling processes.

Today, integrated safety systems upgrade PFS with safety features without involving additional steps for pharmaceutical companies or the contract manufacturing organisations (CMOs) in charge of the filling operations. But despite great products, moving towards brand new safety systems appears to be challenging. Indeed, introducing changes appears to be costly and requires time-consuming efforts regarding the regulatory constraints and the industrial processes take years to be implemented.

To overcome these challenges and speed up adoption of innovative safety systems for PFS, Biocorp has been developing a passive safety system requiring no change for pharma companies. Therefore, traditional industrial processes remain unchanged while providing patients and healthcare providers with an innovative and effective safety system preventing injuries before and after injections.

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Figure 1: Newguard™, a passive safety system integrated with PFS.

NEWGUARD™, A PASSIVE SAFETY SYSTEM INTEGRATED WITH THE PFS

Newguard™ is a passive safety system integrated with PFS (Figure 1) and designed to be compatible with any existing syringe manufacturer's products. Newguard™ combines two functions in a single product: the function of a rigid needle shield (RNS) and the function of a safety device. The ultra-compact version fits 0.5 mL and 1 mL PFS and a specific version is available for 1 mL short and 2.25 mL syringes.

Newguard™ is the result of Biocorp's commitment to develop innovative solutions with simple implementation processes. Applying design for lean manufacturing methods in product and process development, Biocorp's R&D team has designed a solution providing an effective safety system for handling PFS, with minimal impact on industrial processes. As a consequence, every step of the PFS production process remains unchanged – despite the addition of Newguard™ – thus ensuring a cost-effective solution and a smooth and simple implementation for pharmaceutical companies and CMOs.

Indeed, integrating Newguard™ with a PFS is similar to the process of adding standard flexible/rigid needle shields on syringes. The assembly process takes place on the syringe manufacturer's production line for sterile format in nest packaging. Newguard™ is integrated with the syringes, replacing the RNS mounting. Thus, the number and the sequence of operations remain identical.

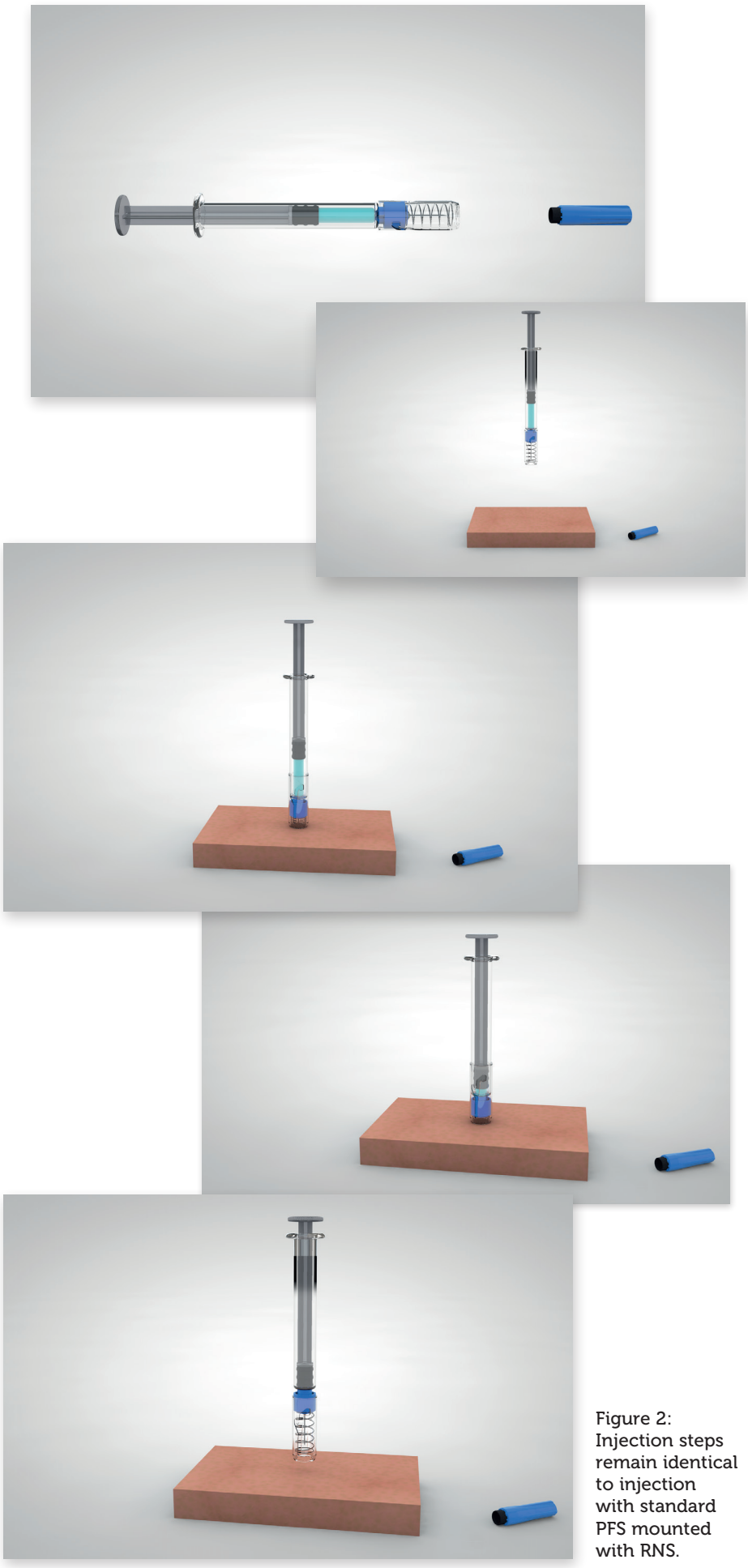

Figure 2: Injection steps remain identical to injection with standard PFS mounted with RNS.

Figure 3: Newguard™ is compatible with 0.5 and 1 mL PFS and fits nest tray packaging.

> "Newguard™ is definitely a cost-effective solution upgrading the safety standards of PFS without changes being required."

The same applies for end-users: the injection process should remain unchanged compared with a PFS equipped with a RNS (Figure 2). As a matter of fact, adoption of new passive safety systems integrated to PFS is strongly related to the balance between benefits and inconvenience perceived by end users.

This is the reason why Newguard's design has been welcomed by patients and healthcare providers. Human factors studies revealed Newguard's shape is very close to a traditional PFS; it looks less daunting and more familiar thus making patients feel safe before, during and after injections. This sense of safety has been enhanced with Newguard's "spring effect" adding comfort and confidence at the end of the injection process.

ENHANCE SAFETY WHILE KEEPING PROCESSES UNCHANGED

Upgrading your PFS with Newguard™ doesn't require you to change your procurement strategy, supply chain or regulatory files.

Newguard™ has been designed to ensure full compatibility with glass syringes and elastomers available on the market. Hence, it offers an open source solution meaning pharmaceutical companies and CMOs are free to choose partners. Adding the Newguard™ safety system doesn't require a change to the purchasing strategy. Since Newguard™ is delivered pre-assembled on the PFS, it avoids an increase in the number of items to be purchased. Similarly, Newguard™ is a passive safety system compatible with PFS 0.5 and 1 mL. Therefore, purchasing a unique passive system suitable for both 0.5 and 1 mL PFS allows a reduction in the cost per unit.

Newguard™ is a new generation of passive systems designed to reduce the total cost of operations (TCO). Indeed, the filling process remains unchanged as well as the packaging process. As the Newguard™ is assembled directly on PFS, available in bulk or packaged on validated nests (Figure 3) and/or tubs and sterilised like standard PFS, there is no requirement to change the secondary packaging or the sterilisation process. The supply chain remains unchanged.

Newguard™ is definitely a cost-effective solution upgrading the safety standards of PFS without changes being required. The primary packaging remains intact avoiding constraining and time-consuming modification of the regulatory files. Furthermore, the filling operation remains unchanged and doesn't require additional process validation.

CONCLUSION

Newguard™ is a unique safety solution for PFS and generates new benefits for pharmaceutical companies in terms of supply chain, TCO and packaging, and meets both the economic criteria and the end-users' protection requirements.

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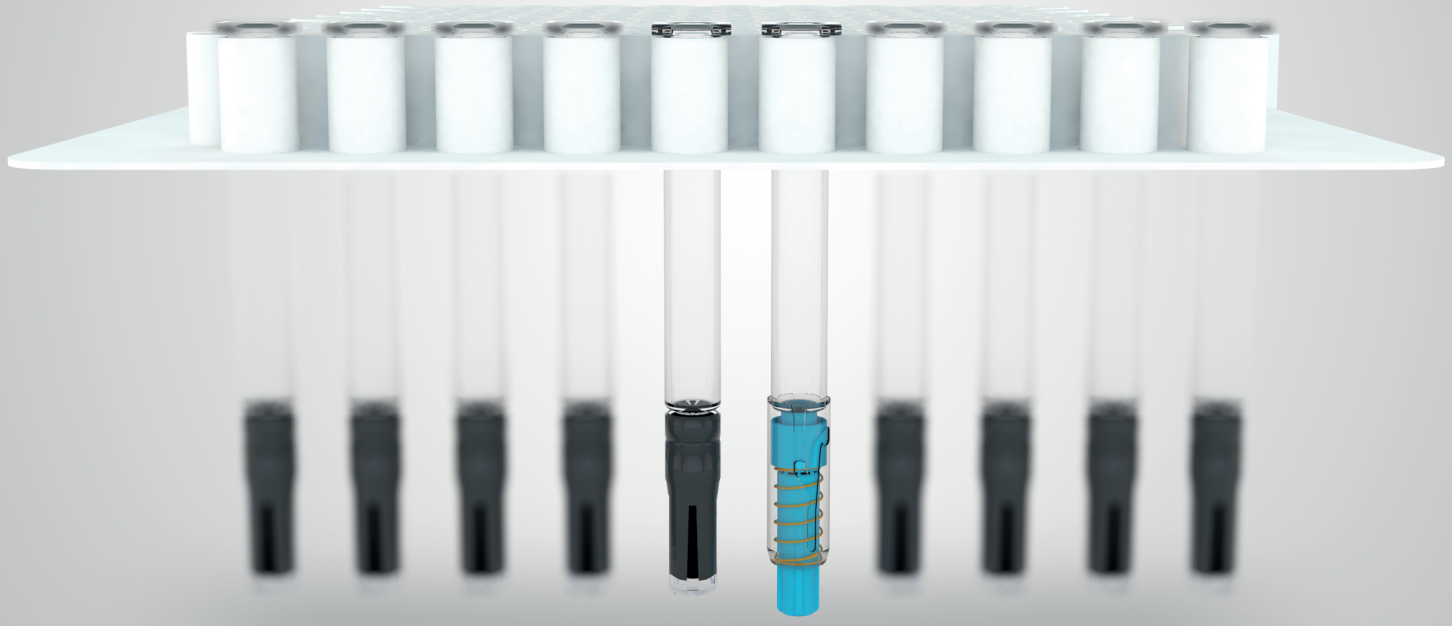

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WEIBEL CDS AG
safer, easier and faster drug delivery

DRUGDELIVERYSYSTEM FOR STANDARD 1 ML LONG PREFILLED SYRINGES

How can drug delivery systems help in patient compliance? What are the challenges to be encountered with novel drugs filled in 1 mL long prefilled syringes? These questions are discussed in this article by Ludwig Weibel, Chief Executive Officer, and Hans Peter Manser, Business Director, of Weibel CDS. A novel and innovative approach is presented meeting the requirements of today's and future drug applications.

SAFER, EASIER AND FASTER DRUG DELIVERY

Following our mission to support safer, easier and faster preparation and administration of drugs, we have developed and produced innovative, user friendly, application-oriented injection systems and devices. All functions and parts needed for a specific drug application are integrated into one product. The user only opens one package and the complete handling is done in a closed system in order to reduce contamination, handling errors and needlestick injuries, combined with saving time.

TODAY'S SITUATION

Prefilled syringes are increasingly becoming the primary packaging standard for new drugs, especially for biologic drugs. Changes in drug administration to improve drug acceptance require strict adherence to the regimen given by the pharmaceutical company or the doctor prescribing the drug.

Today's solutions are often based on the use of autoinjectors with two limiting factors. Firstly, although the injection itself is automated it still depends on the patient's ability to handle the system as well as more importantly their adherence to the timing given to inject. Secondly, using autoinjectors means always making a bolus injection within seconds, not allowing for a regimen spread over minutes, hours or even days, thus limiting the possibilities for long-term treatment.

> "Besides the requirements defined by the drug itself, the cost factor is, and will increasingly be, a major element in the decision-making process of pharmaceutical companies."

CHALLENGES TO MEET

Besides the requirements defined by the drug itself, the cost factor is, and will increasingly be, a major element in the decision-making process of pharmaceutical companies. The overall cost of applying a specific drug will be focussed on the healthcare setting rather than the cost of the drug itself as outpatient and homecare treatments gain importance.

Yet, as described by the authors in a previous article,[1] the big challenge for such systems is to be ready to use as well as preloaded, since handling by the patient may lead to dangerous situations due to the toxicity of the drug or handling errors.

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Figure 1: The system is small yet all the functions are incorporated.

Figure 2: The plastic holder includes the 1 mL long syringe.

> "Patient compliance with the regimen is the key to the efficacy of the drug prescribed achieving the desired result."

Another set of challenges is given by the drug itself. High viscosity of drugs for stability reasons is increasing. In some cases the viscosity may even exceed values of 1000 centistokes. Also shear forces can have a negative effect on biological drugs in either turbidity or molecular weight due to damage done to the protein chains during application, for example by the pump.

Last but not least, patients' rising expectations in mobility as well as having total freedom to move about are adding to the list.

IMPROVED PATIENT COMPLIANCE

Patient compliance with the regimen is the key to the efficacy of the drug prescribed achieving the desired result. Various elements may impact on this, for example, the preparation required since self-medication is heavily dependent on the ability of the patients to prepare and manipulate the injection device. This can be a major issue especially for elderly patients.

The exact starting time of the injection or infusion as well as the speed of injection or infusion is another critical element. Speed is especially important as a low speed may positively reduce side effects.

SYRINGE-BASED DRUGDELIVERYSYSTEM

This system is designed to accept standard 1 mL long syringes (Figure 1). It is extremely small yet still incorporates all functions required including a unique pump system, a needle insertion system, a battery, a drive and an electronic control unit.

Designed to suck out the drug instead of pushing it out, the system doesn't require any type of plunger rod so the overall length is barely larger than a 1 mL syringe.

The system is designed as a patch pump with all required functions built-in. The device may be operated via an external control unit. Depending on the drug, it may be attached to the patients' body – often the abdomen – by healthcare personnel or eventually by the patient themself.

If attached by healthcare personnel all the required settings including the starting time of the injection or subcutaneous infusion may be pre-set so not requiring patient interaction at all. Visual and audio signals will alert and inform the patient once the administration starts and when it is finished.

Syringe Pre-loaded in Plastic Holder

The 1 mL long syringe is pre-loaded in a plastic holder (Figure 2) enabling healthcare personnel or the patient to control the drug prior to its use. The needle shield is taken off with a plastic cover protecting it prior to the insertion of the holder including the syringe into the system. The needle size of the 1 mL long syringe is non-critical and can be chosen by the pharmaceutical company. The length should preferably be half an inch (12 mm).

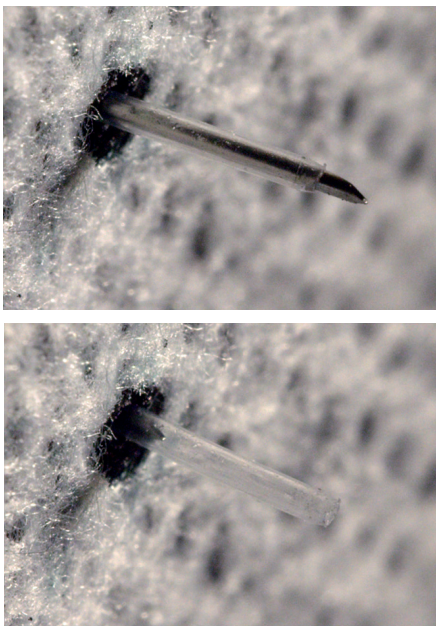

Figure 3: Automatic needle insertion system with soft cannula remaining in the body after insertion.

Automatic Needle Insertion System
The automatic needle insertion system, including a soft cannula, assures the highest comfort to patients (Figure 3). After launch, the steel needle penetrates the tissue and sets the soft cannula in place. Immediately thereafter the steel needle is retracted and moves into a locked position making a dual use impossible and most importantly eliminating the risk of needlestick injuries.

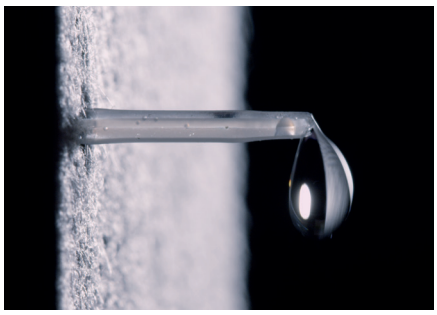

Figure 4: The proven pump system can deliver drugs at a high viscosity.

Proven Pump System
The proven pump system, also used for 3 mL insulin cartridges, is extremely powerful overcoming the break-loose forces and offering a smooth gliding of the rubber stopper during injection (Figure 4). Depending on the pump size, the lowest dose increments of 16 nL to 5.6 µL are achievable resulting in highest accuracy for both basal and bolus injections. If required, a purge function may be included prior to administration.

The pump system has been tested for accuracy as well as for its ability to deliver drugs with a viscosity of 1000 centistokes and more (Figure 4). Furthermore it has been proven that there is no damage to proteins due to shear forces and thus no negative effect on biological drugs in either turbidity or molecular weight.

System Control
The software used to control the DRUGDELIVERYSYSTEM offers the highest degree of flexibility. Various levels of access are provided to guarantee its proper use. The pharma company can set the overall limits relative to the drug administered, doctors or healthcare personnel can define the patient's specific settings and the patient can, for example, start the injection or infusion by pressing a button – or this step can be done by healthcare personnel.

Options
Other syringes sizes besides the 1 mL long are possible requiring only a change of the device housing as the connection of the syringe with the device remains the same.

CONCLUSION

The DRUGDELIVERYSYSTEM offers full integration of all functions and parts. The advantage for the end user is a saving in time and a reduction in:

- Contamination
- Handling errors
- Needlestick injuries.

Pharmaceutical companies can differentiate themselves from competition. The final design is according to your specific needs from a functional as well as design perspective.

PORTFOLIO

Weibel CDS also offers:

- LVDs (Large Volume DRUGDELIVERYSYSTEM) based on our MiniBagSystem concept for micro infusions of up to 30 or even 50mL.[1]
- DRUGDELIVERYSYSTEM 3mL cartridge based.[2]
- DRUGDELIVERYSYSTEM with automatic reconstitution functionality.

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

The Reconstyringe® product family is first in offering a fully automated reconstitution of lyophilised drugs. The drug is contained in its original vial, the solvent in the MiniBagSystem. With a spring mechanism and holder plates the content of the MiniBagSystem is emptied into the vial. Like a Swiss watch, it runs through the full reconstitution cycle. Finally, the drug is drawn into the SuperCapSyringe® for injection.

Both the SuperCapSyringe® and the Reconstyringe® were discussed in greater detail in previous issues of ONdrugDelivery Magazine.[3]

Squeezer Test and Application System for stability testing of drugs in the MiniBagSystem. For clinical studies and small-scale productions Weibel CDS offers CMO filling services, facilitating your project and giving you a head start without the need for large investment.

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

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DrugDeliverySystem
Syringe based

Designed to accept 1mL long syringes, yet barely larger than the syringe itself, the system is extremely small and still incorporates all functions needed.

safer, easier and faster drug delivery

International patents pending

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PRODUCT SHOWCASE: PremiumCoat™

Aptar pharma

"The first design to be released in 2015 was a 20 mm coated stopper. We widened our PremiumCoat™ range introducing a 13 mm coated stopper in 2016, and we are now striving to extend our offer with our 1 mL plunger."

PremiumCoat™ (Figure 1) is a novel range of elastomeric stoppers developed by Aptar Pharma and 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. As a result, compatibility of the drug and the closure is significantly superior.

The first design to be released in 2015 was a 20 mm coated stopper. We widened our PremiumCoat™ range introducing a 13 mm coated stopper in 2016, and we are now striving to extend our offer with our 1 mL plunger. 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. It was to meet this demand that Aptar Pharma developed the PremiumCoat™ range of elastomeric stoppers.

PROVEN INNOVATOR

Our experience in elastomeric closures and container closure systems is supported by the capabilities of our International Technical Center 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.

Figure 1: PremiumCoat™ The alternative coated components for sensitive drugs. (Image courtesy Aptar Pharma)

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US FACILITY EXPANSION

Furthermore, in Congers, NY, US, Aptar Pharma is also nearing completion of its expansion at its state-of-the-art manufacturing site (Figure 3). The new space will enable the company to better serve North American pharmaceutical customers, as injectable elastomeric component manufacturing will be completed in the US for the first time by Aptar.

Final construction is planned by the end of the first quarter of 2017 so that Aptar Pharma can anticipate shipping validation batches to customers in the second quarter. The expansion is part of a stepped program to increase Aptar Pharma's footprint in the US.

The increased facility space enables the company to conduct all of our finishing operations in the US, including PremiumCoat™.

Bas Van Buijtenen, President of the Injectables Division of Aptar Pharma, said: "We are bringing all of our knowledge and the value-adding parts of our process closer to the customer. We want our customers to know us better, to understand what we can do for them on an entirely different level."

PREMIUM 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 PHARMA

Aptar Pharma 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 Pharma Injectables 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.

Aptar Pharma is part of the AptarGroup family of companies, along with Aptar Beauty + Home and Aptar Food + Beverage.

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

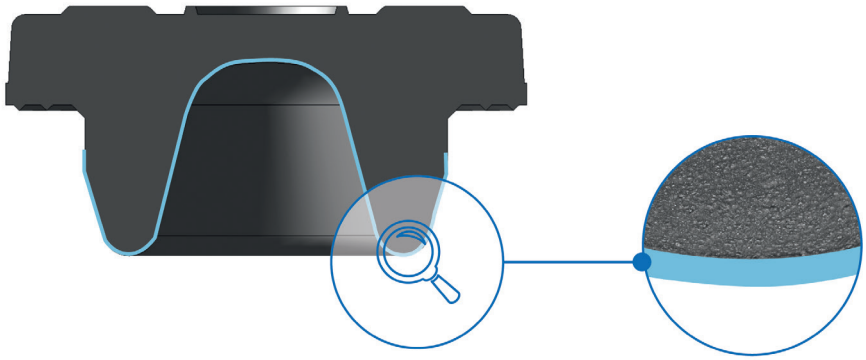

Figure 2: A barrier film covers the drug contact area. (Image courtesy of Aptar Pharma)

Figure 3: Aptar Pharma nears completion of injectable elastomer component capacity in its existing Congers, NY, US site. The new space will enable the company to better serve North American pharmaceutical customers. (Image courtesy Aptar Pharma)

PREMIUMCOAT™ AT PHARMAPACK EUROPE

Aptar Pharma will showcase PremiumCoat™, the alternative coated stopper for sensitive drugs, at Pharmapack Europe, Paris, France, on February 1-2, 2017.

Joel Cotten, Business Development Director, Aptar Pharma, will give a presentation entitled, "Interest and Limits of the Coated Stoppers Offering" on Day 2 (Thursday, February 2nd, 2017) in the Learning Lab from 3.20-3.50pm.

Joel Cotten leads Aptar Pharma's business development activities in the injectable field. Mr Cotten is an expert in business development related to medical devices, primary containers and self-injection devices.

Visit Aptar Pharma at Pharmapack, Booth Number F7.

SPRING DEVELOPMENT FOR MEDICAL DEVICES

This article by Neil Fletcher, Technical Sales Manager, Advanex, provides a spring manufacturer's perspective of how springs can be used in medical devices, and how a lengthy and extensive device development process affects normal custom and practice in our industry. The report focuses on spring technology and highlights some of the challenges that spring manufacturers face daily.

Many global organisations will be familiar with our work already but many are not. We believe mechanical springs in drug delivery systems offer the best value for money despite increasing regulatory requirements that are today shared by the entire supply chain. Springs are frequently key to the device function, operation or retraction so it should not come as a surprise to hear that any proposed change in the spring manufacturing process is treated by customers and the regulatory bodies with extreme caution. Lots of extensive device testing and revalidation has to be carried out in response to a relatively small change in how the spring is made.

"Springs are frequently key to the device function, operation or retraction so it should not come as a surprise to hear that any proposed change in the spring manufacturing process is treated by customers and the regulatory bodies with extreme caution."

As a leading spring manufacturer and component supplier to the medical device market we have witnessed many changes in our business over the years. For instance, traditional spring manufacturing methods would allow different equipment to be used for the same spring dependent on machine availability and workload. Today, only specific validated equipment can be used and in many cases each machine is dedicated to one part only.

Obviously, a carefully controlled and clean working environment approved to ISO 13485 should be maintained, and equivalent processes made available to ensure business continuity and guaranteed supply. Multiple locations, all capable of producing identical components on identical equipment, are also important to minimise strategic or catastrophic risk.

This responsibility should never be underestimated because a patient's life could depend on it! This comment may seem extreme, but if risks can be avoided, they must be avoided. You can see from the photograph that equivalent machines are used and identical process flows are carried out for high-volume production (Figure 1).

Traditional ways of working with spring materials have also evolved into widespread Good Manufacturing Practice (GMP), and accredited practices with extensive controls and de-risking activity. It is comforting to report that extensive testing

"Essentially the company that is registered as the design authority assumes overall responsibility for the function of the device in conjunction with the drug supplier. This is supported by extensive testing and product and process validation work over many years. Components are specified by the design authority and the supplier agrees to supply parts to a detailed user requirement specification (URS) rather than just a component drawing."

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Figure 1: The factory floor at Advanex.

of all products in a medical device is carried out by everyone in the supply chain, and even the spring manufacturing process has to follow a clearly defined validation plan.

It is an added bonus that general purpose spring coiling machines can be used for low-volume developments and, at a later stage in the engineering process when cGMP product is required, more bespoke production equipment can be offered and supplied specifically for higher volume commercialisation.

Dimensional control and extensive quality assurance are the key factors here, but of course the unit cost of each component is crucial when devices are complex and contain lots of features. Spring manufacturers in Europe offer either low volume development capacity or high volume manufacturing capabilities but few offer the complete package. Some companies, such as Advanex, choose to design and develop their own production equipment prior to commercialisation. Our engineering process route is shown in Figure 2.

Confidentiality is key here and supply companies have to sign detailed secrecy and non-disclosure agreements with their clients to protect know-how, intellectual property, and any unique features of the device that create a competitive advantage.

Time-to-market here is constantly being driven downwards as competition in the lucrative drug market increases, and the choice of devices under development continues to grow. Manufacturing and supply contracts are also quite complicated for any spring manufacturing company, and as official documents are compulsory and usually generated by the client, it is worth taking legal advice before signing.

FIT FOR FUNCTION

Essentially the company that is registered as the design authority assumes overall responsibility for the function of the device in conjunction with the drug supplier. This is supported by extensive testing and product and process validation work over many years. Components are specified by the design authority and the supplier agrees to supply parts to a detailed user requirement specification (URS) rather than just a component drawing.

Risk analysis is frequently carried out and combined with statistical process controls at the source of manufacture, and consistency of supplied product is maintained and supported by test data with every batch. Full traceability is provided with unique production data and batch samples retained for many years.

Minimising particulate is critical and today we have become just as experienced in cleaning stainless springs as we are with spring manufacturing. Bacterial testing on spring batches can also be provided on request too.

DESIGN FOR MANUFACTURING

Critical features of the component are agreed. Practical working tolerances are specified and the most suitable materials are sourced from the same manufacturer. However, various heat numbers are introduced during validation to monitor this crucial variable.

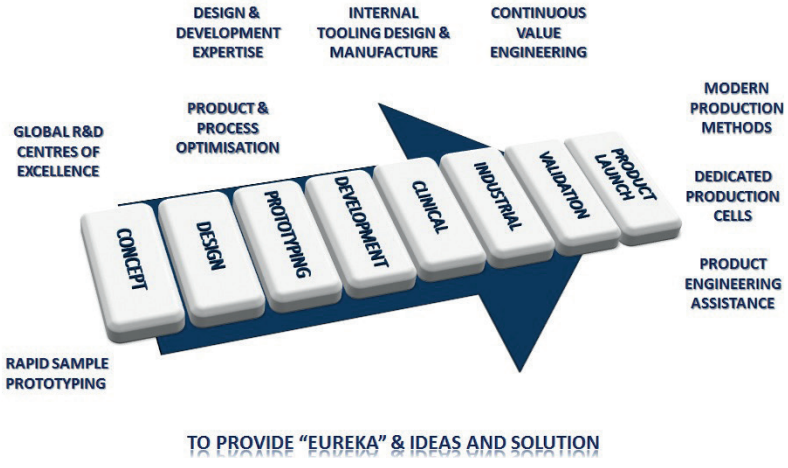

Figure 2: The engineering process route.

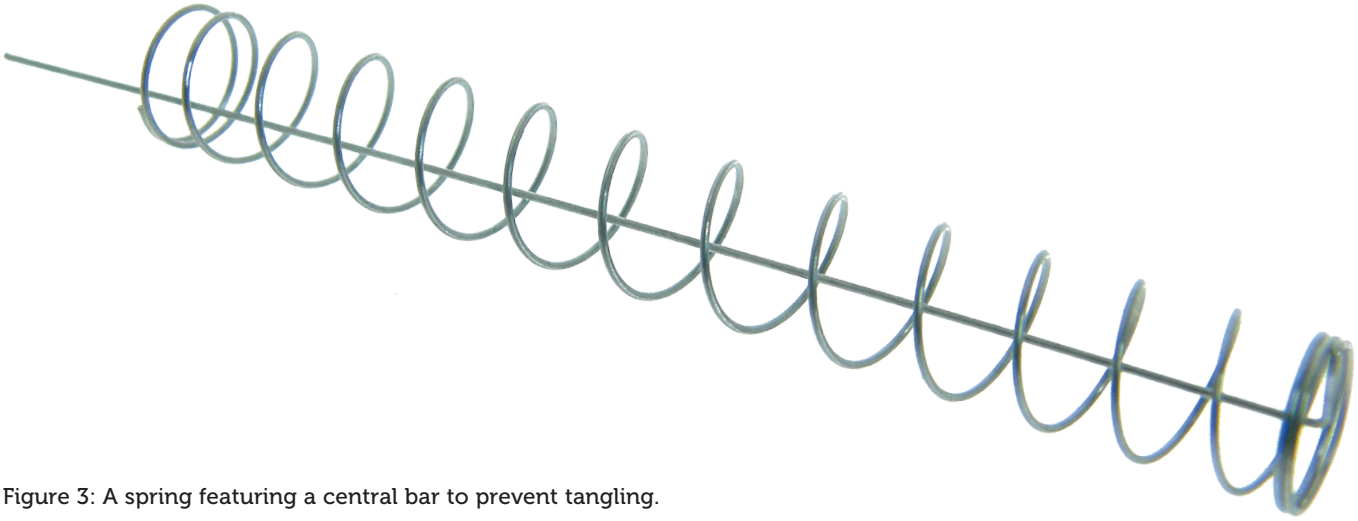

Figure 3: A spring featuring a central bar to prevent tangling.

DESIGN FOR PERFORMANCE

Springs are normally heat stabilised immediately after forming. The loading requirements at selected positions will determine what spring shape is required but once selected the shape can be specified as part of the dimensional control and features.

Heat treatment on stainless steel springs is necessary to relieve the stresses induced in the wire drawing and spring coiling processes, to stabilise the spring dimensions, and to raise the elastic limit. This process is usually carried out by means of an in-line oven. The heat treatment temperature requires careful consideration since, ideally, the spring will benefit functionally, from temperatures of 400-450°C, although temperatures this high can result in discolouration of the wire, which most design authorities do not like. The heat treatment temperature selected therefore represents a compromise between optimum performance and acceptable surface colour.

Likewise, low temperature heat treatment is recommended for carbon spring steels. For these materials, the temperature is normally in the range 200-375°C.

Critical features of the design as described in the URS are monitored during production and data collected at an agreed frequency. The specified components have to withstand ageing and extreme environmental testing, and must not prevent the device from working, sometimes years into the future. Usually, device testing of this nature provides the most relevant data but selected component testing may also support this activity.

DESIGN FOR ASSEMBLY

Several highly experienced suppliers of automatic assembly equipment provide practical solutions to improve handling and feeding of components during assembly. However, the spring supplier can also advise on how their components can be supplied and protected during transit by relatively low-cost improvements. The most common practice of using re-useable tray packing in rigid containers is favoured due to the small footprint required for a tray handling system.

One novel design concept for high index compression springs includes a central bar which prevents tangling. The bar has to be removed during final assembly but then this delicate spring (Figure 3) can be bowl fed into the perfect position for loading in to the device.

Springs in medical devices often have large indices. The index of a spring is calculated by dividing the mean diameter by the wire diameter, and the result is used by springmakers as a measure of coilability. The normal spring index range is considered to be 5 to 13, but the higher limit is frequently exceeded in device applications. Values of over 20 are common, and figures over 30 are certainly not unknown.

> "For many years now, safety syringes have been available as the preferred alternative to the conventional syringe that is still extensively used by doctors and hospitals around the world."

The spring pitch is also an important feature. The pitch is the distance between the centre of the wire on any coil to the centre of the wire on the adjacent coil. If the pitch is around two wire diameters in size, the springs may tangle badly when parallel to each other in processing or storage. Larger pitches may allow 'cross tangling' to occur. Frequently, the spring may be designed with closed-coil sections, at each end, and/or in the centre, with the intention of reducing or eliminating the likelihood of tangling. The designs of medical device springs though, often mean that a degree of tangling is inevitable, so the device assembler must decide if this difficulty is acceptable, or

Figure 4: An ISO Class Clean Room at Advanex.

whether bespoke packaging is needed to avoid the issue fully. If this is necessary, the cost of the springs will be increased by the need for manual packing, or for automated packing if the required volumes are large enough to justify the investment in robotic equipment.

Also of importance in spring geometry is the slenderness ratio. This is calculated by dividing free length of the spring by its mean diameter, and is a measure of stability. If the relative deflection of the spring exceeds a calculated critical value, the spring will buckle, meaning that it will require support if this is to be avoided. A spring which needs support will be less predictable in terms of the forces it will deliver. This is because there will be a degree of friction between the inner or outer diameter of the working coils of the spring, and its mating components. This friction may interfere with the calculated force at any given position.

APPLICATIONS

Safety syringes have a safety mechanism built into the syringe. One very successful patented design uses a mechanical spring to retract the hypodermic needle back into the syringe body after only one use. The spring is held under load for a considerable time until it is activated. Therefore relaxation and ageing tests are extensively carried out under extreme conditions.

For many years now, safety syringes have been available as the preferred alternative to the conventional syringe that is still extensively used by doctors and hospitals around the world. Originally designed to prevent needlestick injury to both health professionals and patients, the single-use safety syringe has, without doubt, saved millions of lives over the years. Using a more expensive safety syringe has its own commercial challenges of course but as the number of units increase the unit cost will fall and the cost differential to conventional syringes will reduce.

As you might expect the required level of cleanliness of the spring component here matches, and in some cases exceeds, that of inhalers, and extensive testing and regulatory approvals have to be gained and maintained.

SUMMARY

This article is not a detailed scientific report and is based on the personal experience of the author and our industry knowledge only. The intention here is to share our experiences with a wider audience and does not intend to favour any one manufacturer of devices. We regularly see many innovative and creative ideas during our development work but these are always supported by full confidentiality agreements. Therefore we are not allowed to share details of any such device and have deliberately limited direct references to devices that have been in the public domain for over five years, and our know-how on design and manufacturing of springs for medical devices.

For further information please contact Jonathan Dyas, Global Marketing & Sales Assistant, Advanex, +44 1636 815 555.

THE AUTHOR

Neil Fletcher, Technical Manager, has worked for Advanex for over 39 years in a variety of technical roles. Neils' role as Technical Manager involves offering support and advice to customers regarding their spring requirements.

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PRODUCT UPDATE: SCHOTT's adaptiQ® and Vials DC

SCHOTT
glass made of ideas

"The adaptiQ® concept permits pharma firms to fill different container formats on one production line while minimising burdensome changeover times in between."

ADAPTIQ® PORTFOLIO EXPANDED

SCHOTT has expanded its adaptiQ® portfolio of ready-to-use pharma containers (shown in Figure 1) to meet growing market demand from drug manufacturers. The latest nest format will be able to hold 20R, 25R, or 30R ISO vials when it is released this year, and will add to the existing 2R to 15R formats.

The adaptiQ® concept permits pharma firms to fill different container formats on one production line while minimising burdensome changeover times in between. SCHOTT developed adaptiQ® to be compatible with the industry's filling and finishing equipment, and collectively, industry leaders such as Bausch & Stroebel, Bosch Packaging Technology, Groninger, Optima and Vanrx have tested and verified adaptiQ® on a large number of machine types.

This ready-to-use packaging solution enables pharma companies to react more quickly to new industry trends without building specific manufacturing capabilities. The vials are nested securely, protecting them from scratches caused by vial-to-vial and vial-to-machine contact, and reducing breakage and contamination. As they are already sterilised, pharma companies can load them directly onto filling lines without expensive and time-consuming washing, sterilising, and depyrogenation.

Figure 1: adaptiQ® concept allows different container formats to be filled on one production line.

"Razor-thin margins and regulatory pressure have forced pharmaceutical manufacturers to make smarter packaging choices," said Christopher Cassidy, Vice-President of Sales and Marketing for SCHOTT's Pharmaceutical Systems Business in North America. "When the 20-30R ISO format comes online, SCHOTT will give pharma companies even more flexibility. The entire portfolio of ready-to-use vials allows pharma companies to trim costs while boosting efficiency, leading to higher profits."

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"The question of how effectively buffer systems can be stored in the new bottle was examined more closely. The result: if the respective substances were stored in SCHOTT Vials DC, the vials remained stable and no glass delamination was observed."

SCHOTT VIALS DC NEW SCREENING STUDY

Separately, a new series of studies has once again demonstrated the effectiveness of SCHOTT Vials Delamination Controlled (Vials DC, Figure 2). These pharmaceutical vials have a particularly high chemical durability and are therefore less susceptible to delamination. SCHOTT has had this property confirmed in various storage studies.

First, substances were used that have already caused product recalls due to delamination. In a second series of studies, the question of how effectively buffer systems can be stored in the new bottle was examined more closely. The result: if the respective substances were stored in SCHOTT Vials DC, the vials remained stable and no glass delamination was observed.

The delamination studies were conducted in accordance with USP1660 using two different types of formulations: a KCl 15% solution and a $Na_2S_2O_3$ 10% solution for both of which recalls due to delamination had been announced. Nevertheless, established buffer or formulations that are often used to develop drugs were also tested, for instance ultrapure water, citrate buffer, phosphate buffer, sodium bicarbonate buffer and ethylendiamintetraacetic acid (EDTA).

Figure 2: SCHOTT Vials DC bring delamination under control.

Product Manager Florence Buscke said: "Both series of studies clearly show that switching to SCHOTT Vials DC as primary packaging materials significantly reduces the risk for pharmaceutical manufacturers to experience delamination recalls."

AVAILABLE IN MANY SIZES

Thanks to SCHOTT Vials DC, pharmaceutical companies now have an interesting alternative course of action against the phenomenon of delamination, the detachment of flakes from the inner glass surface due to interaction of the formulation with the pharmaceutical vials. SCHOTT Vials DC are based on established hot forming principles without any additional post process steps and can therefore replace the packaging that is already being used with approved drugs without causing expensive re-registration. The vials are available in the ISO sizes 2R to 10R. SCHOTT has also already produced larger sizes to meet individual customer needs, for example, a large-scale 50 ml vial for a biotech company based in the US.

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ZAHORANSKY
PERFECTLY DIFFERENT

MORE PRODUCT EFFICIENCY BY FULLY AUTOMATED PRODUCTION PROCESSES

In this article, Harry Pruner, Freelance Journalist, Pruner Marketing Services, gives a run-down of the machines and production lines manufactured by ZAHORANSKY for the production of ready-to-fill, prefillable syringes.

Downtime costs money. This is why ZAHORANSKY Automation & Molds GmbH from Freiburg has always developed machines with high uptime. A good example of the implementation of high requirements such as these is the unmanned, fully automated production of drug delivery systems. The in-house machine and mould construction by ZAHORANSKY connects the various upstream and downstream machine assembly groups of plastics processing into one fully automated process chain. ZAHORANSKY thereby offers the complete production process and the entire process chain of added value from a single source. This means that the complete control of the peripheral devices runs via the central, user-friendly system control which is also programmable from memory.

Z.BLIZZARD SYSTEM FOR GLUELESS PRODUCTION OF STAKED-NEEDLE SYRINGES

The process of the complete system starts with a Needle Feeding system and the Z.BLIZZARD system (Figure 1) for the glueless production of staked-needle syringes (Figure 2). Z.BLIZZARD is an integrated automation solution in a modular design, allowing the isolation and glueless overmoulding of cannulas. The Z.BLIZZARD system features both a needle feeding system (Z.NFS) and the injection moulding machine with mould (Figure 3) 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 thus be aligned automatically and then carried to downstream processing.

> "In order to exclude the disadvantages of side gating systems completely, ZAHORANSKY decided on a different and brilliantly simply solution. A specially developed hot runner nozzle injects the thin-walled medical part directly at the flange. This surprisingly easy solution enables the creation of the perfect injection point."

ZAHORANSKY offers needle isolation systems 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 readily handled and there are plans for more model sizes to enlarge the delivery range.

PATENTED STACK MOULD SYSTEM

Medical engineering makes very specific and high demands on the design

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Figure 1: Z.BLIZZARD automation solution for the glueless productions of staked-needle, ready-to-fill prefillable syringes.

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

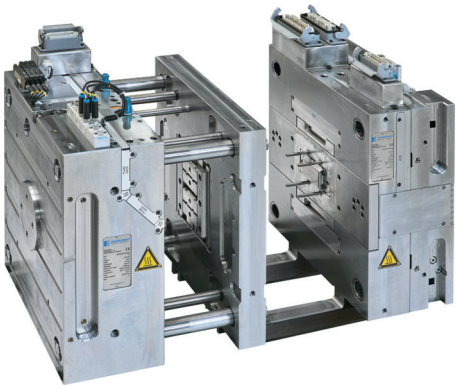


Figure 3: Injection mould for staked-needle syringes.

and construction of injection moulds. The preferred systems involve full hot runners with needle valves. For long, thin and tubular injection mouldings – for instance for syringes – a gating solution has its limits. For side gating, there are the commercial open systems, or gating to the moulding must be made via a cold runner as a compromise. In the needle valve technique, the limits of the feasible are quickly reached, however.

In order to exclude the disadvantages of side gating systems completely, ZAHORANSKY decided on a different and brilliantly simple solution. A specially developed hot runner nozzle injects the thin-walled medical part directly at the flange. This surprisingly easy solution enables the creation of the perfect injection point.

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 energy loss and quickly accomplish a thermal equilibrium in the system. The material used is a high-grade technical polymer, mostly cyclo-olefin copolymer (COC) or cyclo-olefin polymer (COP).

The closing needle and/or the closing mechanism can be controlled pneumatically or via servomotor depending on the application. In turn, needle control is integrated in the control of the complete system. This offers significant advantages in particular for medical items which are produced in clean-room conditions.

> "In the near future, intelligent production will become standard in the industry. This includes the close interconnection between IT and production technologies. The people, machines, production means and products thereby closely communicate with one another."

MOBILE EXTENSION UNIT FOR AUTOMATED EXTRACTION

The mobile extension unit Z.SIROC (Figure 4) is the heart for the integration of all upstream and downstream processing. This is a standardised unit for the automatic feed-in, assembly and removal directly at the injection moulding machine, used exactly where it is necessary for part removal. This module including its safety housing can be easily moved by hand lift truck and be adapted to any appropriately equipped injection moulding machine.

The take-out unit is currently available in three different versions: the overhead or vertical unit fitted with a six-axis robot made by Kuka (Augsburg, Germany), and the unit with sideload using a linear robot.

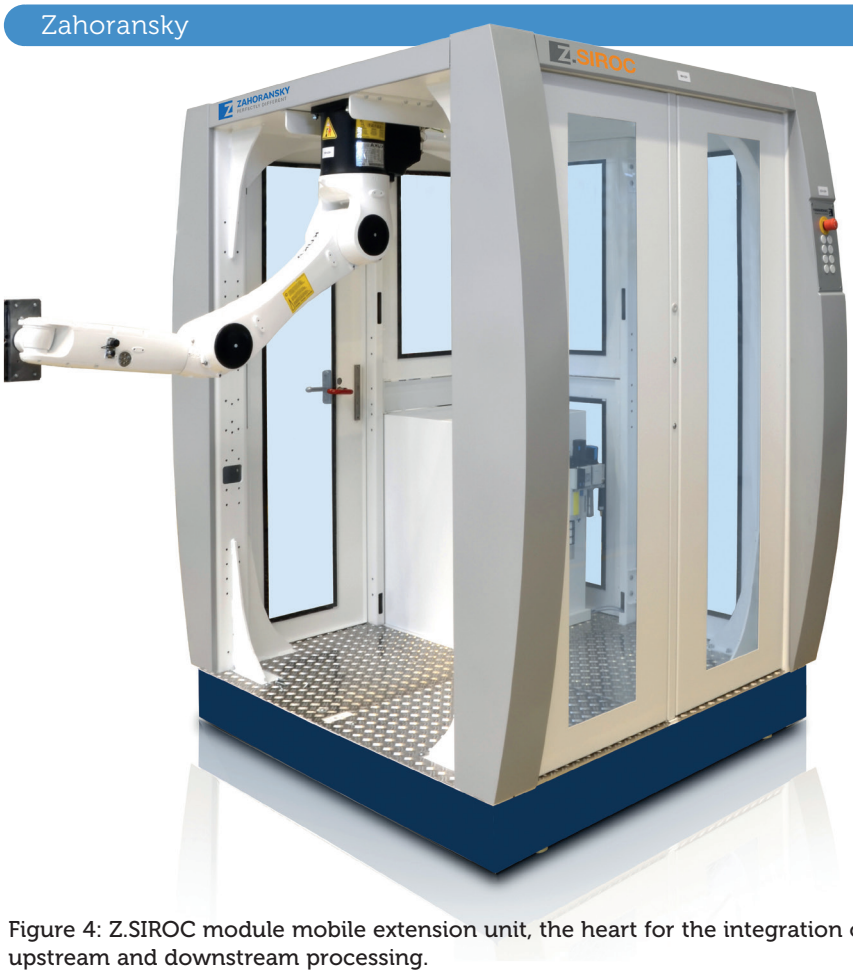


Figure 4: Z.SIROC module mobile extension unit, the heart for the integration of all upstream and downstream processing.

UNIVERSAL LOADING & UNLOADING SOLUTION FOR INTELLIGENT PALLETISING

The produced injection moulded parts are removed by a tray loading and unloading unit with linear pass of the trays. The downstream palletising system Z.LODOS (Figure 5) automatically stacks the trays including the parts for further production steps. A six-axis robot removes the finished parts from either a tray-unloader or a side conveyor.

HOLISTIC SAFETY ASSESSMENT

Safety technology is an aspect which is often neglected during the setup of integrated facilities. Laying out the individual components of a facility according to the applicable machine guidelines is not sufficient. It is essential for the operators of such plants to ensure that a uniform safety guarantee in the form of CE conformity is applied to the entire plant. Professional generation of an overall CE marking on the basis of years of system technology experience is given upon customer request. In this case, a specialist department not only tests the CE conformity of in-house components, but it also tests and secures the facility components applied by other manufacturers.

In the near future, intelligent production will become standard in the industry. This includes the close interconnection between IT and production technologies. The people, machines, production means and products thereby closely communicate with one another. The major advantages of this data connection are:

- Quick adaptation of capacities to machine variations
- Short-term adaptation of production to various product variants.

With the implementation of a fully automated procedure for the complete process chain, ZAHORANSKY has come one step closer to the vision of Industry 4.0.

Figure 5: Z.LODOS downstream palletising module for tray handling.

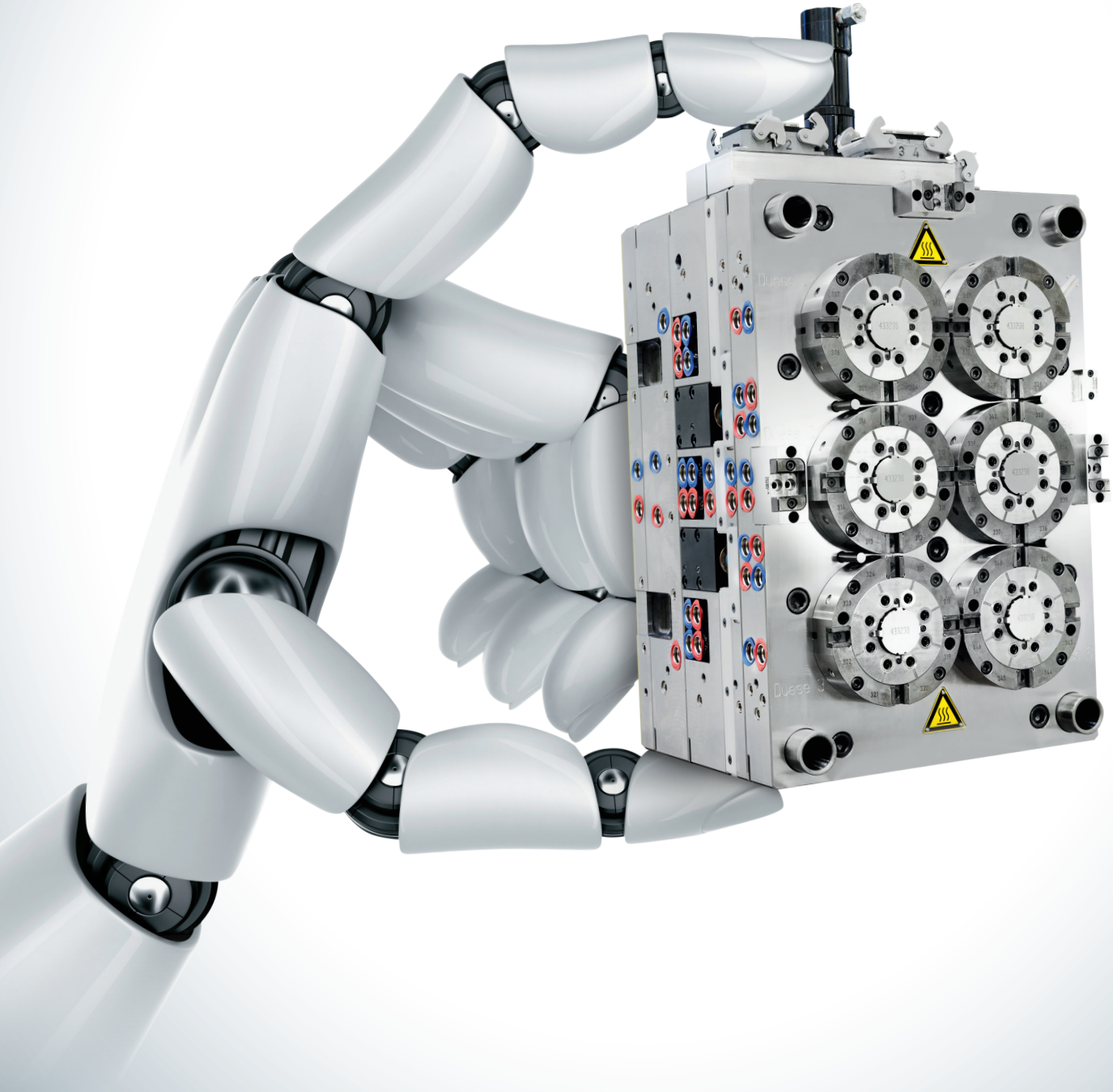
ADDED VALUE FROM ONE SINGLE SOURCE

System technology offers across-system solutions for the injection related automation. These systems are based on injection moulds by ZAHORANSKY and on established systems from different modules of automation. Intelligent and injection-related automation solutions can be composed with these modules. ZAHORANSKY serves the areas industrial automation and medical devices, with pre-configured solutions provided for medical engineering.

ABOUT THE COMPANY

ZAHORANSKY AG is a full-range supplier of 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.

The One-Stop Solution Provider
for Automation & Molds



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COMPANY PROFILE: AVERY DENNISON

GLOBAL R&D AND TECHNICAL SUPPORT

As labelling technology continues to develop, pharmaceutical labels are making an increasingly significant contribution to operational efficiencies, and to security and compliance. Smarter and more dependable labelling solutions are important in often safety-critical clinical environments.

Developing and delivering such solutions requires an in-depth understanding of segment needs, along with diverse and substantial manufacturing resources.

The Avery Dennison Label and Packaging Materials division today works with more than 10,000 label converters, brand owners and retailers. It has helped to transform operations in a wide range of differing segments, including key innovations within medical applications. Worldwide, Avery Dennison operates in more than 50 countries, with 25,000 employees and revenues of US$6 billion (£4.9 billion).

MEDICAL EXCELLENCE

Avery Dennison specialised pharma materials are widely used to create blood bag labels, security and tracking solutions, drug delivery device labels and functional labelling components. Among the core benefits are assured availability and compliance, and high-performance pharma adhesives including hot-melt, solvent and emulsion options.

Our technologies allow the most challenging applications to be delivered with confidence. These include small containers such as syringes (Figure 1) with diameters down to 7 mm; challenging substrates (including glass and plastics); and thin-walled low-density polyethylene (LDPE) containers where low migration is essential.

Examples of Avery Dennison pharmaceutical solutions include:

- S717P adhesive for small diameter and low surface-energy substrates (especially cyclo olefin polymer (COP) and cyclo olefin copolymer COC), designed to reduce edge lift. This adhesive is US FDA approved and cytotoxicity tested in accordance with ISO10993-5 standards, enabling accelerated re-certification
- S692NP adhesive, designed to meet the low migration challenge. Applications using S692NP are growing as the use of plastic containers increases
- TT Sensor Plus™ intelligent labels; using an NFC microchip that monitors temperature over time during the transit of sensitive drugs.

"S717P adhesive for small diameter and low surface-energy substrates (especially COP and COC) is designed to reduce edge lift. This adhesive is US FDA approved and cytotoxicity tested in accordance with ISO10993-5 standards, enabling accelerated re-certification."

RESEARCH AND DEVELOPMENT

Intelligent labelling is a rapidly emerging medical application area, using technologies where Avery Dennison is already an important global player. Such technologies are already showing enormous promise that extends well beyond conventional bulk logistics applications. For example, hospitals are beginning to explore the use of RFID labels to distribute drugs to individual patients, in order to reduce the likelihood of medication errors.

There is also great interest in the potential to improve patient adherence for self-administered drugs. A chronic condition such as diabetes can be treated

Figure 1: Avery Dennison labelling technology allows the most challenging applications, including small containers such as syringes with diameters down to 7 mm; challenging substrates; and thin-walled LDPE containers where low migration is essential.

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label.averydennison.eu

"A chronic condition can be treated more effectively if an autoinjector device can communicate with a mobile device via NFC or bluetooth. Smart labels are an easy way to achieve this kind of added functionality"

more effectively if an auto-injector device can communicate with a mobile device via NFC or bluetooth, alerting the patient to a missed injection, or an injection that is due shortly. Smart labels are an easy way to achieve this kind of added functionality.

Bespoke development of solutions such as these is a core strength of Avery Dennison, and advanced tamper-evident/security labelling solutions can also be created for specific application needs, with full support from Avery Dennison technical specialists.

Innovation has been at the heart of Avery Dennison ever since the company's founder, Stan Avery, created and patented the world's first self-adhesive die-cut labelling machine in 1935.

Today, more than 450 engineers and scientists work in a dozen Avery Dennison research laboratories across the globe – located in Centers of Technology and Innovation in the US, the Netherlands, Brazil, Belgium, China and India. Continual development is designed to meet a huge range of end-user needs, with many strands of research into next generation technological breakthroughs and platforms that anticipate future trends.

A FOCUS ON COMPLIANCE

Compliance is critically important for medical applications. Issues include not only performance of the packaging, such as avoiding contamination from migration, but also anti-counterfeiting measures and complying with the EU Directive on Falsified Medicines (2011/62/EU).

Meeting such a broad range of criteria requires much more than a product portfolio alone, and Avery Dennison maintains a dedicated compliance team which is ready to help manufacturers and healthcare segment suppliers arrive quickly at an appropriate solution. Products, documentation and full technical support are all readily available.

OUR COMMITMENT, YOUR **AD**VANTAGE

Avery Dennison teams across the globe are focussed on creating new products and services, and supporting all those working in the medical segment as they grow their business. Whether you are looking for the most suitable product, technical assistance or even in-house product t raining, we are committed to sharing our knowledge and expertise. Avery Dennison will work alongside you to arrive at the required result.

PharmaED RESOURCES, Inc.

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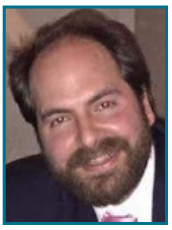

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With the Pre-Filled Syringes market expected to top $16 billion dollars by 2021, the industry is looking for next generation materials, technologies and production strategies to streamline commercialization and to adapt quickly to a changing regulatory environment. Pharma Ed Resources, an industry leader since 2004, in delivering market-driven research on PFS, is proud to announce its 2017 Pre-Filled Syringes Forum. Pharma Ed brings together top scientists, regulatory experts and innovators to share best practices and the latest research in this field, enabling you to maximize your organization's leverage in this dynamic and growing market.

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A labelling solution for demanding pharma applications

THE PHARMA LABELLING CHALLENGE

Label 'lift' is a major challenge for pharma applications such as plastic and 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 S717P offers excellent performance on difficult containers and a rapid re-certification process. It is also a stable product with formal change management control. Indeed S717P is part of the Pharma (P for 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.

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PACKAGING & MACHINERY ENGINEERED TO GO HAND-IN-HAND

At its production units in Grabs, Switzerland, Dividella exclusively manufactures machines for packaging pharmaceutical products. The focus is totally on the packaging of parenteral pharmaceuticals in Top-Load boxes. These sensitive products demand well thought-out packaging solutions. Together with customers, Dividella's specialists develop the ideal packaging for these particular products. Here, Christoph Hammer, Chief Executive Officer, Dividella, explains.

Swiss packaging company Dividella is generally known for its first-class Top-Load cartoning machines. But very few people are aware that pack design plays a key role from the very beginning. Both depend on the specialists at Dividella – the packaging and the machine.

THE TOP-LOAD / TOP-OPENING CONCEPT

Usually, packaging has to be developed for new pharmaceutical products, but also, every now and then, for existing products. In most cases they are parenteral drugs, i.e. liquid pharmaceuticals which are packaged in syringes, cartridges, vials, auto-injectors and the like. On Dividella machines, these products are packaged in Top-Load/Top-Opening boxes (Figure 1).

> "The pharmaceutical manufacturer's project team is closely involved in the entire development process right from the start, in particular the marketing departments who generally have a significant impact on the design of the pack."

The medicines are inserted from above and can then be removed very easily by the consumer from the top of the pack.

Since Dividella sees itself first and foremost as a provider of solutions, and in particular as a machine constructor, packaging design is a very high priority. Even though no purchasing decision in the classic sense usually takes place for prescription medicines – patients get what the doctor prescribes for them – the appearance and the packaging are nonetheless of great importance for pharmaceutical manufacturers.

DEVELOPMENT IS TEAMWORK

The pharmaceutical manufacturer's project team is closely involved in the entire development process right from the start, in particular the marketing departments, which generally have a significant impact on the design of the pack. All products which are to be packaged are therefore defined precisely at the beginning of each project. The aim is to package as many medicines as possible using the same design and therefore on the same machine. To make the packaging process as efficient as possible, Dividella's packaging specialists will make proposals on harmonisation of the customer's portfolio, if requested.

After that, the products for which new packs are required are clarified, and the packaging designers create initial concepts. The form of these concepts can vary:

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Figure 1: Top-Load/Top-Opening boxes. Medicines are inserted from above and are readily removed by the consumer from the top.

on some projects samples are produced at the very beginning which are designed and erected manually. On other projects, various possible packaging solutions are put forward in the form of 3D presentations. On the basis of these presentations, the customer indicates a general direction and a sample is then produced. The blanks for the samples are made by Rondo AG in Allschwil (Switzerland), one of Dividella's sister companies. Erection and testing of the samples for correct functioning then takes place, again at Dividella.

The joint production of the samples is logical: Rondo is not just Dividella's sister company but also one of the leading folding-box manufacturers in Europe for the pharmaceutical industry. Involving Rondo in Dividella projects at an early stage ensures that the designs not only meet the customer's needs and can be produced on the machine, but also that they meet the requirements of the folding-box manufacturer. Particular attention is given to the grades of paperboard which are used, the perforations and a number of other stamping details. Dividella's senior management attach great importance to designing packaging solutions from the outset so as to ensure that production subsequently functions smoothly.

FROM THE SAMPLE TO THE PACK

Once the pharma producer receives the selected samples, they generally carry out various tests before opting for a packaging solution. One of these tests is the so-called handling test: this checks how the end user handles the pack. Does he or she open the pack correctly intuitively? Is any tamper-evident protection handled correctly, for example? In the event that the pack contains products for people with motor disabilities, how easily can they open this pack and remove the drug?

Another test, which is also frequently applied, is the transport test. This verifies that the boxes and packaged products can be transported safely. There are companies which dispatch entire cartons and pallets around the world for this purpose. Others carry out vibration and drop tests in the laboratory to check whether the medicines remain undamaged.

THE 'FLUTE' CONCEPT

Dividella's special design concept (Figure 2) ensures that products can be transported safely and that space is saved in the packaging. Since the whole box is made of cardboard, customised "flutes", specially adapted to the products, are easily glued inside the box. The product is usually 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.

Figure 2: The variable "flute" concept. Syringe, vial and adapter are packaged securely in the shatter-proof combi pack.

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.

MEETING 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 able to be readily and accurately used whenever required. The proper selection of the package and the attention to its design will promote

> "...what good is the most elegant design if the packaging solution does not then work properly in industrial production?"

the benefits of the product in addition to fulfilling these fundamental functions. The syringe or device is not viable without a primary 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 have been removed, if that last product is to be safeguarded. The printing of the package should 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 important. 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.

VOLUME SAVINGS OF UP TO 50%

Dividella folding boxes are pure mono-material packaging, i.e. the folding box is made from 100% recyclable 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 (Figure 3). Dividella reports volume savings of 25-50% compared with traditional blister packs.

These figures are important in that many 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 where general practitioners keep products such as sensitive vaccines.

THE RECIPE FOR SUCCESS: DESIGN PLUS MACHINE

Dividella are machine constructors in their heart and soul – but with brains. Because what good is the most elegant design if the packaging solution does not then work properly in industrial production? The packaging specialists emphasise from the outset that the product is perfectly packaged in accordance with the requirements AND that a solution is provided which can be processed on a machine and which ensures reliable, trouble-free production.

Figure 3: Syringe examples. To achieve volume savings of up to 50% products are packed securely as closely as possible and can be removed individually from the TopLoad pack with its integrated tamper evidence.

ABOUT THE AUTHOR

Christoph Hammer CEO at Dividella in Grabs. He holds a lot of experience in the food and pharmaceutical packaging industry in the fields of engineering and consulting. His expertise covers the capital equipment industry, and through extensive sales activities he has an excellent knowledge of international markets. Christoph was educated as an electrical engineer with additional degrees in Business and Production Technology.

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KEEP YOUR PRODUCT SAFE AND GO FOR THE RIGHT PACKAGING

..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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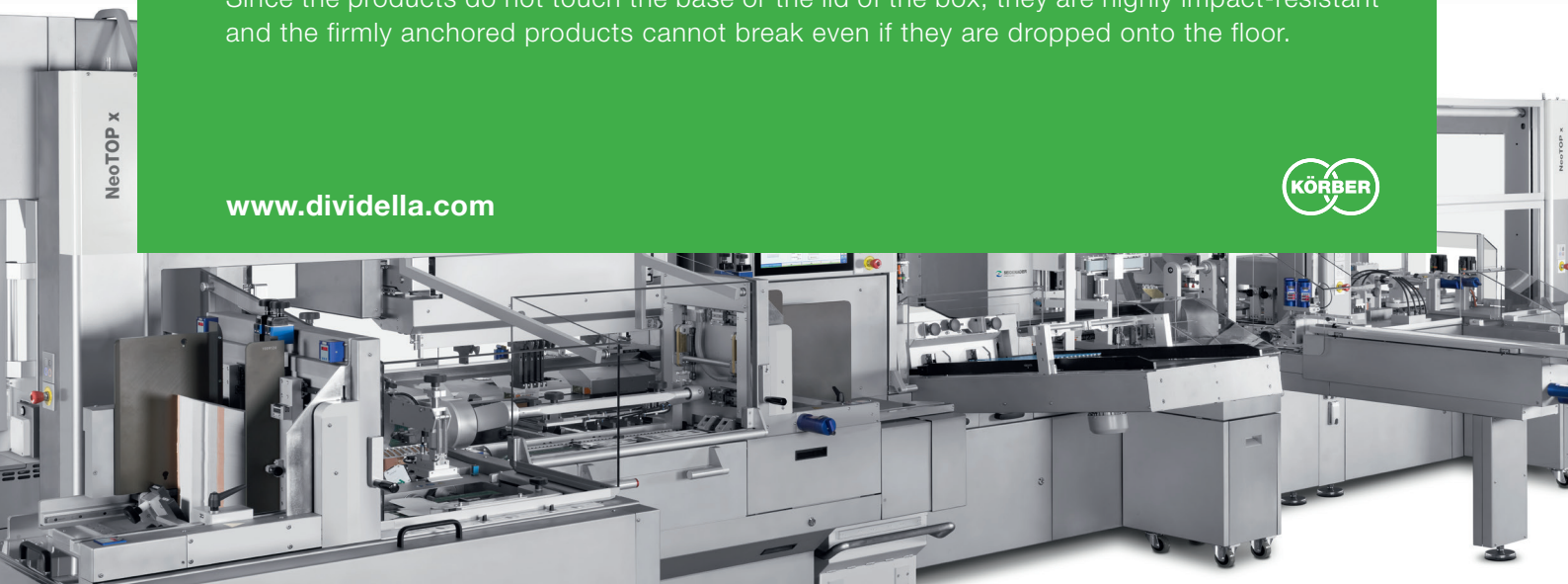

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