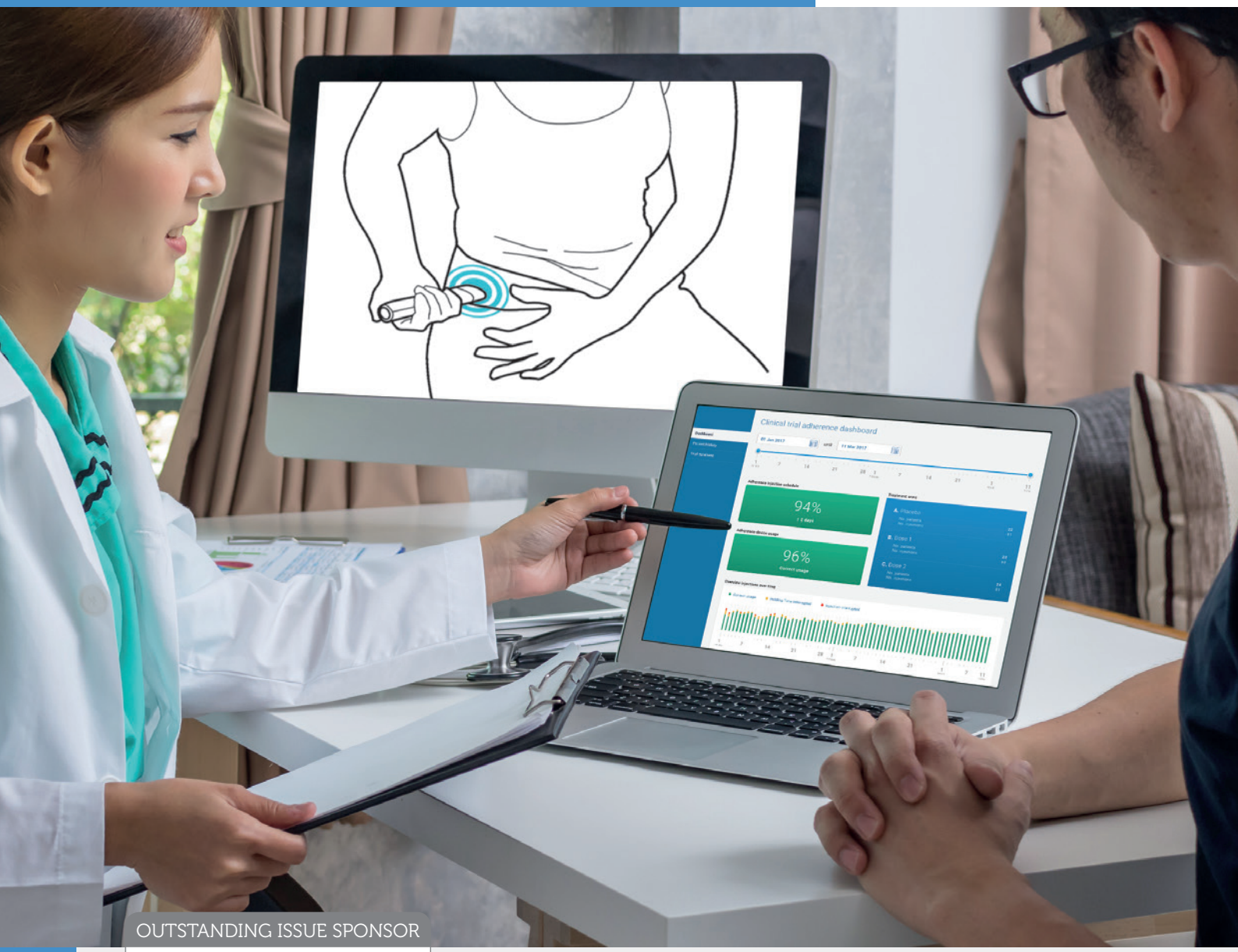
PREFILLED SYRINGES & INJECTION DEVICES

ON drugDELIVERY



OCTOBER 16TH 2017 • ISSUE Nº 79

PRE-FILLABLE SYRINGES

INCREASED FILLING LINE PERFORMANCE

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

HIGH COMPATIBILITY BETWEEN DRUG AND PACKAGING

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

RELIABLE INCORPORATION IN INJECTION DEVICES

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

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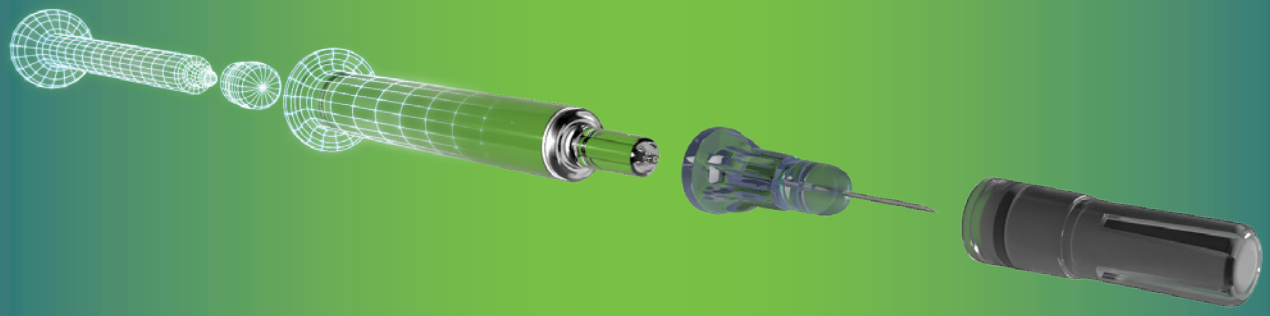
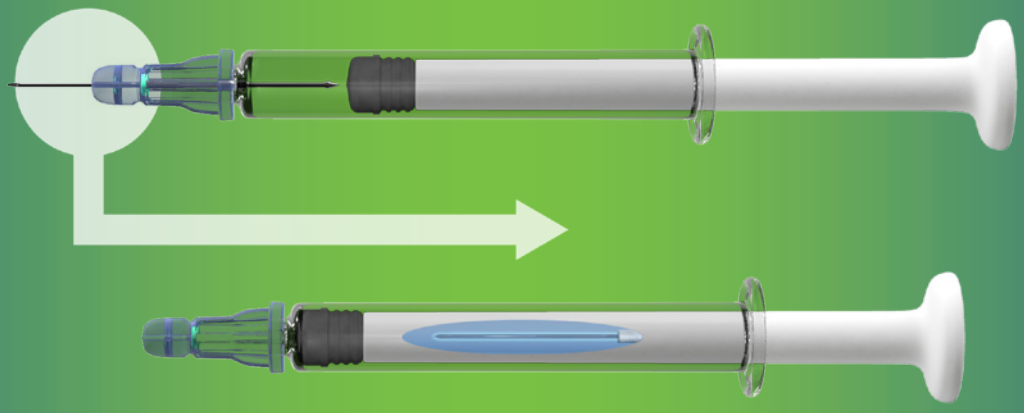


IMPRESS | PRESERVE | PROTECT

See the Companion at PDA's Universe of PFS and PODD



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CREDENCE MEDSYSTEMS

ONdrugDelivery Issue N° 79, October 16TH, 2017

PREFILLED SYRINGES & INJECTION DEVICES

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

2017/18 EDITORIAL CALENDAR

Nov	Pulmonary & Nasal Delivery
Dec	Connecting Drug Delivery
Jan '18	Ophthalmic Delivery
Feb	Prefilled Syringes & Injection Devices
Mar	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Devices Focus
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Delivery
Dec	Connecting Drug Delivery

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ONdrugDELIVERY

YPSOMED
SELFCARE SOLUTIONS

A NEW VALUE PROPOSITION OF SMART DEVICES: ADVANCED MEDICATION ADHERENCE MONITORING IN CLINICAL TRIALS

Andreas Schneider, PhD, Business Development Manager, Ypsomed AG, explores a new value proposition of smart injection systems that has received little attention so far: remote monitoring of medication adherence during large multi-centre clinical trials. Introducing how advanced adherence monitoring services resolve some of the key challenges of clinical research practice regarding costs, adherence, data quality and integrity, Dr Schneider explains which technical features are needed for smart devices to provide value-adding adherence monitoring services. The article concludes with a case study describing how such advanced adherence monitoring services are realised with SmartPilot for YpsoMate, a reusable smart add-on that transforms the proven auto-injector platform into a fully connected system.

HOW TO MAXIMISE THE VALUE CREATION OF SMART DEVICES

Healthcare is one of many industries being transformed by innovative digital products and services. Although healthcare may seem to lag behind others in unleashing the full potential of smart connected technologies, pharmaceutical companies and device manufacturers are vigorously pursuing joint R&D programmes to develop novel digital solutions. For example, with the ever-growing global diabetes pandemic, particular efforts are being made to lower the cognitive and emotional burden of insulin therapy with the help of smart devices and digital health platforms. Other therapeutic areas that require repeated self-administration will also benefit, such as hypercholesterolaemia, asthma or rheumatoid arthritis.

Although emerging trends toward outcome-based payment systems, real-time therapy monitoring and patient convenience are driving innovators to develop digital solutions that accelerate drug product market uptake, value propositions may remain vague for patients, healthcare professionals and payers. Tracking medication events and wirelessly transmitting such data to health platforms reflects a necessary, yet insufficient, condition to trigger behavioural change and in turn improve therapy outcomes. It is thus important to shed more light on the value proposition of smart devices for adherence monitoring in clinical trials. In fact, some of the most pronounced challenges investigators and participants are confronted with in large multi-centre trials relate to the absence of advanced adherence monitoring services.

> "Correct dose administration according to the study protocol is at the heart of assessing safety and efficacy endpoints for new investigational drugs."

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"The burden of extensive paperwork for patients ...continues throughout the trial."

CHALLENGES IN CLINICAL RESEARCH PRACTICE TODAY

Investigators face many obstacles that, in sum, reduce the motivation to participate in clinical research. These hurdles start with the recruitment of suitable patients but more significantly relate to the administrative burden of conducting and documenting clinical research. Due to busy patient practices, investigators typically devote little time to actual research. They need to complete large amounts of paperwork, prepare for regular audits and reviews, or are confronted with the ever-increasing complexity of visit schedules and assessments. Efforts are made to understand whether patients' routine administration of the investigational drug is in line with the study protocol.

Current practices advise investigators and study personnel at each site to assess adherence using dosage counts or data patients have captured manually, which are then transferred to the source document after each visit. Phone calls are required to remind patients to take the investigational drug according to the injection schedule or clarify questions. There are also key challenges in tracking whether the correct presentation of the investigational drug was allocated to the assigned treatment arm and recorded in the source document accordingly. For instance, investigators have to detach part of the product label manually and affix it to the patient's unique number in the corresponding source document before dispensing the packaging to the patient.

Similarly, patients value participation in clinical trials based on their perceived individual cost-benefit ratio. Despite today's multi-centre set-up of clinical trials, travelling to the nearest study site may still take up significant time and impose costs. This is particularly relevant if such visits relate to simply monitoring health status, filling in questionnaires or performing dose administration. Furthermore, there is the latent risk of missing doses and hampering the validity of the study. In fact, patients are typically asked to record medication intake manually and inform about dose schedule adjustments or interruptions during the study. As such, the burden of extensive paperwork for patients is not limited to the informed consent process but continues throughout the trial.

Also, there is an overall trend to reduce the injection frequency of novel second-generation biological drugs. Although the added convenience compared with first-generation medications is obvious, investigators are confronted with patients forgetting how to perform the procedure between injections. This may provoke handling errors, trigger additional interactions with trials centres and further diminish overall adherence.

CROs are similarly under pressure to reduce costs and optimise logistics for clinical trial monitoring. These activities target supplies strategy and planning, expiry management or return and destruction of investigational drug supplies. Most importantly, complexities also arise with trial site and patient management, such as patient enrolment and visits, treatment allocation, dosing and dispensing.

Currently there is no mechanism available targeting adherence data quality and integrity or data collection mechanisms. This is all the more surprising in that correct dose administration according to the study protocol is at the heart of assessing safety and efficacy endpoints for new investigational drugs.

SMART DEVICE REQUIREMENTS FOR ADHERENCE MONITORING SERVICES

Smart devices must feature certain sensing capabilities in order to be used as effective advanced adherence monitors. Let me illustrate these core requirements with

Figure 1: SmartPilot for YpsoMate (right) is a reusable smart add-on, transforming the two-step auto-injector YpsoMate into a fully connected combination product. Advanced sensing capabilities to track device usage and guide patients through the injection process are at the heart of effective adherence monitoring. Relevant injection data is then transmitted to a gateway, such as a hub or mobile app (left), to be made available to clinical trial sites.

SmartPilot for YpsoMate, a reusable add-on that transforms the proven and unchanged two-step auto-injector platform into a fully connected smart product system (Figure 1).

At its heart, SmartPilot contains a contactless sensor solution that differentiates between various states of the two-step auto-injector platform. In so doing, SmartPilot not only tracks whether an injection event

"SmartPilot enables authentication of the combination product at the point-of-use. As such, it may alert users in case a batch of investigational drug has to be corrected or removed from the clinical trial."

has occurred according to the medication schedule but also whether that injection was successfully completed. Additionally, it can guide patients step-by-step through the injection process. Guidance includes direct visual and audible feedback on the SmartPilot add-on itself or the remote real-time display of the instructions for use on a companion mobile app.

SmartPilot adds another dimension to patient guidance: it identifies investigational drugs, tracks medication allocation to treatment arms, and thereby simplifies clinical trial supply monitoring. SmartPilot enables authentication of the combination product at the point-of-use. As such, it may alert users in case a batch of investigational drug has to be corrected or removed from the clinical trial.

Most importantly, SmartPilot enables

SmartPilot Capabilities	Description	Benefits			
		For CROs	For Investigators / Study Site	For Participants / Patients	Pharma Companies
Tracking injection time/date	Advanced sensor to automatically track and wirelessly transmit date/time of injection events	• Remotely monitor adherence to injection schedule as defined in study protocol • Real-time access to usage patterns "outside visits" • Define measures based on detailed insights (e.g. adherence patterns per site) • Reduced efforts in site and patient management • Overview of patient IDs at risk of exclusion due to non-adherence	• Automated data capturing in source document/case report form • Automated patient reminder/notification systems • Remote adjustments to participants' medication schedule • Automated notification services (e.g. in case a patient risks exclusion from study)	• Convenience through automated entries in injection diary • Reminder and notification services • Ensuring medication schedule is up-to-date • Overview of injection history and schedule of future injections	• Automated adherence tracking to improve overall data quality and integrity • Real-time overview of adherence data "outside" visits • Cost efficiencies due to lower administrative overhead/shorter duration of clinical trials • Prevent patient exclusion due to non-adherence (injection schedule)
Step-by-step patient guidance	Guide patients real-time and step-by-step through the instructions for use, advise on critical use steps, and inform about potential handling errors, if any	• Implement specific measures at study site (e.g. device training campaigns due to unusual usage patterns) • Insights into use patterns per treatment arm/study site	• Notification services in case of repeated use errors (i.e. "call to action") • Automated patient interaction on device usage throughout clinical trials	• Further confidence in effectively using devices • Avoid use errors due to forgetting proper procedure between injection events • Less traveling to study site to administer drug	• Complete picture of adherence, including actual device usage • Real-time insights into usage patterns across sites (i.e. differences in geographies/countries) • Prevent patient exclusion due to non-adherence (device usage)
Identification of drug product	Authentication of investigational drug product based on unique identification number	• Track-and-trace of investigational drug to increase transparency of drug supply • Additional efficiencies in trials monitoring	• Confirm correct allocation of investigational drug to treatment arm • Automated database entries to avoid conflicts between various sources of raw data	• Confirmation that correct YpsoMate is at use (e.g. dose strength versus placebo) • Alert users in case certain batches have to be corrected or removed from clinical trial	• Increase patient safety with track-and-trace solutions • Simplify drug allocation to sites and treatment arms
No modification to injection device	Sensor solution does not require any modification to auto-injector mechanics; same configuration used for clinics and commercials	• SmartPilot platform adherence monitoring infrastructure used across customer-specific YpsoMate variants • Proven auto-injector device used in clinical studies	• Known auto-injector platform subjected to advanced adherence tracking services • Injection could be performed at study site without smart connected SmartPilot add-on	• Same handling concept used for clinical studies as for commercial phase • No mechanical interface visible on YpsoMate to avoid patient confusion/ complaints	• No change to auto-injector required when moving from connected clinical to commercial configuration • SmartPilot platform used as adherence monitoring tools across clinical trial programmes

Table 1: SmartPilot's sensing capabilities translate into value-added services for key stakeholders in clinical trials.

> "SmartPilot enables advanced adherence tracking services without requiring any physical modification to YpsoMate."

advanced adherence tracking services without requiring any physical modification to YpsoMate. The same auto-injector configuration can be used flexibly with SmartPilot for clinical trials or without for commercial drug product.

SmartPilot sensing capabilities enable a number of value-adding adherence monitoring services during clinical trials. In doing so, SmartPilot sets the foundation for more patient-centric clinical trial design. Advanced notification and reminding services not only reduce the frequency of patient visits but also help to increase patient interest and enrolment in trials. Furthermore, automated adherence data tracking significantly reduces the administrative burden at clinical trial sites. For instance, certain sites may configure an automated alert if a patient repeatedly injects a partial dose only.

Table 1 summarises SmartPilot's core functionalities as related to the various stakeholders' value propositions.

The ability to monitor the progress of clinical trials in real-time is equally important to CROs and pharmaceutical sponsors. Remote trial monitoring dashboards may include insights into detailed patient adherence patterns. Innovative decision-making tools enable CROs to quickly respond to, and take appropriate measures against, emerging peculiarities in adherence patterns during clinical trials (Figure 2). For instance, CROs may think of device training and education seminars at certain clinical sites should handling errors accumulate over time.

Figure 2: The clinical trial adherence monitoring dashboard sheds light on the two critical dimensions of adherence monitoring throughout clinical trials: injection schedule, as per study protocol, and correct dose administration. The summary report enables real-time monitoring of adherence patterns and, for instance, allows swift action to be taken if handling errors accumulate at certain clinical trial sites.

CONCLUSION

The soaring costs in designing, implementing, and monitoring clinical trials point to a clear need for a fresh approach. New designs are required that minimise administrative tasks at trial sites and reduce the burden of participation on patients. Here, I described how such innovative, patient-centric trial designs can be enabled by advanced adherence tracking services, realised through smart devices. These services facilitate safe and effective self-administration of investigational drugs, enable complete remote patient monitoring and improve the quality and integrity of adherence data (Figure 3).

This article illustrates how the integration of smart devices in clinical research practice offers a unique value proposition and addresses some of the greatest challenges in performing large multi-centre clinical trials. It also disentangles what sensing capabilities a smart device must have in order to unleash its full potential as an effective clinical trial monitoring aid.

ABOUT THE COMPANY

Ypsomed is the leading independent developer and manufacturer of innovative

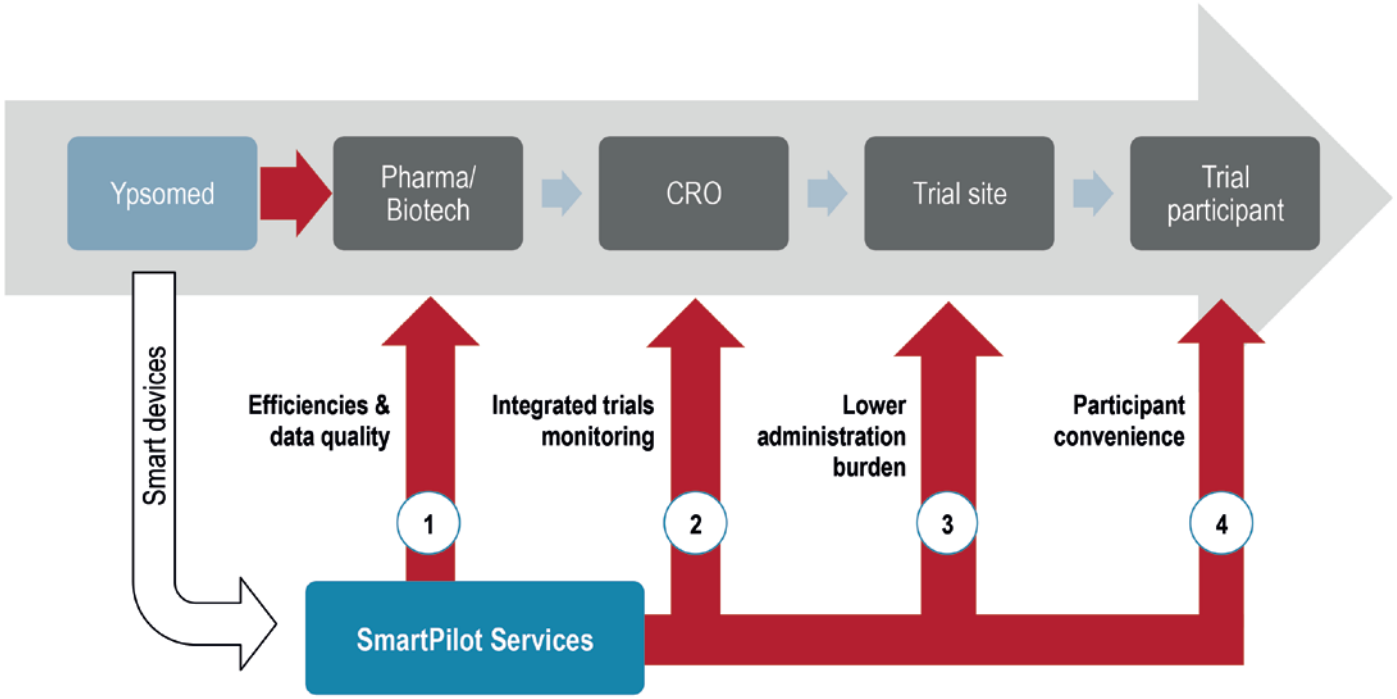

Figure 3: Overview of how SmartPilot clinical trial monitoring services create value for stakeholders. SmartPilot reduces the burden of participation in, and administration of, clinical trials that in turn creates cost efficiencies for pharmaceutical sponsors and improves data quality and integrity.

auto-injector and pen injector systems for self-administration. Their customisable product platforms cover auto-injectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, reusable pens, ready-to-use prefilled wearable bolus injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement their broad self-injection systems product portfolio.

With more than 30 years of experience and pioneering spirit in the development and manufacturing of innovative injection systems Ypsomed is well equipped to tackle digital healthcare challenges and is strategically working on the development of a range of smart devices. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals Ypsomed moves beyond purely connected entities. Its smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters and processing them to facilitate the self-management of diseases. It leverages unique in-house capabilities in electronics, software and connectivity for the development of new smart products and services.

Ypsomed's platform products are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by both pharma customers and regulatory agencies.

ABOUT THE AUTHOR

Andreas Schneider is Business Development Manager with Ypsomed Delivery Systems. His responsibilities at Ypsomed include the definition and development of new platform devices with a particular emphasis on connected and smart device systems. As such, he has been actively involved in the design and development of SmartPilot for YpsoMate, a reusable connected add-on that transforms the proven two-step auto-injector into a connected system. Dr Schneider has published various articles and held presentations in the areas of innovation management and drug delivery. He received his PhD in Innovation Management and Organisation Sciences from ETH Zurich, Switzerland.

NEWGUARD – PAVING THE WAY FOR A NEW SAFETY STANDARD

Needlestick injuries remain a serious concern for pharmaceutical companies involved in injectable drugs. Biocorp has been developing NewGuard™, an integrated passive safety device to tackle this problem. Throughout the development phase, Biocorp defined key elements to ensure NewGuard™ will not require unnecessary changes to be made to the PFS manufacturing process. This innovative and cost-effective solution is now ready for launch. Philippe Lesaulnier, Business Development Manger, and Eric Dessertenne, Head of Business Development, both of Biocorp, explain more.

Enhancing safety for syringe use has been an increasing concern for pharmaceutical companies. Still all too often, the handling of prefilled syringes (PFS) leads to needlestick injuries. For this reason, Biocorp has been developing NewGuard™: an integrated passive safety device that gives protection before, during and after the injection process (Figure 1).

SUMMARY OF PRODUCT CHARACTERISTICS

NewGuard™ is a passive safety system that is integrated with PFS and designed to be compatible with any existing standard PFS (Figure 2). NewGuard™ combines two functions in a single product: a rigid needle shield (RNS) and a safety device (Figure 3). The ultra-compact version fits 0.5 mL and 1 mL PFS and specific versions will be available for 1 mL short and 2.25 mL syringes.

BENEFITS FOR END-USERS

Recent user studies conducted in the US and Europe with groups of patients and healthcare professionals have shown that the compact size of NewGuard™ and its safety features are highly appreciated (Figure 4). The all-in-one concept has also been much praised by end-users. This high level of acceptance confirmed the concept and design inputs of NewGuard™ on its main safety features, easy handling and downsizing approach.

> "Recent user studies conducted in the US and Europe with groups of patients and healthcare professionals have shown that the compact size of NewGuard™ and its safety features are highly appreciated."

MEETING PFS MANUFACTURERS' REQUIREMENTS

Whilst developing a user-friendly device for end-users is essential, it is also important to ensure the whole manufacturing process is as efficient as possible. During the life cycle of a PFS, several stakeholders are responsible for assembling different pieces and filling the syringe. Apparent minor changes on PFS easily increase the total cost of ownership (TCO). Therefore, a holistic approach is required to understand the constraints of the rubber, glass and machine suppliers.

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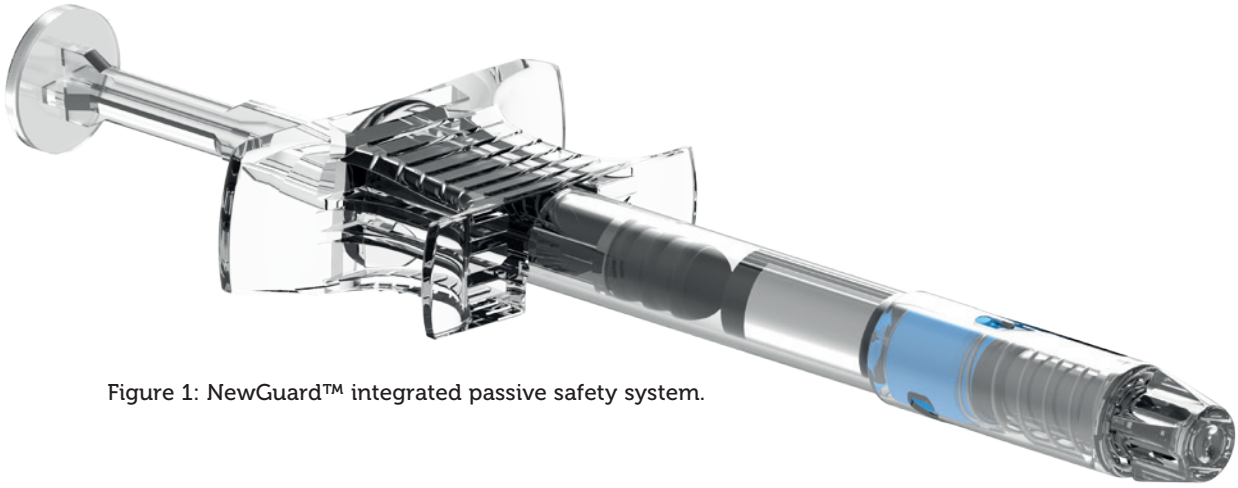

Figure 1: NewGuard™ integrated passive safety system.

Figure 2: NewGuard™ assembled with standard PFS.

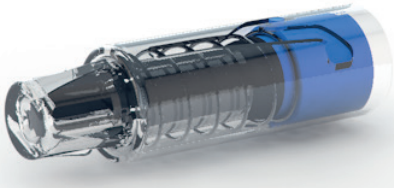

Figure 3: NewGuard™ combines a rigid needle shield and safety device.

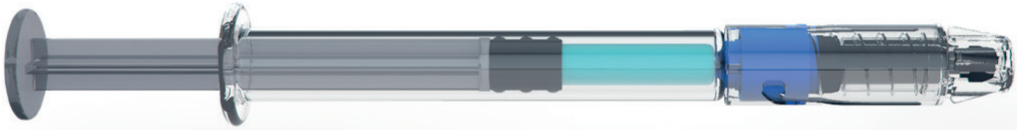

Figure 4: NewGuard™ has a compact size.

Taking into account these requirements, NewGuard™ is the result of Biocorp's commitment to develop innovative solutions with simple implementation processes. Biocorp's R&D team has demonstrated its capability to innovate by integrating all industrial requirements, from machine makers and glass and rubber manufacturers, into the design of NewGuard™.

As a consequence, every step of the PFS production process remains unchanged – aside from the addition of NewGuard™. Indeed, integrating NewGuard™ with a PFS is similar to the process of adding a standard flexible/rigid needle shield to a syringe. For sterile format products with nest packaging, the assembly process takes place on the syringe manufacturer's own production line. NewGuard™ is directly integrated with the syringes – replacing the RNS mounting. Thus, the number and the sequence of operations remain identical and use standard validated components.

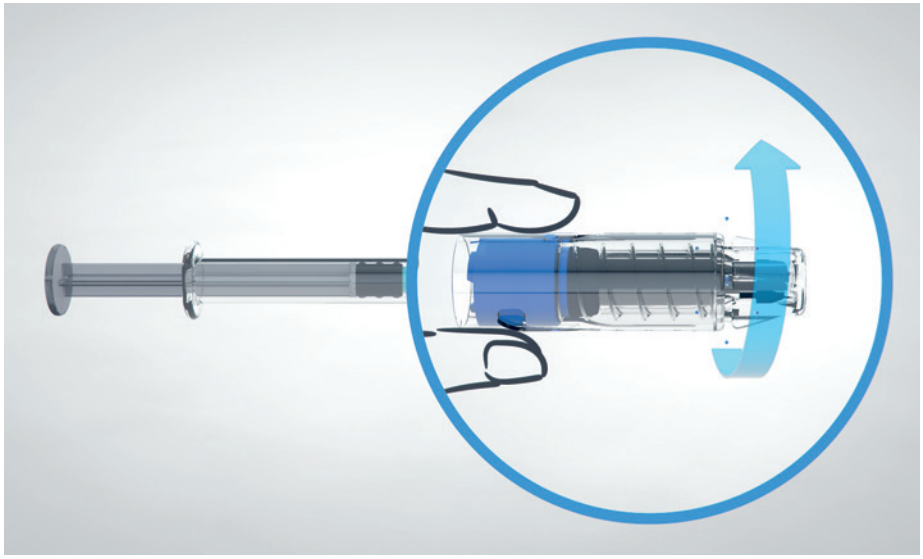

Figure 5: Unlocking NewGuard™ before use.

In addition, NewGuard™ prevents unintentional activation by requiring unlocking before use (Figure 5), avoids coring and pop-off issues, and protects the needle after use (Figure 6), which improves handling, transportation and storage – thus ensuring a cost-effective solution and a smooth, simple implementation for pharmaceutical companies and CMOs.

COMPETITIVE ADVANTAGE FOR PHARMACEUTICAL COMPANIES

Innovative drug delivery systems continue to play a critical role in pharmaceutical companies' strategies for biotherapies. Indeed, they can be a game changer that provides a competitive advantage (Figure 7). NewGuard's passive safety systems bring a solution to pharmaceutical companies by increasing both patient and healthcare professional safety on existing marketed products, providing product differentiation from biosimilars and addressing price-sensitive markets.

Regardless of the strategy, NewGuard™ answers user requirements and could be considered one of the most cost-effective solutions on the market. The product has a low TCO thanks its simple design and standard components – as well as its ready-to-fill process compatibility, reducing indirect assembly costs that could occur on pharma company's sites (Figure 8).

CONCLUSION

Compact, safe and simple, NewGuard™ is entering a new phase which will define a new market standard for PFS passive safety solutions.

ABOUT THE COMPANY

For 20 years, Biocorp has been designing, developing and manufacturing medical devices for the pharmaceutical industry, enhancing drug reconstitution, safety, packaging and delivery. Today, Biocorp continues to innovate in medical plastics, bringing new solutions to the market such as NewGuard™, an integrated passive safety system for PFS compatible with nest, and the Biopass, a reconstitution system with an integrated needle ready to inject. Recognised for its expertise in device R&D, Biocorp has incorporated software development capacities to develop connected drug delivery systems, including the DataPen®, a reusable smart pen injector that automatically transmits data to a treatment mobile app, helping patients to manage their treatment, and a range of add-ons and smart sensors for existing drug delivery devices (pen injectors, MDIs). In addition to its R&D activities, Biocorp also provides manufacturing services for plastic injection, process assembly and blister packaging.

Figure 6: The needle is protected after injection.

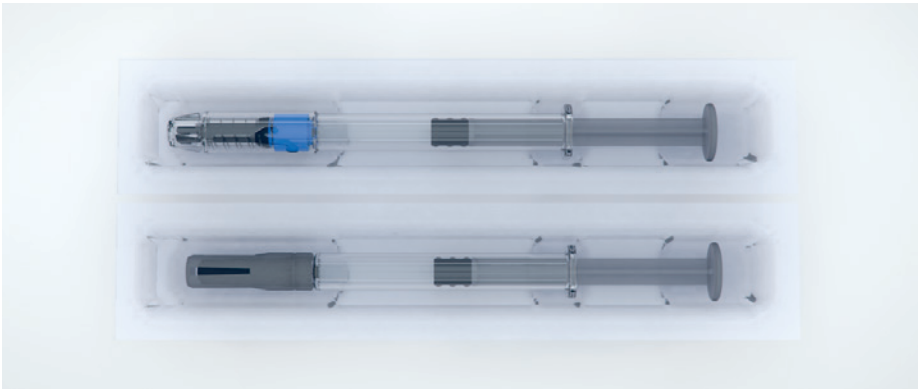

Figure 7: NewGuard™ allows biologics packaged in PFS to be differentiated against fierce competition.

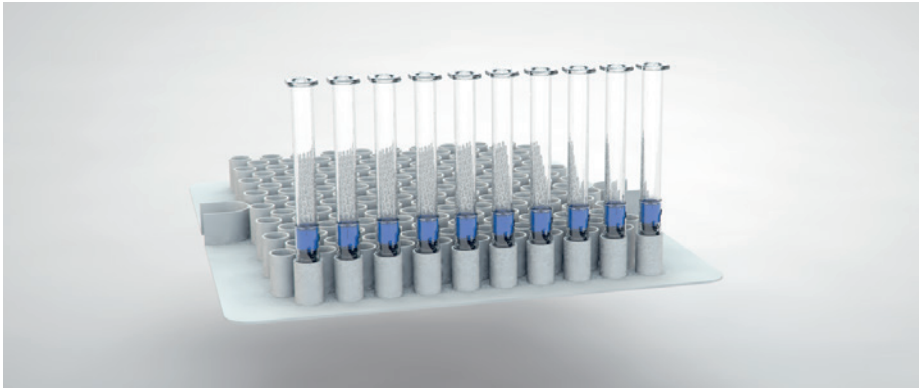

Figure 8: NewGuard™ is compatible with ready-to-fill process.

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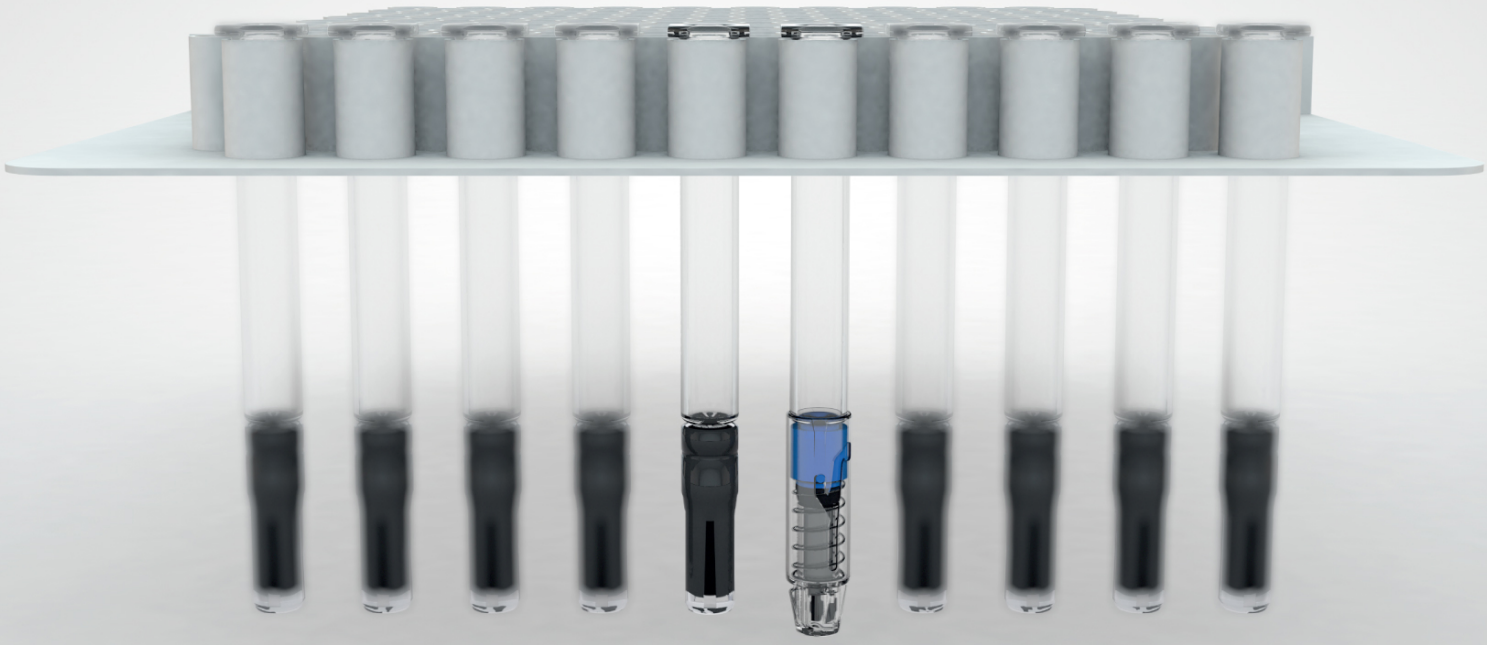

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STEVEN R KAUFMAN, BESPAK

Steven Kaufman is Global Business Development Lead at Bespak Europe Ltd, responsible for business development activities related to injectable devices such as auto-injectors and wearable injection systems. As a member of the commercial team, he works actively with the Bespak Innovation team in Cambridge, UK, which designs and develops advanced drug delivery devices. He is an active member of the Bespak Senior Leadership Team and the Bespak Growth Team.

Mr Kaufman has a biopharma background, broad experience in bringing drug delivery devices to market, and is also involved with strategic alliances with related suppliers and consultants. He has extensive presentation and workshop experience at industry conferences, and has authored several articles related to the drug delivery device field.

Speaking with ONdrugDelivery Magazine here, Kaufman discusses his role at Bespak, the company' activities and capabilities in the injection devices space, and how Bespak meets the current demands from the biopharma industry, in particular in terms of the technology and, crucially, manufacturing and final assembly.

Q Before we delve into the details of Bespak's offering in the injectable delivery space, could you give us a brief update on the wider business – it's structure, recent history, broad business strategies and objectives?

A Bespak is well known for its manufacturing and design expertise and over the last 10-15 years we've spent a great deal of time and effort addressing challenges in injectable drug delivery. We acquired The Medical House in 2009 and soon afterwards set up an Innovation Centre in Cambridge (UK). With those two actions, combined with our prior experience with other types of drug delivery system and in manufacturing, we enabled the development of a substantial amount of intellectual property to resolve some of those challenges. What we focused on some time ago was a niche that has now in fact become very "hot" – viscous and high volume drug delivery. We are quite fortunate to be one of the first companies to have really focused on this area.

Our spring-based auto-injectors are arguably one of the two designs that can allow for highly viscous drug delivery. We are pleased to have worked with great companies and to have addressed challenges that other spring-based technologies have not been able to. One of our devices is probably the only 1 mL single-use disposable injector able to deliver its particularly viscous drug payload. This is a testament to the ability of our technology to deliver such formulations.

"What we focused on some time ago was a niche that has now in fact become very "hot" – viscous and high-volume drug delivery. We are quite fortunate to be one of the first companies to have really focused on this area."

Coupled with that it seems that most people in this space are aware of Bespak thanks to our VapourSoft® technology, where we're using a liquefied gas to facilitate with viscosity issues and also higher volumes, using small canisters as the power-pack to allow for the delivery of as low as 2 mL to as high as 10 mL. The canisters are all the exact the same size but use different types of liquefied gas and different volumes. We found that this resonated really well with the market, and so we've focused on this.

We feel there is an unmet need that we are able to address by being able to offer spring-based and VapourSoft®-based single-use auto-injectors that allow for the delivery of highly viscous, high volume formulations. We have also spent time recently looking at the delivery of even higher volumes via wearable devices powered by VapourSoft®.

Q How do the respiratory side of Bespak and the CDMO API/finished dosage form business, Aesica interact with the injectables side of Bespak? How does the presence of this broader organisation benefit customers and patients?

A The VapourSoft® technology has its origins in our respiratory business and so this is a very tangible way, in terms of our injection technology, that the broader business has brought benefits.

Also, the company has hired many high calibre people over the years including in the commercial-scale manufacturing part of the business. With experience comes knowledge and with knowledge comes better designs and better devices. The presence of such extensive capabilities, and with them know-how and expertise, at the manufacturing and assembly end of the process feeds back to our device design and development activity so we are always taking manufacturing and assembly into account, right from the beginning and throughout (Figure 1).

Additionally, there is our industry track-record, and goodwill. What we are seeing now are opportunities to work in the injectables space for clients we've had for

Figure 1: Bespak is known for its extensive world-class manufacturing and assembly capabilities.

"Bespak auto-injector technology and IP is in multiple single-use disposable auto-injectors launched on the US and European markets and we have a number of others now coming through the pipeline using our novel VapourSoft® technology."

many years in other areas. Bespak has had the opportunity to work with the biggest and the best biopharmaceutical companies in the world. By leveraging that past experience and trust having worked with them, we feel that it's an excellent connection with the injectables side of the business.

At the same time, we've had instances where we're working on the injectable side and that has also sparked other opportunities. As I said before, we're looking increasingly at our final assembly offering in the injectables space and this really is an excellent way for us to differentiate. Bespak is one of the few – possibly only two – companies that have a launched device and final manufacturing and assembly capabilities, whereas in other instances it would have to be the pharma company themselves or a contract filler who would have to perform this role.

Q Tell us about Bespak's injectable delivery device portfolio in a little more detail?

A So in terms of auto-injectors, we're divided up into spring-based and VapourSoft®-based. Within spring-based we have simple aqueous auto-injectors. For example, Dr Reddy's Laboratories use our technology in their Sumatriptan device. And then there are the spring-based devices for higher viscosities.

With VapourSoft® we have the Syrina range (see Figure 2) which includes the micro, the mini and the three versions of auto-injector – the S, the AS, and the AR. So Syrina S has manual needle-insertion, needle shield extension; Syrina AS has automatic insertion and needle-shield extension; and the Syrina AR has automatic needle insertion and automatic retraction.

Figure 2: The Syrina range comprises, left to right, the micro, the mini and the three versions of auto-injector – the S, the AS, and the AR.

Then in addition to the auto-injectors we have the wearable injector, Lapas® which uses our VapourSoft® technology. We have lots of exciting work to do in that area – some of that is driven by customers and some of it is internal.

Finally, we have Lila®, which uses our stopper-valve technology and enables sequential injections. We can place this stopper-valve in between two different liquids – ie two drugs – and then we can inject those. This is great for companies with products that have co-formulation issues, and several companies are interested in that technology.

Bespak technology is in multiple single-use disposable auto-injectors that are launched on the market and we have a number of others now coming through the pipeline using VapourSoft® technology. What we're really trying to focus on though is keeping up the quality, delivering on our promises to meet expectations, and also anticipating what's next.

I would like to talk a little about what I think could be next. You know, everyone keeps talking about platform devices. I keep hearing this everywhere but there a few true platform devices. One of our devices though could be the solution to that challenge – and that's the Syrina S.

The Syrina S (shown in Figure 3) is the smallest 2.25 mL auto-injector available in the market today using a standard primary container. Also, with minimal change it becomes a 1 mL device. So now we have the potential to use Syrina as a platform for both 1 mL and 2.25 mL with only one changed component, and all assembly processes will be exactly the same.

We know that the Syrina S is being looked at more and more now by industry as a platform. Some companies, because of the type of formulation work they're doing now, don't know whether it's ultimately going to be a 1 mL or 2 mL injection. So it's great to have one device good to go where, depending on the final dose volume, they can just swap out one component depending on whether they need a 1 mL "long" or 2.25 mL device. The benefit can translate into two years of time saved.

Q You joined the company relatively recently and at an exciting time in its evolution. Would you be able to tell us more about that? What about Bespak interested you? What is your role within the organisation? What are your aims?

A I've been at Bespak for more than two and a half years now. I've relocated back to North America and I work in a truly global role for Bespak, spending a fair amount of time in the UK but with a focus on the US, Europe and at times APAC too.

Previously I had the opportunity to work with the market leader SHL and I loved that experience. I worked with a lot of terrific people there and had some exceptional mentors. It was at PDA 2013 in Basel that I first saw the technology that Bespak was bringing into play. When I saw that technology, and the mindset of introducing a disruptive technology that was really out of the box, I realised right away what it could achieve. The second I saw it demonstrated to me, a lightbulb came on and "boom"! It was exciting. I always kept that in mind and then when they offered me the opportunity to relocate to North America to work and to lead business development in the area of injectables globally, I agreed.

So my job title now is Global Business Development Lead and what that means is that any programme that we have that involves an auto-injector or any kind of injectable device, I'll be involved whether the company we're talking with is somewhere in the US, in Europe or in Asia or anywhere in the world. I've always wanted this kind of global role. I had something similar when I was working in marketing but I hadn't previously had it in business development where I focused primarily on the Asian market with some work in Europe and the US.

What I gained and continue to gain from having had this transition over to this new role is experience of another way of doing things. On one hand I have the benefit of working in a company that has 60 years of experience being very well regarded in their industry, and on the other I have the freedom to work with new people and build up new relationships.

As for my goal, I want to ensure that Bespak is recognised as a key player in the injectable devices field. With two launched devices using our technology, we can comfortably claim to be a player of course, but I want more. Additionally, I want Bespak to be viewed by the global industry as among the most innovative companies in the area of injection devices for highly viscous drugs and high volumes.

I spend much more of my time building relationships, helping to find solutions and negotiating now rather than promoting, and within those negotiations I'm talking a lot about freedom to operate and IP, and really finding the right solution for our clients rather than selling to them. It's kind of nice. We're creating deals that really deliver for our partners, based on timelines we can all keep to.

Q Both today and into the future, what do you see as the most significant demands from the industry on injection device companies like Bespak, what drivers are behind those demands, and how does Bespak meet those demands?

A I've already mentioned high viscosity and high volume. I think the key demand is for a technology that can deliver these kinds of formulations but at the same time coming from a company that can offer solutions in terms of manufacturing infrastructure. Reducing time to market is another major demand and, as always, cost is a critical consideration.

I think we're there as far as having the technology and the infrastructure but we will continue to build up our infrastructure. We have a facility in Milton Keynes (UK) that we're going to expand. It's going to house some of our injectable programmes in the future. We also have our facility in King's Lynn (UK). What we're doing to prepare for all of the different programmes that will be coming through is to put more of the right people in place.

Bespak is really good at producing billions of components and assembling them into hundreds of millions of devices. We can do that. Now we are looking at ensuring we are able to produce just millions of devices comprising tens-to-hundreds of millions of components. So it's a bit of a shift. Companies like Bespak know how to scale – as we produce at these smaller volumes and then, should the market change, ramp up rapidly. Our unparalleled tooling, moulding and assembly experience are critical – we don't talk about this enough. You have to get the tooling right because this impacts on your ability to supply the market. To me the subassembly line and the tooling with moulding are the most significant elements determining cost and

Figure 3: The Syrina S, pictured here with the AR, is the smallest 2.25 mL auto-injector available in the market today using a standard primary container.

investments in any of these programmes, and pricing is an important consideration of course. There is huge pressure on pharma companies to keep costs at affordable levels.

With some of the other companies' solutions we've seen for highly viscous formulations, the costs appear to be rather high – really premium prices. But if you look at the price-points of the systems we're offering they are still within the range that pharma companies feel comfortable with.

Q What are the major technical challenges injection device manufacturers are facing and, in a highly competitive environment, how does Bespak differentiate itself in the way it approaches these challenges?

A We typically work with partners who have experience with drug delivery devices, but their spring-based systems are now coming up against major challenges. These companies are now saying, "Hey, you know what, we can't get the formulation down below 1 mL so it's going to be a 2 mL formulation or more. And we can't get the viscosity down below 30 cP, and we're having real big issues with stalling and injection time. What solutions are there?"

I'd like to think our VapourSoft® technology is unique. We have strong IP behind it. We were one of the first companies that put forward a technical solution to the major challenges of delivering high volumes and viscous formulations that we were confident would work.

Another aspect is the technology challenges around the equipment. Some companies when they need to develop subassembly systems, they usually throw people at it. We don't. We work with the best subassembly line suppliers in the world and the best toolmakers in the world. We've got people that could build everything on-site, but we prefer to work with companies that specialise, and we oversee the work they do on behalf of our clients. We're not looking to make money from our clients on their tooling and their subassembly equipment. What we're looking to do is to put a good system in place that allows them to have an optimised production process set up within Bespak.

We have that technical expertise for setting up all these different programmes – whether it's for an inhaler, or a medical check valve or a 2.25 mL auto-injector. We run our systems at a higher level; not only Six Sigma but we're also running the majority of our programmes in clean-room environments. Most other companies will be doing this in a GMP room or white room. We try to raise the bar as far as standards go for the production of our devices. We know the value of the drugs is high and we know that any challenges with the devices can lead to really serious issues for pharma companies, so they have to have confidence in the systems we're producing. Being able to troubleshoot, having this deep technical expertise and an excellent reputation, the Six Sigma quality system and regulatory affairs, having clean-room environments – all of these sorts of things combine to give a solid and valuable proposition.

Q In addition to unique technical characteristics of its devices how, in a broader sense, does Bespak set itself and its offering apart in the injection devices space?

A This industry is booming and the market is showing an extra-ordinarily strong demand for devices like ours. Now, the fact is that one or two companies can't make all of these devices. We need five, maybe up to ten companies.

Bespak is not trying to dominate the auto-injector space in the manner that other companies do. We have great regard for the market leaders and key players in the device field. What Bespak offers is simply world-class, excellent design, development and manufacture for customers see value in our IP and a fit with the unique technology that we have.

There is disappointment out there in the industry from biotech and pharma companies who have not been able to achieve what they expected, when they expected it, from their device programs. We are not interested in raising expectations beyond what is possible and are absolutely clear about telling our partners and customers what we can do and what we cannot. We care about making sure that the solution that we're offering is a fit, and the best solution possible, and that we can work to the timelines specified.

We are a well-established organisation. I don't know that there are many other companies that are 60 years old in this industry. It's a company that's publicly listed, under our parent company, we are well vetted, and transparent. I think it's great that Bespak is open about challenges that we face with clients, and works together to find solutions. We're very much a European company, but the irony is we work with so many American companies right now and the question becomes, why is that? I guess this is because some of the US firms are early adopters of new technology. This is the reason so many of them have quickly approached us. So despite being a European company, we have a truly global mind-set and work very well with our US biopharma company partners who represent a lot of what we're doing right now. Clearly we will look to expand our footprint to the US in the near future with the response we have received.

We are eager about the next year or so when the names of some of the companies – US and otherwise – we are currently working with become public as more products begin to enter the clinic and to be launched. These are exciting times.

ABOUT THE COMPANY

Bespak is a full-service drug delivery partner, specialising in innovative patient-centric medical devices. Bespak partners with its customers to design and develop innovative world-class drug delivery solutions, as well as providing "off-the-shelf" proprietary products and contract device manufacturing services from pilot to commercial scale. With more than 50 years' experience in drug delivery we apply our proven know-how and technologies to address the ever-changing needs of the pharmaceutical industry, across multiple applications.

Bespak's portfolio of proprietary products includes devices for injectable devices, inhalation, nasal and ocular technologies, as well as point-of-care diagnostics know-how. Working in conjunction with many of the world's pharmaceutical companies, the company consistently provides regulatory-compliant devices critical to the delivery of therapeutics for treating a variety of medical needs.

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DESIGN VALIDATION TESTING – DRUG DELIVERY DEVICES

From a regulatory perspective, Mark Turner, Managing Director, Medical Engineering Technologies, provides a summary of the current requirements of parenteral device manufacturers in the area of design validation testing.

Design validation testing (DVT) is an important component of the Product Master File for all medical devices, including those used for delivering drugs and/or biologics to their target in the body.

Although this article uses prefilled syringes as an example, the principles apply to just about any drug presentation that is not a capsule, tablet or pessary (unless it has an applicator). It is a review of the testing required to demonstrate product performance.

As might be expected, the place to start with design validation is a risk analysis. This is likely to identify drug efficacy and product safety as the key areas to examine, in short: dose accuracy, toxicity, risk of infection and mechanical risk. Assuming that the manufacturing process delivers the correct materials in the correct place and in the correct quantities, the factors influencing dose accuracy will be the syringe design and its stability, toxicity will be largely governed by material selection and stability, infection control will be a matter of providing robust sterilisation processes and sterile barrier packaging and, finally, other safety factors to consider include needlestick injury and the possibility of damaged components.

STANDARDS

The relevant industry standards are:

- ASTM D 4169 Standard Practice for Performance Testing of Shipping Containers and Systems
- ISO 10993 Biological evaluation of medical devices
- ISO 11040 Prefilled syringes
- ISO 11608 Needle-based injection systems for medical use -- Requirements and test methods
- ISO 80369 Small-bore connectors for liquids and gases in healthcare applications (replaces ISO 594)
- ISO 11607 Packaging for terminally sterilized medical devices

> "Due to a high incidence of incorrect connections being made in practice, ISO 594 has been replaced by ISO 80369 which describes specific connector dimensions for different applications."

- ASTM F 1980 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

DOSE ACCURACY

There are many aspects to ensuring dose accuracy. Some of these come from production processes, for example injectable viscosity, fill-volume and active pharmaceutical ingredient (API) concentration. Others come from the delivery system, including syringe dimensions, effectiveness of actuation and maintenance of formulation (chemical and volume) in storage and transit. The transfer of the drug into the patient must also be effective and without leakage.

Dose accuracy is generally measured gravimetrically. Whilst the balance will be very accurate, attention must be paid to the differences between injecting in air and in flesh. *In vitro* extrusion of the syringe contents will be subject to evaporation, spraying and the retention of a bead of fluid at the needle tip. All of which could produce inaccuracy relative to an *in vivo* administered dose.

ISO 11608 and the US FDA Guidance, *Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4*, provides a number of tests to be considered. **Break-loose force:** the force required initially to move the syringe plunger. This can

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influence the dose accuracy and the speed of injection. Difficulty in operating the syringe due to high break-loose force could cause misplacement, whilst an unrestrained plunger could move in transport.

Glide force: the force required to keep the syringe plunger moving. This can influence the dose accuracy in a similar way to the break-loose force.

Separation force: the force required to remove the needle from the syringe. The FDA recommends the use of a bonded needle to prevent its separation. If the needle is not bonded, the connectivity to any downstream system is important and its integrity and reliability should be demonstrated. Note that due to a high incidence of incorrect connections being made in practice, ISO 594 has been replaced by ISO 80369 which describes specific connector dimensions for different applications.

Unscrewing torque: ISO 11608 gives values for the force required to remove needles which are screwed onto the syringe.

Ease of assembly: another ISO 11608 requirement relating to re-usable pen injectors.

Resistance to overriding: a requirement of screw-on needles and Luer connectors, over-tightening of the needle could damage the thread and reduce the security of the connection.

Stress cracking: this primarily relates to the stress placed upon the male Luer of the syringe by the needle, but other forms of stress cracking should be considered from things such a mechanical or chemical stress, all of which can lead to leakage or particle generation.

Validation of graduation markings: this is a requirement for markings on a syringe barrel or within a dispensing system (e.g. a pen injector). Often the full contents of a syringe will be dispensed and markings are not required. Variable dose dispensers do have markings which can be in the form of a dose selection dial (don't forget to measure the forces required to operate the dial), or on the syringe barrel if there can be a clinical need for a partial injection.

Dead space: air bubbles in the syringes could expand in air transport (causing leakage) or allow oxidation of active ingredients.

Coring needle test: needle blockage will interfere with correct dosage.

Seal integrity testing: this is required to demonstrate that there is no loss of dosage or ingress of liquids and should include verification of any connections, such as Luers or screw-on needles. This can be a difficult test to perform, especially when the syringe is hidden inside an auto-injector. Trace gas leak detection can be applied to good effect as can, in some cases, dye ingress. ISO 80369 gives visual inspection methods using a pressurised system, which should be included in a design validation programme but are not of adequate sensitivity to be used unsupported.

ISO 11608 gives a lot of information about dose accuracy, particularly for products which can be used more than once, such as insulin or growth hormone pens. There is a requirement to maintain the dose accuracy at all cartridge positions, at all dose levels and for the final dose from a cartridge.

Actuation forces are also important for auto-injectors, for example in cases where the force must be such that the device can be operated easily in an emergency situation. In addition, because of the automatic nature of these devices the user cannot verify the insertion of the needle. Therefore, the needle insertion depth and duration of dosing need to be tightly controlled to ensure that the dose is delivered correctly.

BIOCOMPATIBILITY & TOXICITY

An initial review of biocompatibility might suggest that ISO 10993 provides all the answers, but it does not. ISO 10993 considers how a device contacts a patient and for how long. For a prefilled syringe the pathway is generally clear, blood path indirect, short term contact. However, the modes of testing given in the standard do not consider that the contents of the syringe may have been stored in their container for two years or more, or that some devices are used repeatedly for chronic conditions.

The testing chart given in ISO 10993 (with the additions from the associated FDA Guidance) indicates that the required tests for short term contact are: cytotoxicity, irritation, sensitisation, acute toxicity, pyrogenicity and heamocompatibility. In addition, extensive extractables and leachables analysis should be included to account for the risk of the transfer of material into the injected fluid during storage. This need is likely to be highlighted in future versions of ISO 10993, as the emphasis moves from animal testing to chemical analysis. The extractables and leachables study should include consideration of the production processes and materials, the packaging materials and labelling, and, of course, the syringe components and their possible sources of contamination. Particle generation should also be considered in addition to chemical contamination.

For treatments addressing chronic conditions it may be necessary to address genotoxic and chronic toxicity endpoints. In these cases, extremely low levels of migrating material are tolerated. In all cases a toxicological risk analysis should be considered.

STERILITY & STABILITY IN STORAGE & TRANSIT

Parenteral products might be rendered sterile by terminal sterilisation (ethylene oxide, radiation or autoclave) or they may be assembled in an aseptic environment. It is not sufficient to demonstrate that the injectable is sterile at the end of this process: it must remain sterile right through to the point of delivery.

Guidance on the maintenance of sterility comes from ISO 11607. Once sterilisation and packaging processes are validated, the shelf-life and transit security can be addressed. The ageing process can be accelerated by the application of methods set out in ASTM 1980 or the ICH Guidelines. Apart from syringe integrity tests, seal strength and integrity tests should be applied to any sterile outer barrier (e.g. blister or pouch).

ASTM D 4169 provides a framework to simulate vibration and handling in transit, whilst the US Federal Aviation Authority tells us what pressure to expect during air transit. We recommend confirmation of sterile barrier performance following transit and an assessment of pressure changes on the volume of the syringe contents. Also particle generation during this phase of the product lifecycle might be considered (due to vibration in transit).

Similarly the sterility of the product should be confirmed at the end of the product storage life. This testing can be combined with an examination of performance aspects such as delivery forces and volumes, which may have been influenced by changes in the fluid, the siliconisation of the syringe or the composition of the stopper.

MECHANICAL SAFETY

Transit testing will have shown that a product remains intact up to the point of use (glass syringe not broken, needle protection in place, etc.). However, it remains necessary to examine any safety mechanism. If the needle is protected by a simple cover, its removal and re-attachment forces should be ascertained. This and any anti-needlestick mechanism should be safe and effective as recommended in the FDA's guidance document, *Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features*: which cites "connectivity to other devices necessary for use (e.g., needles, adapters, transfer systems, extension tubing, Luer connectors, and sharps prevention features)".

A final consideration is piston seal blowback (the ability of a syringe with a tip cap to hold a certain pressure on the piston).

METHOD VALIDATION

All test results reported in a DVT study should be obtained using validated methods and calibrated equipment. Often the method validation is achieved using trained technicians in a multi-operator study. If risk analysis identifies that a particular product may influence a mode of testing, or behave unusually in any particular test, these tests should be validated for that product.

CONCLUSION

Validation of drug delivery systems requires the review of a wide range of risks, standards and guides. On the one hand, not all the aspects described here are necessarily applicable to every product, and readers can probably think of many more that are. On the other, this confirms that a thorough risk analysis is required and that time must be made available for method and protocol development, followed by comprehensive testing using well characterised systems.

ABOUT THE COMPANY

Medical Engineering Technologies (MET) has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and the Americas. MET knowledgeably, reliably and effectively delivers medical device and packaging testing. Services include protocol development, laboratory testing and data analysis. The laboratory is equipped for performance testing, chemical analyses and sterile barrier verification, and with accreditation to ISO 17025, customers can have complete confidence in the quality and accuracy of the results.

ABOUT THE AUTHOR

Mark Turner is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a perfusionist in the cardiac unit of Kings College Hospital (London, UK) providing experience of the application of medical devices first hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

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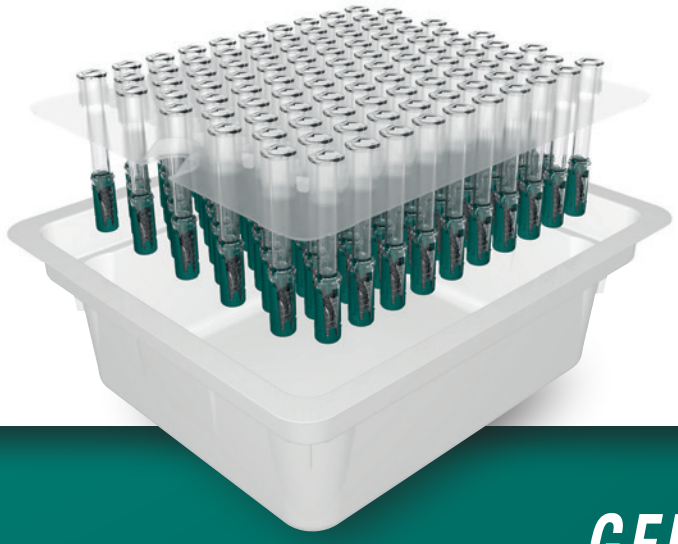

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THE MAKINGS OF INNOVATION IN ADVANCED DRUG DELIVERY

In the context of recent industry trends and market demands, including the emergence of biosimilars and increasingly viscous formulations, SHL provides an update on its portfolio of auto-injector products, including two new devices, Maggie® and Bertha™.

Since almost 30 years ago, when the first commercial auto-injector was created for emergency use, the advanced drug delivery market has continued to grow. In fact, self-administered auto injection and pen injection using prefilled syringes or cartridges has become one of the fastest emerging drug delivery solutions of recent years, with one study forecasting that the market will grow at an annual rate of 7.6% until 2026.[1]

> "By removing the activation button and simplifying the injection process, we were also able to reduce the risk of handling errors. This gave patients an added sense of autonomy during self-administration, helping them feel more confident about self-injection."

The purpose of developing any medicine is to improve the lives of patients, and how the medicine is delivered needs to support this original intent. Initially created for emergency use, the auto-injector was designed to be operated by patients or untrained users. While its range of users has expanded, the auto-injector, by nature, has remained intuitive and easy to use so as to support patient convenience and compliance.

DESIGNS THAT BOOST CONFIDENCE

With nearly three decades of experience designing and developing auto-injection devices for 80% of the world's top 25 pharmaceutical companies, SHL has always been focused on every detail when creating solutions to help its partners benefit the patient. SHL's in-house design team constantly looks into ways to improve devices for better usability. The team works independently or in collaboration with our pharmaceutical partners to conduct human factors (HF) studies that help us gain insight about how the patient uses, understands and accepts the device.

The evolution of the steps required to use our injection devices exemplifies the improvements we have made throughout the years based on user research. While our easy-to-use, three-step auto-injector revolutionised the market standard for injection devices, a significant finding from our HF studies was that buttonless auto-injectors were preferred among a majority of patient groups. Our devices were therefore simplified to include just two steps – uncap and inject – to make the injection process easier and more intuitive. By removing the activation button and simplifying the injection process, we were also able to reduce the risk of handling errors. This gave patients an added sense of autonomy during self-administration, helping them feel more confident about self-injection.

Providing the patients with a clearer view into the self-administration process is also

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Figure 1: The Molly® family of devices (from left to right): Molly 1.0 mL FNS, Molly 1.0 mL RNS and Molly 2.25 mL.

crucial for improving patient adherence and compliance. A way to enhance patient insight is through a clear feedback mechanism, which can be achieved via a combination of audible, tactile and visual indicators, to reduce the uncertainty related to injection.

Our two-step Molly® auto-injector, for example, features two distinctive audible clicks – one at the beginning and one at the end of injection – to indicate clearly when the injection starts and ends.

The Molly® family of devices (Figure 1), which come in 1.0 mL rigid needle shield (RNS) and flexible needle shield (FNS) formats as well as a higher 2.25 mL fill volume, are also designed with large viewing windows to enable real-time visual monitoring of the drug's delivery.

To further enhance confidence and understanding, a range of SHL devices are now designed with a continuous clicking mechanism to provide constant feedback throughout the entire injection process. Other details, such as tactile feedback on the needle guard, also add to the patient's confidence when using the device.

SUPPORT FOR HIGHER VOLUMES & VISCOSITIES

An important factor contributing to growth in self-administered injection devices is the increased prevalence of chronic diseases, and in turn the rise of biological and biosimilar drugs to treat these indications. In fact, the biopharmaceutical market accounts for about 20% of the pharmaceutical market as a whole and, due to their effectiveness in treating chronic conditions, biologics and biosimilars are expected to grow at an annual rate of over 8% per year.[2]

Chronic disease management is a lifelong process, meaning that many treatments are moving from hospitals to the home. Pharmaceutical companies are also developing biologic therapies that require less frequent injections so as to increase patient comfort and convenience, and also to differentiate themselves in the market.

As large molecules, biologics need to be given in high concentrations in order to achieve efficacy and prolong the duration between treatments. This can either result in formulations that are highly viscous and/or have larger volumes. Existing auto-injection devices are therefore being challenged to deliver these new forms of biological formulations effectively, without compromising patient comfort.

This challenge led to the development of Bertha™, a disposable auto-injector created for the delivery of drugs in larger volumes and of higher viscosities. Bertha™ uses SHL's intuitive two-step operation and is compatible with either a 1.0 mL or 2.25 mL prefilled syringe. At the same time, it features the continuous clicking mechanism for enhanced feedback. Its larger design also provides the user with an extra sense of reliability during the injection process.

Meanwhile, SHL's market-proven Rotaject® technology supports biological formulations of even higher viscosities. The Rotaject® uses a clock spring technology, enabling the delivery of a viscous drug at a constant force (Figure 2). This helps ensure that the full dose is safely delivered. The steady and safe delivery also allows us to optimise the patient's injection experience. To meet the request for a wider variety of fill volumes, the technology can be customised into a disposable auto-injector design using either a 1.0 mL or a larger 2.25 mL syringe.

A HIGHER BAR FOR SAFETY

Also supporting the trend for auto-injection systems are a number of advantages associated with using a prefilled syringe or cartridge as a primary container, such as convenience, accuracy, sterility and safety. Once filled with a medication, prefilled syringes can remain sterile for two to three years.[3] This not only helps pharmaceutical companies minimise drug waste, but also allows drug producers to create market differentiation. Meanwhile, the fact that patients do not

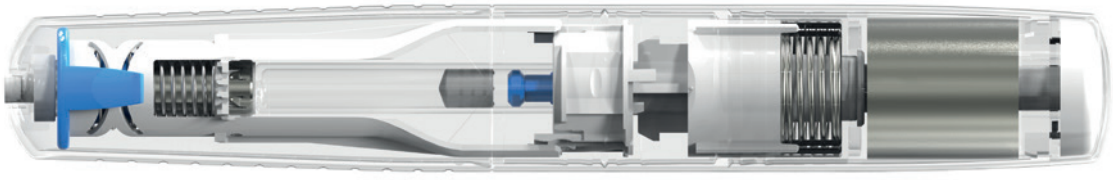

Figure 2: The Rotaject® technology uses a constant force technology that allows the delivery of highly viscous formulations of up to several hundred centipoise.

Figure 3: The cartridge-based Maggie® two-step auto-injector is equipped with SHL's unique Needle Isolation Technology.

need to transfer the drug from a vial to a syringe ensures the delivery of a precise dose.

Auto-injectors using prefilled syringes are designed with pre-attached needles, but those using cartridge-based solutions are not. As a result, cartridge-based solutions pose a challenge in terms of avoiding contamination and preventing needlestick injuries. To address this challenge, SHL developed the Needle Isolation Technology (NIT®), a unique solution where the needle is pre-installed in the device. Using a simple and risk free step, the user initiates the automatic needle attachment process without being exposed to the needle. With this technology, we ensure that the needle is permanently hidden throughout the entire process.

As cartridges offer a broad range of options for fulfilling various drug characteristics and therapeutic needs, this technology widens the scope of container choices, including for both single- and dual-chamber therapy solutions. With a maximum fill volume of up to 3.0 mL, cartridges can also support drugs in higher volumes.

SHL's new Maggie® (Figure 3), for example, uses a 3.0 mL standard ISO cartridge with NIT® to prevent metal leachables from contaminating the drug product. Maggie® has also been designed with a constant clicking feedback. These features were designed to help increase the patient's acceptance of the device and ensure patient safety throughout the injection process.

EFFICIENT MANUFACTURING

Development of a new therapy is a complex process that requires careful planning and meticulous execution. With growing competition in the market of biologicals and biosimilars, speed-to-market is as important as the technical specifications of the device. Therefore when it comes to choosing a device partner, the capacity, scalability and efficiency of their manufacturing capabilities are vital indicators of the ultimate success of a product's launch.

"SHL's new Maggie®, for example, uses a 3.0 mL standard ISO cartridge with NIT® to prevent metal leachables from contaminating the drug product."

As a world-leading solution provider of advanced drug delivery systems, SHL has significant leverage when it comes to the manufacturing of device. The company keeps key capabilities in-house to ensure that each component of a device is considered at the outset of the design phase as well as throughout the entire development process.

Moreover, developing and manufacturing devices, as well as much of machinery that produces them, in-house allows us to customise existing offers in our pipeline. This process also makes it possible for us to develop completely bespoke devices based on the unique requirements of our customers.

The Molly® family of auto-injectors, for example, is part of a preconfigured programme that supports shorter production timelines and faster time-to-market. First made available in a rigid needle shield (RNS) format, Molly® was developed with a range of spring options that can be adapted to suit a variety of drug characteristics. Its intuitive features and compact design also make the device more appealing and less frightening for the patient. But perhaps most importantly, Molly® was designed with a unique power pack that offers the same functionality while using a significantly reduced number of components. For pharmaceutical companies, this means that the timeline and investment required to develop a Molly® auto-injector can be significantly reduced. At the same time, Molly® still offers customisation flexibility that meets the requirements of various drug specifications and branding.

A COMPLETELY INTEGRATED SOLUTION

To ensure a smooth market launch, SHL also offers robust final assembly, packaging and labelling services for SHL-designed drug delivery devices. These services create added value for our partners following the successful design and development of their device. This total integration between device and assembly machine development guarantees faster communications and tighter quality control, resulting in a fully integrated service from device design to commercialisation.

Combining our core speciality in designing patient-centric auto-injection devices with our broad range of in-house expertise and services, SHL continues to lead the market with innovative drug delivery solutions for the pharmaceutical and biopharmaceutical industries. Designed with incredible attention to detail, SHL's innovative auto-injection systems make it easier and safer than ever for patients to self-administer therapies at home, improving their treatment outcomes and their lives.

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OVAL MEDICAL TECHNOLOGIES

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USING POLYMERIC PDC TECHNOLOGY TO IMPROVE AUTO-INJECTOR DESIGN

The limitations of using glass-based auto-injectors, such as contamination, and the need for delivering complex, viscous preparations, have led to a new approach that uses polymeric PDC technology instead. Jonathan Lawson, MSc, Senior Design Engineer, Jonathan Bradshaw, MSc, Device Development Engineer and Susie White, MEng, Mechanical Engineer, all of Oval Medical Technologies, look at what polymeric PDCs can offer in making auto-injectors truly patient-centric.

Over the past 20 years, there has been a shift in pharmaceutical pipelines towards the development of biologics, which now make up around 70% of drugs currently in development.[1] However, although biologics offer better efficacy and safety, the glass-based auto-injector technology used to deliver these drugs has not significantly evolved since the 1950s.

Subcutaneous injection is the preferred route of administration for biologic drug delivery and so, with the need to reduce costs, auto-injectors have become increasingly important. Currently, single-use auto-injectors typically comprise a prefilled glass syringe, an injection mechanism for delivery of the drug and a needle safety mechanism for disposal of the device.

> "Polymeric PDC technology offers a new approach that can resolve many known issues with glass, whilst unlocking opportunities for the delivery of biologics."

There are some advantages to using glass syringes as the primary drug container (PDC) within an auto-injector, including:

- Proven history of drug compatibility
- Regulatory acceptance
- Market familiarity
- Established manufacturing and filling processes.

However, there are known issues with glass syringes, some of which have led to auto-injector recalls:

- Lubricants risk contamination
- Tungsten contamination from glass
- Plunger stiction leading to delivery inconsistency, which can result in wet injections
- Risk of glass breakage
- Formulation viscosity and volume limitations
- Large manufacturing tolerances
- Complex supply chains reliant on specialist suppliers.

The most recent advances in biologics are now presenting new challenges to the design of delivery platforms. Innovative products such as long-acting injectables (LAIs) are being developed to provide slow-release capabilities. LAIs, as with other

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biologics, have a viscous formulation and complex fluid properties (e.g. suspensions and emulsions with non-Newtonian properties). The challenge is then to balance complex drug characteristics with delivered volume, whilst still ensuring a patient-centric approach. It is these requirements that are pushing the limits of current glass-based technology.

Polymeric PDC technology offers a new approach that can resolve many known issues with glass, whilst unlocking opportunities for the delivery of biologics. It is this approach to auto-injector design that allows Oval Medical to support a user-centric approach, unimpeded by the performance, integration capabilities and the limited design freedoms of a glass-based alternative.

A USER-CENTRIC APPROACH

A user-centric approach to the medical device development process is key in ensuring the design of devices which promote safe, correct and effective use. The inclusion of human factors engineering from the outset of the development process allows for an understanding of user-group needs, their anticipated limitations and the environment in which the device will be used. Ultimately, the knowledge space that human factors engineering generates enables the minimisation of usage related risks, and avoids inadequate device design which could compromise the effectiveness of the device's user interface.

The differences between user populations can be vast. For example, patients with migraine may experience aura, causing visual impairment which hinders their ability to identify device features or text. Alternatively, patients suffering from anaphylaxis may require administration from a user with good vision, but who are naïve with respect to auto-injector use. These examples demonstrate that to create a well considered and intuitive device, it is essential to appreciate the various user-group dynamics and integrate them effectively into the design.

A truly user-centric approach must involve consideration of the device interface design. The constraints presented by glass PDC technology can limit the ability of a design to meet all the functionality requirements, which can compromise the user interface. Frequently, the use of a glass PDC leads to compromises in device size, form and/or simplified use steps, preventing a device from fully meeting the needs of its users.

Polymeric PDC technology (Figure 1) bypasses the constraints of glass-based PDC systems by facilitating an integrated approach to device design. Whilst the auto-injector industry has been limited by its reliance on glass-based technologies, polymeric PDCs allow design freedoms traditionally unattainable in many areas, e.g. within user interface design. The result is that a user interface can be fully tuned to the requirements of a wide range of user populations without the burden of potential glass breakage, dimensional variability and other known issues associated with glass.

Use of polymers provides increased geometric options combined with improved tolerance management unavailable with glass. The benefits of using polymer include:

- Delivery speed consistency, preventing wet injections even when injecting challenging formulations, e.g. non-Newtonian fluids
- Shorter injection times for viscous formulations, without the risk of glass breakage
- Needle depth consistency, reducing the risk of adverse events
- Improved user experience through smaller gauge needles.

PDC components can be moulded with features that directly interact with device mechanisms which can overcome issues such as device recoil, variable use forces and injection speed. Ultimately, this reduces the impact on the user, whilst ensuring all required user interface features are present without compromising overall device size or usability. Approaches to solving common user interface pitfalls through high risk, needleless systems or "power source" innovations can detract from fully user-centric devices. These pitfalls could be better avoided through the increased design freedoms offered by a polymeric PDC. This allows engineers the freedom to "design out" user interface weaknesses typically observed with glass-based PDC auto-injectors.

During the development of a combination device, two main streams of development occur; 1) the drug, and 2) the delivery device. It is imperative that any device development process places equal importance on the delivery requirements of the drug, as well as the requirements of the user interface.

For optimal device design and performance, the user interface should not be influenced by the forces required to deliver the drug and, similarly, the drug delivery mechanism should not be

Figure 1: Oval's polymeric PDC technology.

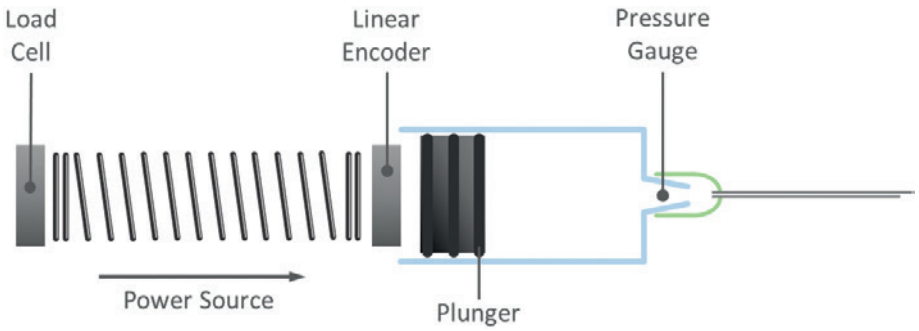

Figure 2: ICS Schematic.

influenced by any force applied through the user interface. However, in practice these forces often conflict: biologics may require high delivery forces, whereas specific user populations may require low operation forces from the user interface. Part of the challenge for engineers is to accept this conflict and design around it effectively.

It is possible to "decouple" the conflicting requirements between the user interface and drug delivery mechanism through use of a polymer PDC. To do this effectively, it is imperative that both the needs of the user and the delivery requirements of the drug are fully understood at an early stage in the design process.

AN APPROACH TO COMPLEX FORMULATIONS

The characterisation of a drug is an important step towards designing a fully integrated device. Oval has developed an Injection Characterisation System (ICS) to thoroughly analyse a range of complex formulations and their properties, allowing an improved understanding of how they must be delivered. This knowledge facilitates designing the optimal auto-injector mechanism specification (e.g. needle bore, spring force and container type), and also identifies factors with the potential to affect the user.

The ICS includes sensing capabilities at key positions (Figure 2) to allow feedback on forces and pressures within an auto-injector system during drug delivery:

- A load cell reports on the amount of force produced by the chosen power source
- The pressure gauge detects the pressure within the drug container
- The linear encoder provides data on the location of the plunger which can then be extrapolated into delivery speed.

Figure 3 shows the outputs of these sensors which can then be used to inform the design of the delivery system. Observing the relationship between the internal pressure, P, and the speed of the plunger during delivery, v, reveals information about the formulation properties. By using the modified form of the Hagen-Poiseuille equation,[2] the viscosity of any formulation can be evaluated:

$$P = \frac{8L\mu Av}{\pi r^4}$$

L – Needle length
μ – Viscosity
A – Plunger surface area
r – Internal needle radius

Testing the same formulation under different conditions (e.g. speed, needle gauge and temperature) allows for full characterisation of drug viscosity and the uniformity between conditions.

Many simple drug formulations are Newtonian (their viscosity will not change with shear force), however, complex formulations are becoming more common. These formulations may take the form of suspensions, emulsions or highly viscous fluids, often displaying many non-Newtonian characteristics, such as:

- shear thinning
- shear-thickening
- pseudo-plastic behaviour.

Comparison between the viscosity of the formulation and other characteristics will reveal any non-Newtonian behaviour, allowing it to then be modelled accurately.

The power law equation is the most common function used to model non-Newtonian fluids. It is assumed that rather than a direct correlation between shear stress, τ, and shear rate, $\dot{\gamma}$, as in a Newtonian fluid, the shear stress is proportional to a power of the shear rate.[3]

Newtonian fluid	$\tau=\mu\dot{\gamma}$
Non-Newtonian fluid	$\tau=K\dot{\gamma}^n$

"Oval's integrated device design philosophy has ensured that the subcutaneous platform has overcome many inherent issues seen with existing glass-based systems."

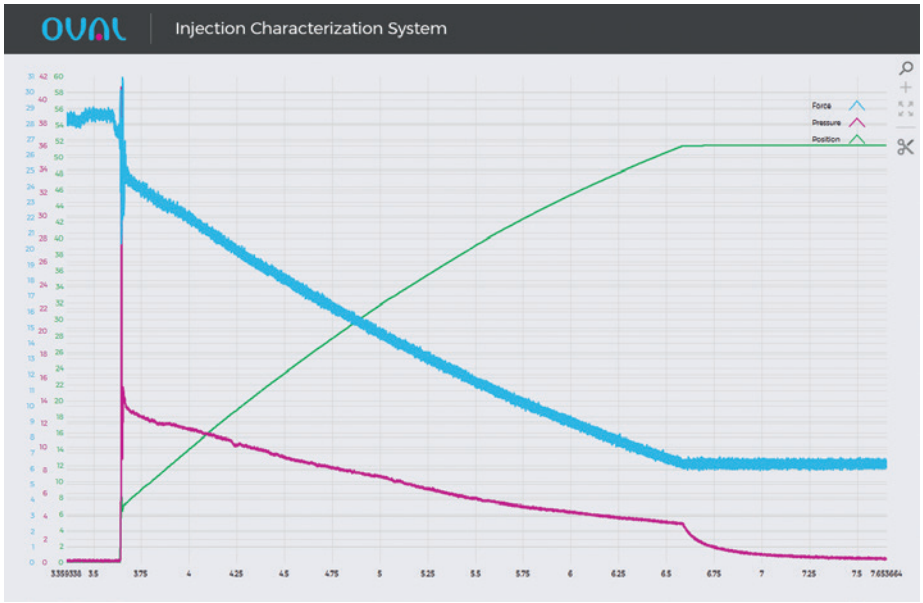

Figure 3: Output plots from the ICS during an injection. Plunger position in mm (green), delivery force in N (blue) and container pressure in bar (pink) against time in seconds.

Characterising formulations is a vital step towards developing an accurate numerical model for the behaviour of an auto-injector. It allows prediction of both delivery characteristics and the potential effects of external factors such as environmental conditions and device tolerances.

The culmination of this characterisation process is that the delivery mechanism can be optimised for each formulation through the appropriate specification of required functions and components, such as needle gauge and length, container dimensions and power source. Extensive knowledge of the drug delivery requirements allows for this aspect of the device to be decoupled from that of the user interface. This results in a fully integrated solution which has been developed with consideration to both the user and drug requirements, offering reduced risk, quicker development times and a competitive advantage over glass-based systems.

COMBINING USER AND DRUG REQUIREMENTS

Oval's subcutaneous platform embodies this integrated philosophy to device design (Figure 4). Combining both user and drug requirements into its development, the platform provides a patient-centric device for delivery of Sumatriptan to migraine and cluster headache sufferers.

The cyclic olefin PDC provides the option to configure component geometry freely, whilst "designing in" strength to manage high viscosities (>100 cP). This permits the delivery of complex drug formulations alongside the inclusion of a full range of features (e.g. automatic needle insertion, end of delivery feedback and passive needle safety), within a simplified and compact form. The subcutaneous auto-injector platform actively decouples the drug delivery requirements from those of the user interface. The use of separate springs for needle insertion and for drug delivery reduces the risk of recoil and excessive force on the patient, whilst retaining the ability to deliver challenging formulations.

Figure 4: Sumalen Ovali, 6 mg/0.5 mL Sumatriptan single use auto-injector for the treatment of migraines and cluster headaches.

This integrated approach is intended to improve clinical outcomes through the greater management of key device aspects, such as needle depth. Oval has taken three steps to ensure that the Sumalen Ovali delivers into the correct tissue (i.e. subcutaneous):

- **Specify an appropriate needle depth:** Informed by "state of the art" population research (e.g. ultrasound studies), correct inserted needle depth is essential to avoid compromising drug pharmacokinetics.
- **Manufacture with controlled tolerances:** Enabled through the use of a moulded polymeric container which ensures needle depth and mechanism interface accuracy.
- **Reduce injection depth variability:** The device is designed to promote consistent tissue compression during use, reducing needle depth variation from user technique differences or high activation force requirements.

Overlaying the needle length for 30 Sumalen Ovali devices (pink) with the results of 30 established Sumatriptan reference products (grey), Figure 5 demonstrates the impact of needle depth on the risk of an intramuscular injection at the thigh. The tissue depth risk profile is derived from two ultrasound studies of the thigh in >400 adult subjects.[4,5]

In summary, the needle length of the Sumalen Ovali is better specified for the population, achieving tighter manufacturing tolerances than the glass-based reference products (σ = 0.09 mm versus 0.20 mm). Tissue compression has the potential to further increase the risk of intramuscular (IM) injection. It should be noted that the IM risk estimates may be conservative, particularly for the reference product that incorporated a secondary activation button.

Oval's integrated device design philosophy has ensured that the subcutaneous platform has overcome many inherent issues seen in existing glass-based systems. Combined with their drug characterisation and user research capabilities, Oval is paving the way towards greater compatibility between auto-injectors and the delivery of biologics.

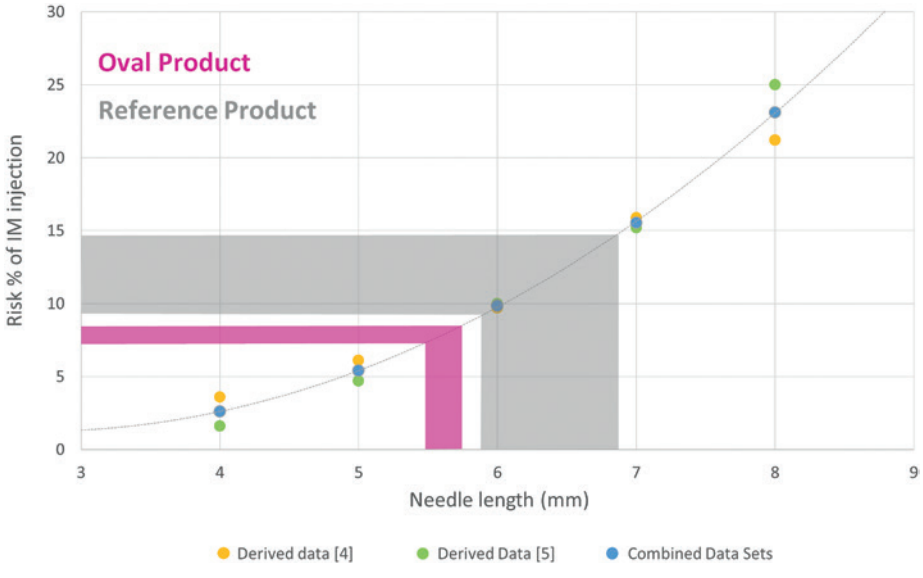

Figure 5: Injection depth versus risk of intramuscular injection at the anterolateral thigh.

ABOUT THE COMPANY

Oval Medical technologies was founded in 2010 by Matthew Young for the development of new generation auto-injector platforms, intended to meet the needs of patients. Matthew had previously worked for a leading medical device design consultancy, as Head of Product Design. In this role he worked on eight auto-injector projects for pharmaceutical companies to resolve design issues that impacted product performance and patient safety.

While working on these projects Mr Young concluded that glass syringes – which were designed in the 1950s for use by a human hand – did not provide a good starting point for auto-injector design. He considered that, in order to design devices that are intuitive to use whilst giving optimal performance, including consistent delivery times, a new design of primary drug container would be required.

Oval was therefore set up to design auto-injectors that meet the needs of patients and a broad range of drugs, including biologics. Current Pharma pipelines include formulations that pose a number of challenges, including those that are fragile and easily degraded, viscous formulations (some of which exhibit non-Newtonian characteristics) and, increasingly, delivery volumes of up to 3 mL. Owning the primary drug container allows integrated devices to be designed. This design freedom enables novel mechanisms to be introduced, smaller devices to be developed and the use of polymeric materials, giving customers complete control over critical component tolerances and control over their supply chain.

The acquisition of Oval by SMC Ltd, a US-based medical device manufacturing company in 2016, has provided access to world-class device manufacturing capabilities in multiple locations in the US and India. Oval/SMC can now provide customers with a complete service, from customisation of subcutaneous and intramuscular platforms, to production of clinical trials devices and commercial scale manufacture. SMC can also offer integration of filled primary drug containers with secondary packaging and distribution if required.

ABOUT THE AUTHORS

Jonathan Bradshaw is a Design Engineer with a background in industrial design and a Masters in Medical Device Engineering. Jonathan has experience in the design, development and commercialisation of fluidic dilution and dosing systems, cardiac catheterisation devices and more recently drug delivery technologies. Currently Jonathan works as a Device Development Engineer within Oval Medical Technologies where he focuses on furthering the development of their novel PDC and auto-injector technology to ensure their devices offer reliability and consistently high performance in combination with usability benefits.

Jonathan Lawson is a Design Engineer with 15 years' experience of the medical device industry, including the last five years working within the pharmaceutical industry on auto-injector technologies. Jonathan has developed an expert understanding of the medical device design process and has managed and delivered a range of novel development projects from artificial implants and surgical instrumentation through to drug delivery technology. Jonathan currently works within Oval Medical Technologies where his experience is helping to unlock the potential of their novel PDC technology through improved auto-injector designs. Specifically, Jonathan manages the corresponding design, test and risk management programme to ensure devices offer reliability and consistently high performance whilst introducing usability benefits.

Susanna White has worked as a Mechanical Engineer at Oval Medical Technologies for the past five years, where she is involved in the design and test programmes for their innovative polymeric PDC. Much of her work has focused on the study of highly viscous and non-Newtonian drug formulations – using numerical modelling techniques in combination with experimental investigation in order to achieve the most appropriate delivery system for challenging formulations. Susanna graduated from the University of Cambridge with a Masters in Engineering for the Life Sciences.

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DOES THE NEW EU MDR SPELL THE END OF GRANDFATHERING?

Here, Helen Simons, Quality Specialist, and Stephanie Ward, Quality Assurance Engineer, both of Cambridge Design Partnership, describe how the new EU Medical Devices Regulation will impact on "grandfathered" devices that were approved under old regulation and are currently on the market, but do not necessarily comply with current/updated regulatory standards, and explain the potential implications for device manufacturers.

The new European Medical Devices Regulation (MDR), introduced by the European Commission to replace the Medical Device Directive (MDD), has led to a lot of discussion about the implications for products on the European market.

It is worth remembering that the CE marking of medical devices under the MDD was actually optional, as with all EU directives (such as the Low Voltage Directive or the Machinery Directive). However, we all followed it closely as it provided an effective framework to demonstrate to EU authorities that our products were safe and effective. Now, under the MDR, these guidelines have become law, and all manufacturers, distributors, importers and notified bodies must follow them if they wish to sell medical devices in the EU.

> "Some companies may have implemented a post-submission vigilance programme to review regulatory requirements, and hence developed new versions of products or updated their products when significant changes came into force. However, this was not mandatory. This leads to a situation where products are on the market as they were at the time of submission – but it is not clear if they would be acceptable on review today."

With the regulation being a weighty 175-page document (compared with the 43 pages of the MDD), it can be easy to miss details in the text that may have significant impact. One such detail is only two sentences long, yet has wide-ranging implications:

"Manufacturers shall ensure that procedures are in place to keep series production in conformity with the requirements of the regulation. Changes in device design or characteristics and changes in the harmonised standards or CS by reference to which the conformity of a device is declared shall be adequately taken into account in a timely manner." Article 10, Part 9.

In short, the MDR is enforcing continual improvement. Manufacturers must ensure that all their products on the market meet the most up-to-date safety and performance requirements, as well as updates to harmonised standards used within the product submission to show conformity to the regulation.

HISTORY OF MEDICAL DEVICE SUBMISSIONS

To understand the implication of this enforcement of continual improvement, let's take a step back and look at how devices have been treated in the past.

Previously, when devices were put on the market there was no requirement to follow up on changes in standards or regulation on existing products. There was a requirement for companies to carry out "vigilance" during product development so that a device was developed to the applicable requirements at that time but, once submitted, the design was frozen.

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Future changes were required to be managed through change control, with consideration of current regulatory requirements as part of the impact assessment. But if the design remained the same, how could an impact assessment be triggered?

Some companies may have implemented a post-submission vigilance programme to review regulatory requirements, and hence developed new versions of products or updated their products when significant changes came into force. However, this was not mandatory. This leads to a situation where products are on the market as they were at the time of submission – but it is not clear if they would be acceptable on review today.

Such products, known as "grandfathered" devices, pre-date a now applicable standard, directive or regulation. For example, under the 1993 MDD, previously marketed devices were exempt from meeting the new directive and allowed to continue being marketed. The devices were sold on the basis that they were compliant before any new releases of requirements and had proven their safety by not having any reportable incidents. Therefore it was deemed acceptable for the devices to continue being on the market, without the added strain on manufacturers to conform to the new directive.

In addition to specific changes in regulatory requirements, best practice when it comes to developing medical devices has changed over time – each subsequent generation of regulation brings with it new requirements which need to be met. In recent times, the focus on human factors has been increased through the issuance of many US FDA guidelines. Similarly, the EU MDR now puts more focus on risk management and post-market surveillance, looking to ensure that data from complaints or reportable incidents is used to update the probability/occurrence scores in the risk analysis. The risk analysis is then reviewed to determine if the new information has affected the benefit-risk profile of the device – or even dictates a change of class of the device. The risk management process is now iterative throughout the lifetime of the product, rather than a static file compiled at the time of submission.

THE IMPACT ON DEVICES

In addition to regulations updates, harmonised standards, to which devices may conform, are regularly reviewed and updated to be in line with cutting-edge practices and thinking within the industry. So what does an update to a harmonised standard mean in terms of what would have to be done to make sure a product is compliant with the MDR?

To demonstrate this, let's use a drug delivery device which conforms to the current version of ISO11608-1 as an example. A hypothetical update is made to this standard which introduces new requirements for testing of the needle-based injection system. The device would then need to be tested against the new version of the standard to ensure it conforms to the new requirements. If any out-of-specification results arise from this testing, the design will require review and, perhaps, updating to bring the factors back in line with the new standard. Any design changes would then require a further impact assessment and would likely require, at minimum, an update to the risk management file to assess any new or changed risks. Other documents, such as the design inputs, would also need to be updated to reflect the requirements of the new standard.

On closer inspection, the activities that are required to comply with Article 10, Part 9 are beginning to sound much like a product development iteration. Many companies already have robust change control processes in place, as required by ISO13485 and current good manufacturing practice (cGMP), which would handle this. These just need to be expanded upon to integrate vigilance for existing products and ensure that they are updated as required.

It is important that companies have someone responsible for vigilance, who can be aware of upcoming relevant publications, and also the timescales required for any applicable changes. If any complex changes are required, considering both the design and any related aspects of the manufacturing processes, planning and implementing these changes in a timely manner is essential.

THE DEADLINES

Every device available on the market must comply with the MDR by the date of application (May 26, 2020). However, as with all legal documents, tucked away at the back there are provisions that allow manufacturers time to get their devices compliant with the MDR beyond the three-year transition period.

Article 120 details all the exemptions for medical devices with a valid MDD or Active Implantable Medical Device Directive (AIMDD) CE-mark certificate that expires after the May 26, 2020 deadline (Figure 1).

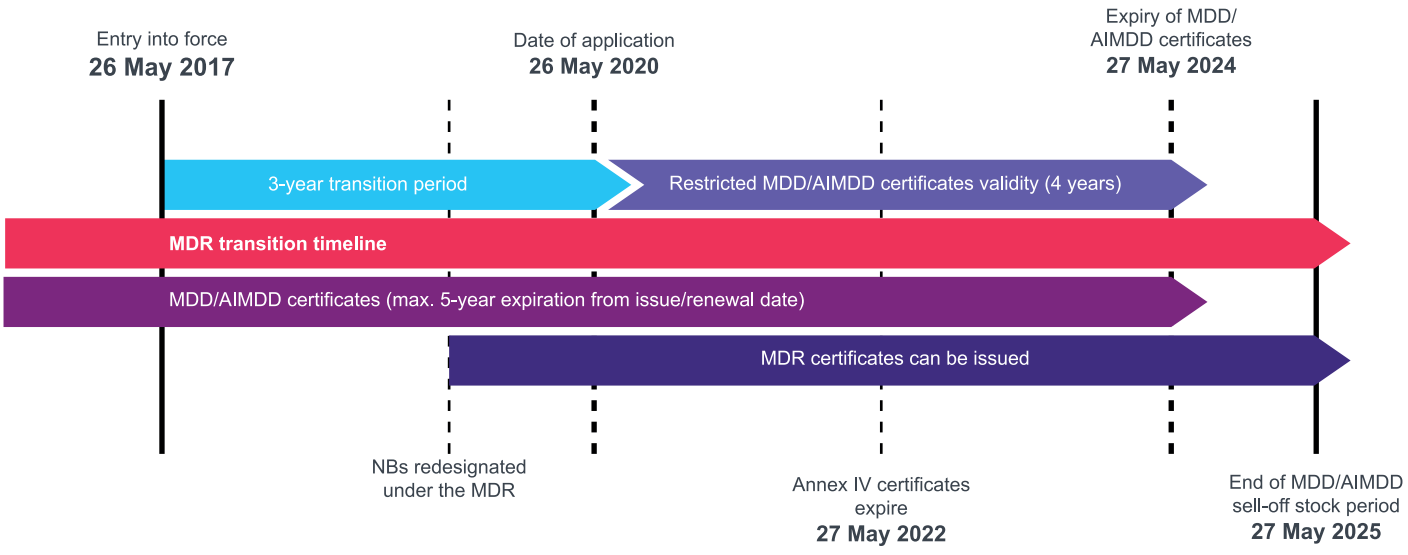

Figure 1: Article 120 transition timescales.

It outlines that a certificate issued prior to May 25, 2017 shall remain valid until the end of the period indicated on the certificate, unless it exceeds May 27, 2024, by which point all MDD/AIMDD certificates will become void (unless the certificate was issued in accordance with Annex IV of the directives, in which case it will become void, at the latest, by May 27 2022).

A manufacturer can continue to distribute CE-marked devices for five years beyond the date of application deadline if the device was placed on the market prior to May 26, 2020, or placed on the market after May 26, 2020 if a valid certificate is in place (as previously mentioned). This would mean a manufacturer generating stock under a MDD/AIMDD certificate prior to May 26, 2020 and placing on the market with a declaration of conformity to the applicable directive. Any remaining stock will be required to be removed from the market by May 27, 2025.

A manufacturer can also continue to manufacture and distribute a CE-marked product that complies with the MDD/AIMDD until May 27, 2024 (four years after the date of application) providing the following apply:

- The manufacture has a valid MDD/AIMDD certificate
- The product continues to comply with either of those directives
- There have been no significant changes in design and intended purpose
- The manufacturer complies with the new MDR requirements for post-market surveillance, market surveillance, vigilance, registration of economic operators, and registration of devices, whilst not making any significant changes to the device design (as per the previous point).

The challenges of manufacturing and distributing medical devices under a MDD/AIMDD certificate after May 26, 2020 mean it is not "carry on as normal", and manufacturers should be planning for the MDR transition in earnest to meet the three-year implementation deadline. A thorough transitional plan allows for any additional time given by Article 120 to be used to sell pre-MDR stock.

IN CONCLUSION

For some companies, the new MDR will not mean a massive change – they will already have procedures in place that ensure they continue to meet the regulatory requirements. But many organisations with grandfathered devices face a huge jump from potentially pre-MDD to MDR, and they are unlikely to have the sound groundwork of the MDD on which to base the additional requirements of the MDR. These companies will not only have to ensure they comply with the new MDR, they also face the task of updating or creating processes, procedures and documents to comply with the vigilance and surveillance requirements to make sure their products meet the new standards.

How well companies adapt to these challenges will be seen in how many products are removed from the market due to non-compliance with the MDR. It could even mean the loss of small medical device manufacturers who find the cost of compliance is too high.

TORSTEN MASCHKE, DATWYLER SEALING SOLUTIONS

Torsten Maschke has been Chief Executive of the Sealing Solutions division of Datwyler and a member of the group's Executive Board since October 2016. Before joining Datwyler Group, he was responsible for the worldwide distribution of sealing and damping solutions for the automotive industry at Freudenberg Group (Weinheim, Germany). Prior to this – having completed his education in 1996 – he was employed in various international management roles within the automotive business of the Freudenberg Group. Maschke earned degrees in Mechanical Engineering from Münster University of Applied Sciences (Münster, Germany) and Industrial Engineering from Bochum University of Applied Sciences (Bochum, Germany).

Interviewed here, Mr Maschke discusses some of the major trends and changes that are sweeping the healthcare and pharmaceutical industries, and highlights the significant role Datwyler's offering – in the area of parenteral primary packaging components – will play in the future as the industry evolves and new technologies emerge.

Q In your opinion, what are the biggest challenges for the pharma and healthcare sectors in a growing, global and competitive environment?

A The pharma and healthcare markets are continuously facing challenges and undergoing changes that are directly linked to the transforming needs of state-of-the-art healthcare. This applies not least around clean manufacturing. In a growing, global and competitive environment, pharma and healthcare companies need a deep understanding of the industry's current and upcoming requirements, and opportunities for future growth. Let me pick out three examples. Firstly, the increasing demands from the pharma industry's highly sensitive drugs, such as biologics and biosimilars. These require cleanliness in production, such as cleanroom manufacturing – especially with a view on the existing regulatory framework. We already have a zero-defect philosophy in place at Datwyler to ensure the highest product quality. Secondly, digital health is another hot topic for the healthcare sector with huge growth potential, as it is getting increasingly important for clinical, therapeutic and even individual purposes. Finally, it is important to combine global knowledge and local manufacturing expertise to leverage lean production processes and build on an optimised supply chain.

> "The demand for biologic drugs still remains strong, and the biosimilars market is following in its footsteps. Growth here is likely to exceed expectations and might well go into double figures. Therefore, requests for coated products, e.g. cartridge components, are rising."

Q How do pharma and medical manufacturers have to position themselves to keep up with international competition?

A First of all, it is essential to listen to your clients and to constantly observe market developments. In a competitive healthcare market, pharma and medical manufacturers rely on partners who can assist them in mastering the challenges of the global healthcare sector, enabling them to recognise their potential. This includes deep engineering competence regarding innovative technologies and, furthermore, technical knowledge transfer. Finally, manufacturers have to meet customers' business challenges with comprehensive industry expertise and lean production processes. That means providing reliable product solutions on a global scale throughout the entire product lifecycle.

Q Do you expect the pharma market to grow with the same speed in the next few years as it did in the last? Or will it slow down?

A It is difficult to provide precise forecasts, or even predictions, on market growth. For the pharma market, growth is estimated at 6-10% but always with regional differences that we as a globally acting company have to take into account. However, looking at the general population growth, and the correlating increased number of medical treatments needed, we can definitely expect more growth within the pharmaceutical market in the future.

Biologics and biosimilars are especially in the spotlight. The demand for biologic drugs still remains strong, and the biosimilars market is following in its footsteps. Growth here is likely to exceed expectations

and might well go into double figures. Therefore, requests for coated products, e.g. cartridge components, are rising. High value products will be an essential driving factor for growth because biologics and biosimilars in cartridge or pen packaging can under no circumstances be contaminated, e.g. with silicone oils.

Q Which trends and future topics do you expect to shape the pharma market in the next five years?

A As a globally acting company in the pharma industry we need to anticipate any upcoming trends. There are several developments that we see as important and interdependent trends in the pharma market right now. One important field is evolving around injectable drugs and their future forms of administration.

Other very important developments are happening in the treatment of diabetes patients, especially regarding the form and administration of their medication. The devices used to treat diabetes are changing and will continue to do so – both to facilitate drug administration and to provide more comfort for the patient.

Closely connected with diabetes are the developments in the digital health sector and wearables, which monitor and administer drugs. This also falls into the growing field of self-medication, particularly when we lay the focus on patients in emerging markets who may not yet have access to the facilities and infrastructure of the Western world. This leads us to the very important topic of patient safety. Safe and secure access to, and administration of, drugs will be even more essential in the future.

> "Investments in research and development are essential to stay ahead of shifting market dynamics and to always remain competitive. As innovative drugs emerge, there is also a need for the development of new and compliant packaging materials."

> "We entered into a partnership with the Interuniversity Microelectronics Center (IMEC) in Belgium to conduct research on wearable devices and sensors with focus on earbuds and brain monitoring platforms. This partnership has been very beneficial for both sides."

As mentioned before, we expect the field of biologics and biosimilars to grow further. The requirements for drug packaging and elastomer components are always evolving and rapidly changing. Market trends indicate a growing demand for packaging solutions and components with the lowest possible risk related to drug stability and compatibility, minimised by providing extremely low particle levels and supported by a detailed lifecycle management strategy. With regard to patient safety, for a therapeutic protein the exact chemical make-up and three dimensional conformation can influence the efficacy of the drug product. Interactions with leachables, including silicone oil, can present a risk to the safety of therapeutic proteins and finally prevent the success of the drug product.

To summarise: there are several strong trends, especially if we consider the shift of some countries towards a more highly regulated market for the coming years. It is important to see their interdependencies and put them in the overall context of the development within the fast paced healthcare market.

Q Has the importance of R&D changed over the years? Has it increased?

A Investments in research and development are essential to stay ahead of shifting market dynamics and to always remain competitive. As innovative drugs emerge, there is also a need for the development of new and compliant packaging materials. As a supplier, we always need to be able to cater to these needs. This ensures not only that the market requirements are met, but that future-oriented solutions can, and will, be provided.

Co-operations and partnerships are very important to achieve these goals. For example, at Datwyler we entered into a partnership with the Interuniversity Microelectronics Center (IMEC) in Belgium to conduct research on wearable devices and sensors with focus on earbuds and brain monitoring platforms. This partnership has been very beneficial for both sides.

Q Oncology and molecular therapies have been growth drivers for the pharmaceutical market in the past few years. Is this development going to continue?

A Particularly for molecular therapies, it will likely stay that way. There are more and more drugs being developed and registered for this field. At the moment, many drugs are in the clinical trial phase or in the process of being approved.

There are several factors which play into this. New drugs have to be developed for indications which had not been present in the market in the past, so innovative therapeutics are needed. Take diabetes for example, this disease is continuously growing more common – and so the demand for new types of drugs to battle the disease will also grow. Following closely are new methods for drug administration, including novel medical devices. New forms of therapy allow diabetes patients to monitor their blood sugar levels and health status themselves. The next step for patients is automatic drug administration via a wearable device, meaning that the patients themselves will not have to be hyper-aware of their disease at all times.

Q Will those new forms of diagnosis and therapy also create new business models?

A Most definitely. New, highly individualised ways of treatment will create new business opportunities and the potential for new products. This is a development that we are anticipating and preparing for. Wearables and body sensors are just a few examples of areas we are currently exploring.

We are constantly screening the market for new trends and business opportunities. As I emphasised just now, co-operations and partnerships are key. A lot of our customers have their own innovation centres, with

which we are in close contact. The issues they are working on are important in helping to identify new trends that we can explore together. Particularly as a global supplier, we can adjust or enhance our rubber components to support our customers, contribute to trends and benefit from them too. In the past few years, this has been especially important for digitally based and/or digitally supported methods of diagnosis and treatment.

Q So, is this a demand from your customers? They tell you as a company that they would like to involve you in the R&D process?

A Generally, yes, because the main objective is always to make the whole approval process as lean and efficient as possible. And naturally it is very important that all components come together as soon as possible, to further the development.

At the end, we always need to have a strong sense for future trends in order to advance global healthcare. Simultaneously, we have to provide tailor-made and smart solutions that meet current challenges and requirements.

Q How strongly will new technologies (such as imaging processes, new analytic methods, genetic research, predictive analysis, data exchange between patients and doctors, and electronic patient files) influence the market?

A I expect these technologies to be used for enabling patients to get a fast and comprehensive diagnosis and to introduce an effective therapy. Many of these new technologies can be used as preventative measures, for example, to diagnose or predict conditions even before the illness can break out. We want to contribute an essential part in this process with our products.

Q Apps are already being used in the US to collect data for clinical studies. Are such developments in the best interest of the patients?

A The whole issue of digitisation and the collecting of individual data is not only a challenge for the pharmaceutical industry. For example, we have been following the discussions to what extent personal data can be stored and used in the automotive sector for quite some time now. I am sure that the ongoing legal discussion around it will provide us with clear guidelines and laws. The discussion is also pressing for the pharma industry, but in the end patients will have to decide for themselves if, and to what extent, they want to use these opportunities.

Of course, questions of data safety will come up if sensitive data on health statuses or conditions can be found online. In my opinion, this is not just a question of the legal framework in each country, but one that should ideally be aligned globally. It is also a question of how far each individual is willing to engage with and participate in the new digital health world. I expect that it is just a matter of time before our society will accept, and even embrace, the possibilities of digital health. And essentially it is already beginning. We have apps on our phones, or even watches, which already measure and monitor certain health factors. Theoretically, you could already monitor your blood pressure or your temperature with a smartwatch that helps to generate a shareable picture of your health status. Finally, it enables a better understanding of patients' conditions and the appropriate therapies. This should be in my interest as a patient. Nevertheless, it is up to patients themselves how their data is dealt with. It is important to be aware of the advantages and disadvantages.

Q In summary, the pharma industry needs to look to the future, screen for trends, watch the markets, observe the legal situation and actively take part in all developments?

A Exactly. We certainly have several challenges we must take on. However, I think that the industry is well prepared and interested to invest in a safe and promising future in creating products, offering new services and generating sustainable, lasting results to improve the medical experience of patients. I am confident that the industry is on the right track to face the aforementioned challenges in order to offer the right solutions for the future.

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UNISAFE®: THE IMPORTANCE OF ROBUST DESIGN PREDICTIONS IN DEVICE MANUFACTURING

Here, Damian Holland, UniSafe® Design Lead at Owen Mumford, outlines how the design team went about creating a safer and user-friendly springless safety syringe – UniSafe® – which bypasses some of the problems associated with spring-based devices.

The global healthcare landscape is complex, and current changes in approach are driven primarily by the need to protect the end-user's health and safety.[1] With healthcare moving towards safety – accelerated by increased regulation scrutiny and healthcare reform – medical device manufactures are exploring new ways to protect end-users and healthcare professionals.

To respond to these conditions, advances in design and manufacturing technology are necessary. The requirement to achieve a market-ready device in an efficient and timely manner has encouraged medical device manufacturers to evolve quickly. In an increasingly competitive landscape the output achieved must meet the desired device specification, market regulations and end-user requirements all in one go.

However, in reality achieving this is not always straightforward. For medical device manufacturers and their partners, steps must be taken to simulate or predict the performance of a device ahead of production to minimise development risk.

> "A key design feature – the removal of the spring – would ensure that the end-user could clearly see the drug had been administered, whilst also allowing an easier view of the labelling without having to spin the syringe barrel."

THE CASE FOR A NEW DEVICE

Injections have become one of the most commonplace medical procedures worldwide. Most injections are delivered by retractable and non-retractable safety syringes, which are activated through a spring component. Using a spring in safety devices has previously led to challenges. One issue is accidental activation, where a device may activate in transit; another is accidental underdosing, where it may be difficult for the user to confirm visually that the full dose has been delivered. This is common when a spring is placed at the front of the syringe barrel, obstructing the view.

The design team at Owen Mumford undertook an observation period and conducted research to identify the challenges facing healthcare providers and end-users. We responded to a requirement for an effective safety device, which the team met through the design and development of UniSafe®. The device would be springless, designed to work with existing, prefillable syringes, and offer a safe, comfortable experience to the end-user. A key design feature – the removal of the spring – would ensure that the end-user could clearly see the drug had been administered, whilst also allowing an easier view of the labelling without having to spin the syringe barrel.

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DESIGNING A NEW DEVICE

Working with an array of different materials and design specifications can present challenges, so research and analysis work is imperative in getting the device design correct. Close collaboration between project teams ensures our devices are designed for manufacture whilst still keeping end-user satisfaction in mind.

The first option explored when developing UniSafe® was to start with an existing, proven prefilled syringe and build a spring driven safety mechanism around it. This idea was quickly rejected on the basis that it may introduce other compromises to device performance. Another possibility was to design a completely new safety syringe and provide a brand new solution from scratch. However, this would mean the use of an unproven primary container, a prospect that would be considered unattractive by pharmaceutical companies. Furthermore, this idea would be difficult to integrate into existing filling lines, and would increase training requirements within the healthcare system.

It was clear that a new approach was required. To achieve a result that would meet end-user treatment needs and the requirements of the pharmaceutical industries, we had to combine forward thinking alongside data analysis to define the appropriate design.

Use of Computer-Based Simulation

The use of computer-based simulation helps any new design to be tested rigorously and ensures that a device will perform as required, both during manufacture and when received by the end-user. In the development of UniSafe®, undertaking stress analysis was a key component of this, and the use of Finite Element Analysis (FEA) allowed us to determine potential areas of stress and strain experienced by the device during use – permitting design optimisation before developing the concept further. One particular area of focus was the locking mechanism, which had to resist override forces after activation, as defined by our human factors assessments (Figure 1).

Next, we wanted to ensure that the parts required would fit together seamlessly, meeting design intent. Statistical analysis was undertaken to define the physical limitations and geometric tolerances of the components to balance device performance with process capability.

In order to determine if the design specifications would be achievable for the manufacturing process, we used known process capabilities to model and predict potential variations that could arise within the manufacturing process and thus modified the design accordingly to better accommodate these fluctuations.

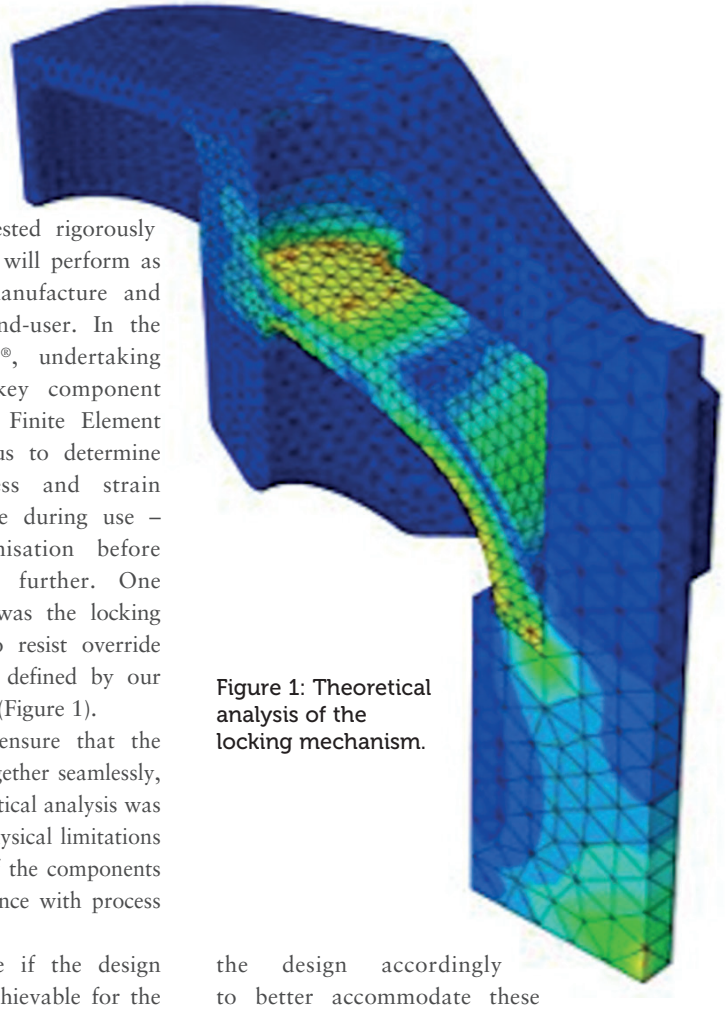

Figure 1: Theoretical analysis of the locking mechanism.

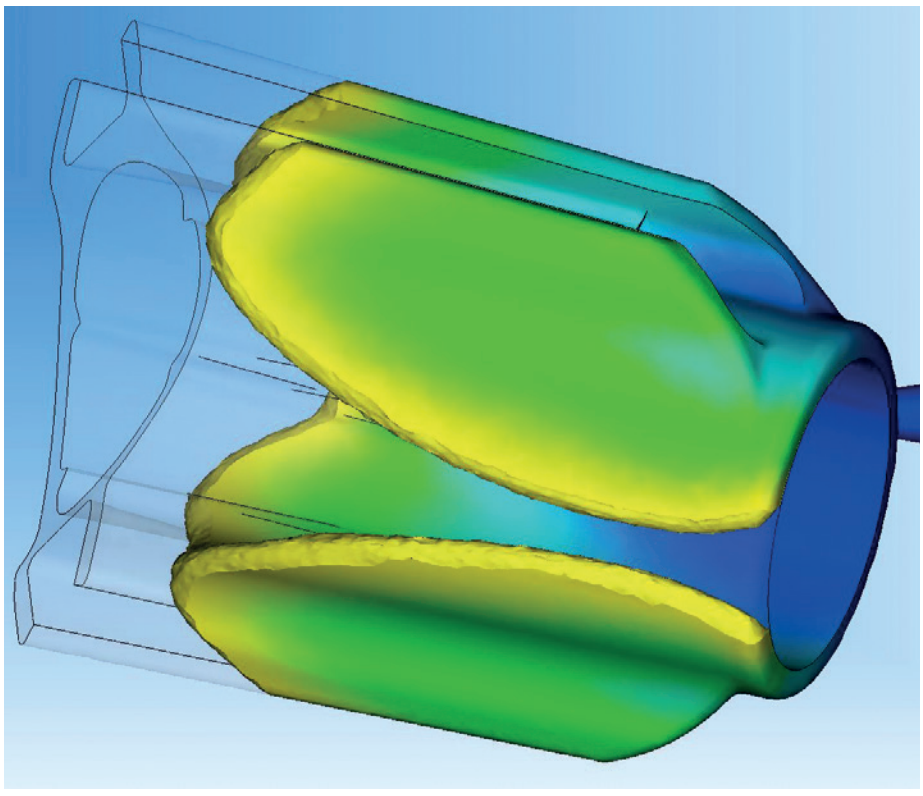

Figure 2: Computer simulation of the moulding process.

We also utilised computer-based simulations to analyse and predict the behaviour of the polymers during the injection moulding process (Figure 2). These simulations allowed us to identify how stable the component geometry would be after moulding and where any potential stress points may propagate, permitting further design iterations before placing tool orders.

However, it is vital that attempts to improve production viability do not compromise the quality of the product: an appropriate balance must always be maintained. Due to the low part count, minimal component interactions and overall simplicity of the UniSafe® design, it has been possible to achieve wide production tolerances without negatively affecting the performance of the device.

Of course, not all development work can be virtually simulated, so we also utilised our in-house 3D printing and external soft tooling capabilities to further test and iterate upon the design.

Refining the Device

Once the device's performance was deemed acceptable, the prototypes we created were used in human factors studies to identify

further improvements that could be made to better optimise UniSafe® for the end-user.

Early formative studies demonstrated that the safety plunger and finger flange did not offer enough support to the user, whilst activation needed to be improved as part of the passive safety feature mechanism. An effective design requires constant feedback, and this input fed into a further design iteration of UniSafe®. We increased the surface area of the plunger and flanges to improve comfort and a unique thread mechanism added to the passive safety feature mechanism made the activation smoother.

This rigorous prediction, testing and iteration cycle ensured that we could be confident in the device development, and that the benefits would be maximised for both pharmaceutical companies and end-users.

Building Simulation Into Product Design

The computer-based simulation techniques we use are constantly evolving. As we carry out ever more advanced simulation analysis on behalf of our manufacturing clients, we can help them to evaluate early designs and know what will and will not work in production. This phase of testing provides better guidance on potential issues in physical manufacturing ahead of committing to real-world investment.

ADVANTAGES OF UNISAFE®

UniSafe® is designed to improve patient confidence when injecting and to reduce any potential barriers to sustained treatment.

The device has a unique passive needle retraction mechanism, so the user does not need to take any additional steps to shield the needle after use. This reduces the risks associated with needle re-use and contamination, and provides additional protection for patients and healthcare professionals.

To improve comfort and user experience, UniSafe® has a larger, more ergonomic plunger head and a smoother, more integrated finger flange. This ensures that the end-user can operate the device confidently and intuitively, regardless of hand size, dexterity or condition. In addition, UniSafe® has been developed with an unobscured prefilled syringe barrel, allowing the user to view the drug and labelling without having to spin the syringe barrel, reducing the risk of underdosing.

> "The device has a unique passive needle retraction mechanism, so the user does not need to take any additional steps to shield the needle after use."

CONCLUSION

UniSafe® brings together our expertise across human factors testing, product design and manufacturing engineering to create an injection system that will help improve lives, reduce healthcare costs and deliver treatments more efficiently.

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 major pharmaceutical and diagnostic companies. Owen Mumford's goal is to improve quality of life, encourage adherence to treatment programmes 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 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 65 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.

REFERENCE

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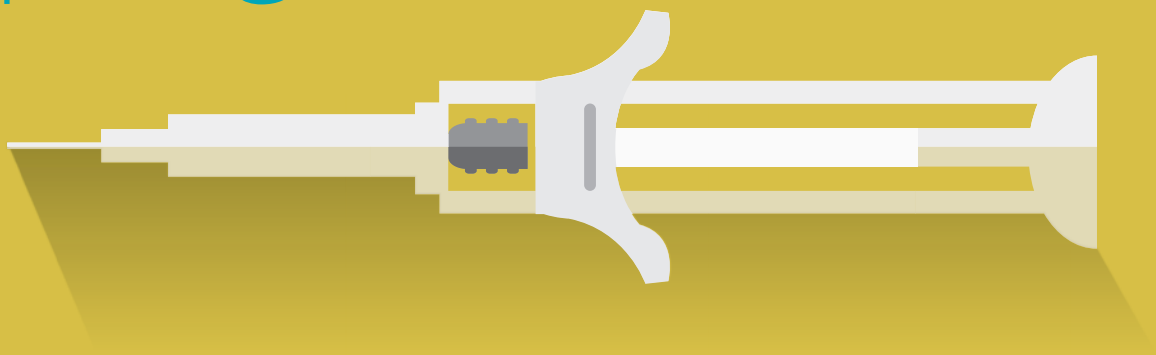
ABOUT THE AUTHOR

Damian Holland is is a design engineer at Owen Mumford and has worked in the medical device industry for four years. He holds a BSc in product design. His current role involves generating new device concepts and developing them through the whole product lifecycle, from initial idea to production.

UniSafe®

Safety is Springless



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SPECIALTY COATING SYSTEMS™
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CRITICAL MATERIAL CONSIDERATIONS FOR DRUG CONTAINMENT

Here, Dick Molin, Medical Market Segment Manager, Specialty Coating Systems, highlights some of the hazards that arise through the use of traditional lubricious coatings, such as silicone oil in syringes, pumps and other parenteral delivery devices. Particular focus is paid to the problems of protein aggregation and trace impurities leaching from elastomeric components before going on to describe how the polymer Parylene, applied as a very thin coating using the company's unique deposition method, avoids them.

THE GIVEN NEED FOR SAFETY

The safe and effective containment of pharmaceutical products is paramount to the successful treatment of patients. To that end, as new, aggressive drug chemistries and compounds are developed, choosing the right packaging material is becoming increasingly critical. Newer chemistries have been shown to affect the long-term reliability of some traditional materials, which necessitates a re-examination of the existing materials and strategies used to preserve the purity of medications, particularly those that are stored for an extended period.

For any given containment system (e.g. a vial, IV kit, prefilled syringe or insulin pump), the patient and administrator rely on the flawless performance of each and every material and component. As medications must remain pure, the materials themselves cannot act as a contaminant or as a catalyst for undesired effects. Since today's ever changing list of available pharmaceuticals includes medicines that can indeed be impacted by their containment systems, it is up to materials experts and device manufacturers to ensure the protection of medications. Of concern first and foremost is the preservation of purity, which is achieved through strict control of manufacturing, filling, packaging and storage processes.

> "Parylene conformal coatings have a long history of protecting devices that span the entire medical device application range – from externally communicating to implantable devices. Included in the Parylene portfolio are life-saving and life-enhancing technologies such as cardiac pacemakers, neurostimulators, shunts, cochlear and retinal implants, and electrosurgical tools."

As previously stated, it is critical that medicine loaded into a containment system remains unaffected by any and all surfaces with which it comes into contact.

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One known possibility is the potential for trace contaminants in packaging materials to leach into the medicine, compromising its purity. For example, trace elements in one or more components of a given elastomer blend can be problematic, as can environmental contaminants that are unintentionally added during component manufacture or assembly. Even known materials that are added to enable specific performance characteristics – e.g. to provide lubricity to ensure smooth and reliable dosing – may be an issue. One or more of these concerns may be present and are particularly an issue for elastomeric components, which are vital for making seals, ensuring reliable containment and enabling complete and accurate delivery of the intended dose.

The preference, of course, would be to use a pure, fully compatible material to avoid such hazardous conditions. However, those options are scarce and do not always maintain one critical characteristic – lubricity. A variety of additive materials have been used over the years to improve lubricity on preferred materials, with the challenge being to achieve the desired balance between adequate barrier properties and the appropriate level of lubricity to ensure proper delivery mechanics.

In the examples of a prefilled syringe and an insulin infusion pump, the dosing mechanism may rely on the infrequent movement of a plunger within a reservoir. The use of traditional spray-type lubricants, such as silicone oil, may impart the required lubricity but provide no barrier properties to leachables. Additionally, the longer such spray-type lubricants sit unused, the less reliable they become due to their migration from critical contact surfaces. Silicone oil is also known to create longer-term storage issues related to particle and protein aggregate levels of some common solutions.

Among the more familiar and common protein drugs is insulin, which is typically delivered via standard syringe, pump or prefilled syringe. Prefilled syringe technology is particularly noteworthy as it continues to experience increased adoption throughout the industry. With an estimated three billion prefilled units manufactured in the year 2013, forecasts indicate production will grow to 6.7 billion by 2020. As can be attested to by regular insulin users, medication cloudiness is often observed after weeks or months in storage as a result of aggregation due to the influence of silicone oil droplets. While cloudiness has not been demonstrated to be enough to deem the dose entirely unusable, it has been determined to impact medicinal value – to the detriment of the patient and, consequently, the drug manufacturer. Studies have shown a direct cause and effect between cloudiness and low molecular weight silicone oils. As such, efforts are being made to reduce this effect by tailoring silicone oils, but successes achieved thus far have been limited.

While insulins are the most common medications affected by silicone oils, there are others with which similar issues have been discovered. Monoclonal antibodies (mAbs) are cited to be one example. Chemotherapy drugs are often joined to mAbs to create a targeting mechanism for specific types of cancer cells. Another drug subject in controlled aggregation studies is ranibizumab (Genentech's Lucentis®), an mAb fragment used to treat macular degeneration. These classes of drug, amongst others, stand to lose efficacy over time in storage due to the detrimental aggregation related to the use of silicone oils.

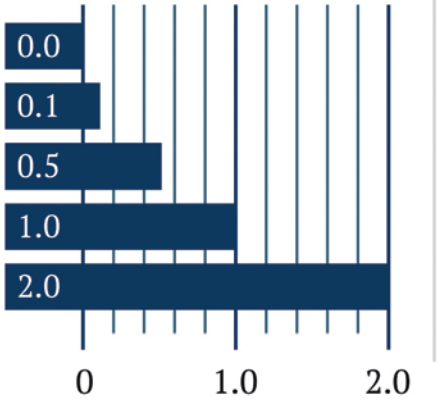
THE PARYLENE ANSWER

The challenge posed by the storage of these (and similar) compounds has been addressed by using a vapour-deposited polymer commonly known as Parylene. Parylene conformal coatings offer a pure, extremely thin, lubricious replacement to silicone oils. Typically applied in thicknesses of only 1-2 µm, Parylenes impart the required lubricity to minimise break-out forces while also providing barrier properties that can enhance long-term solution purity, which may otherwise be compromised by leachable substrate impurities (Figure 1). Also of great benefit is Parylene's benign chemistry, which does not result in the detrimental aggregation seen with silicone oils.

Parylene conformal coatings have a long history of protecting devices that span the entire medical device application range – from externally communicating to implantable. Included in the Parylene portfolio are life-saving and life-enhancing technologies such as cardiac pacemakers, neurostimulators, shunts, cochlear and retinal implants, and electrosurgical tools. Also included are infusion components like needles, barrels, plungers, seals and septa, as well as high-purity storage containers, protecting both the device from the drug and the drug from the device. Additionally, Parylenes are well suited for use on combination devices such as prefilled syringes and drug-eluting coronary stents.

Because Parylenes are applied under vacuum via a vapour deposition process, the size and complexity of components do not inhibit the coating's ability to form a conformal layer of protection. Coating with Parylene has virtually no impact on the dimension of the device, regardless of how small it is, and ensures device and component biocompatibility.

Parts to be coated are placed in the ambient-temperature deposition chamber and the dimer (raw material Parylene) is placed into the vaporiser at the opposite end of the system. The dimer sublimates and is then pyrolised into reactive monomer molecules. The Parylene monomer enters the ambient temperature chamber and polymerises on the substrate (see Figure 2 over the page).



Calcium (ppm)	Aluminum (ppm)	Zinc (ppm)
0.17	4.2	50
0.15	1.8	35
0.03	0.1	12
<0.002	<0.05	0.2
<0.002	<0.05	<0.05

Figure 1: Effect of Parylene C thickness on extractable metals in rubber specimens.

Because it enters the deposition chamber as a gas, the coating material's penetration power is superb, enabling film to grow on all surfaces and edges uniformly. This includes inside the smallest crevices of a substrate and into the porosity of elastomers – porosity that may be inherently problematic from a tribological standpoint.

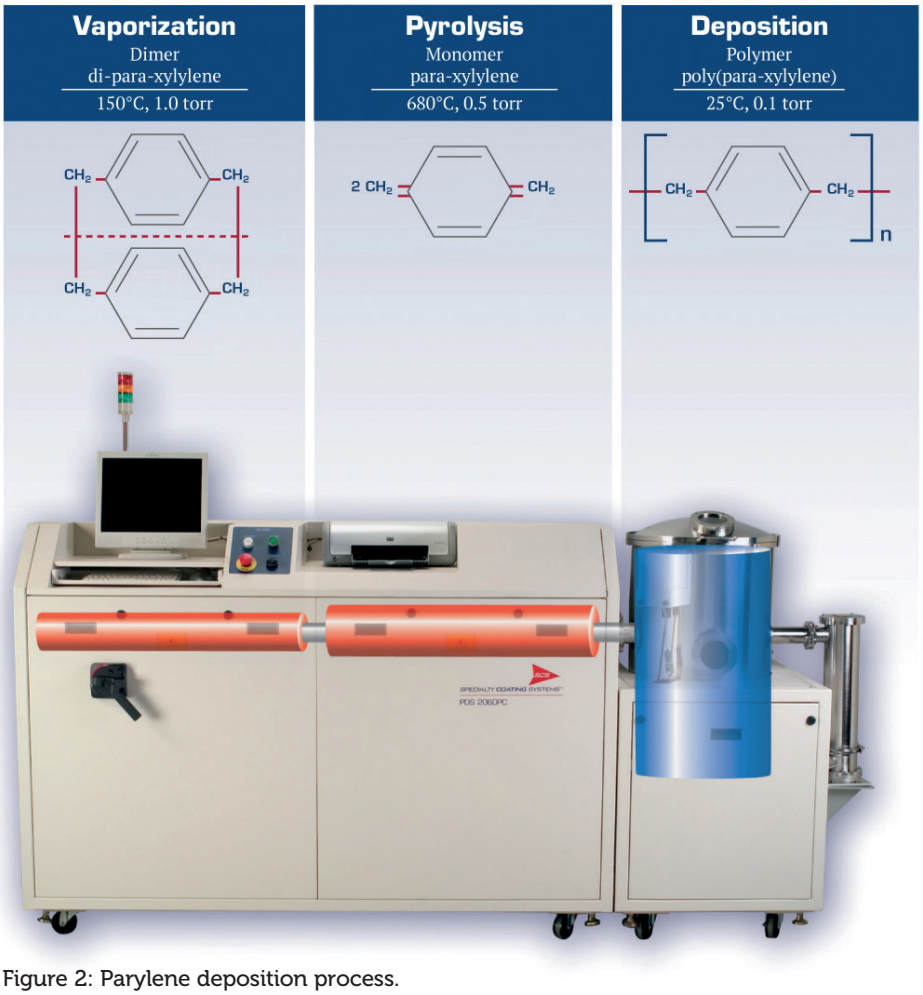


Figure 2: Parylene deposition process.

ISO-10993 BIOLOGICAL EVALUATIONS

	SCS Parylene Variant		
Tests	**N**	**C**	**Parylene HT**
Cytotoxicity	✓	✓	✓
Sensitization	✓	✓	✓
Intracutaneous Reactivity	✓	✓	✓
Acute Systemic Toxicity	✓	✓	✓
Implantation (2 weeks)	✓	✓	✓
Implantation (12 weeks)	✓	✓	✓
Implantation (26 weeks)	✓	✓	✓
Hemolysis	✓	✓	✓
Lee–White Clotting Time	✓	✓	✓
Pyrogenicity	✓	✓	✓

Figure 3: ISO-10993 biological evaluations.

The unique Parylene deposition process allows ultra-thin films to be formed in thicknesses ranging from several hundred angstroms to dozens of microns. Its use has been demonstrated on a host of device classifications that range from surface devices to implant devices, including combination products, e.g. drug eluting coronary stents. Parylene coatings are certified to comply with ISO 10993 as well as USP Class VI biological evaluations (Figure 3).

Whether designers are working on new devices or improving upon existing technologies, one thing remains true: pharmaceutical therapy is continuing to expand both in the technologies offered and conditions treated. As these technologies become more advanced, protection of devices and associated components becomes even more critical. Parylene conformal coatings offer lubricious, biocompatible protection to meet the challenges these devices face, all while increasing functionality and reliability.

ABOUT THE COMPANY

Headquartered in Indianapolis, IN, US, Specialty Coating Systems (SCS) is a leader in Parylene conformal coating services and technologies. As the direct descendant of the companies that originally developed Parylene, SCS has 45 years of experience and expertise that it leverages for its customers through coating facilities throughout the Americas, Europe and Asia.

ABOUT THE AUTHOR

Dick Molin is Medical Market Segment Manager for Specialty Coating Systems (SCS). His focus includes expansion of SCS's medical market activities and new medical applications for Parylene conformal coatings. Molin has over 30 years of experience in product and process development, including 17 years at SCS where he actively worked with advanced materials and processes for Parylene technologies. He earned his Bachelor's degree in Materials Engineering from the University of Arizona and holds a Master of Business Administration in Technology Management from the University of Phoenix.

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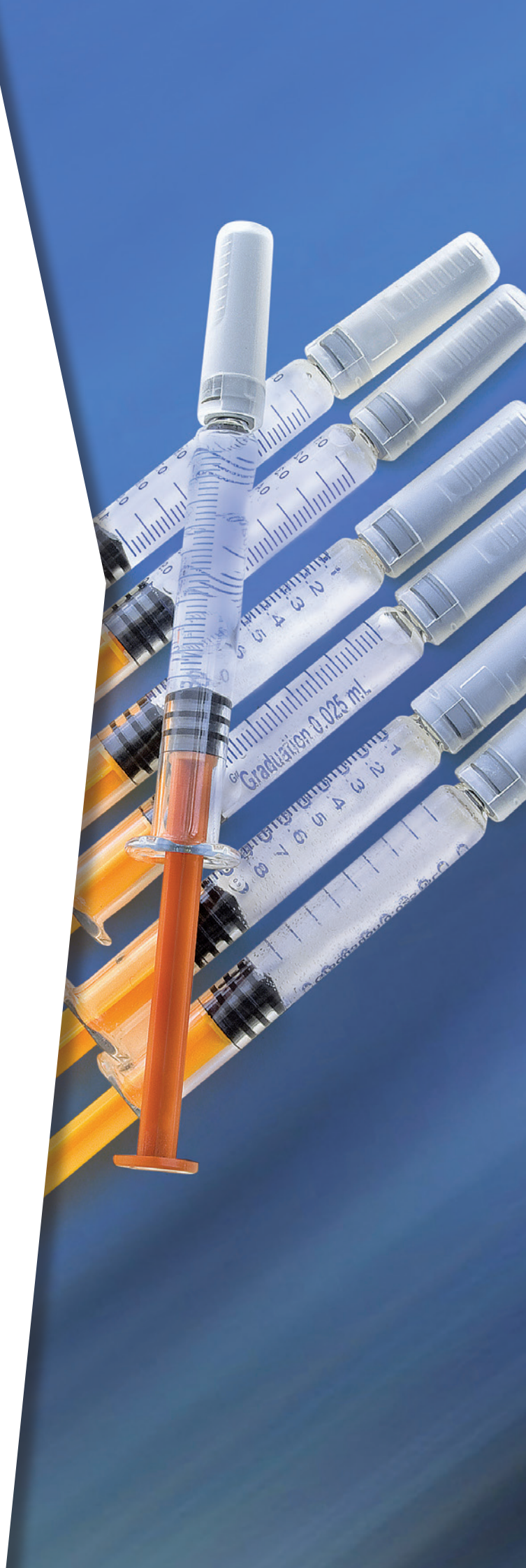
Parylene is an ideal conformal coating for medical and pharmaceutical delivery devices and components. SCS Parylenes can be applied to virtually any material to provide ultra-thin, pinhole-free coatings with superior extractables/leachables barrier properties and excellent non-liquid, low friction/stiction characteristics. Biocompatible Parylene coatings are USP Class VI certified and ISO 10993 tested.

With numerous locations around the world, Specialty Coating Systems is the leader in Parylene coatings and maintains comprehensive FDA Drug and Device Master Files for customer reference.

Contact SCS today for more information about the ways Parylene coatings can enhance the performance and reliability of your medical or pharmaceutical applications.



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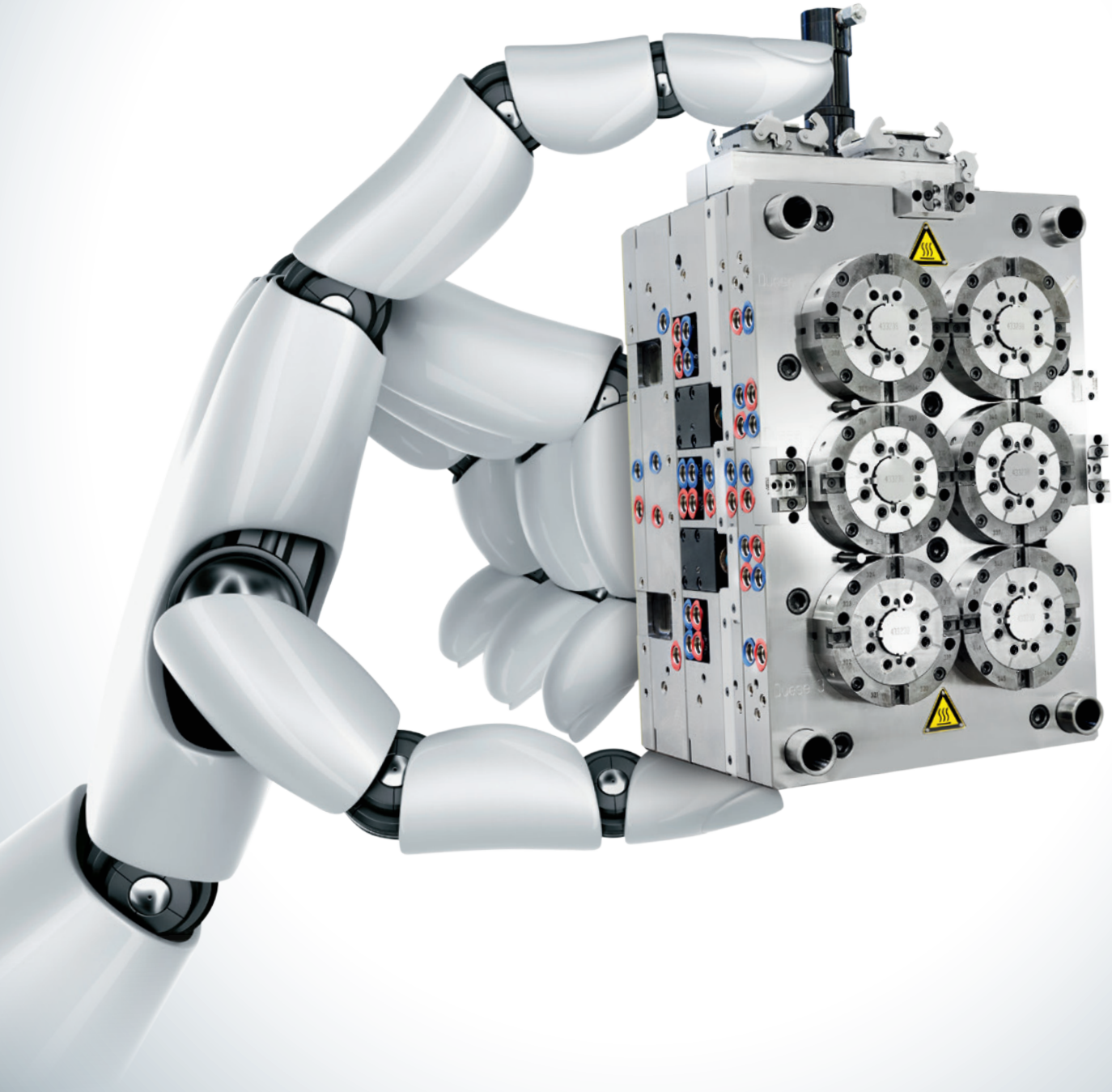

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THE VALUE OF A BD INTEGRATED SYSTEM FOR COMBINATION PRODUCTS

The growing complexity and regulatory rigour of combination products has called for increasingly innovative delivery devices. In this article, Theresa Bankston, PhD, Director, Technical Services looks at the advantages of using an integrated system for these drug-device combination products rather than sourcing components from different suppliers. As well as avoiding problems such as breakage and incompatibility, integrated products can offer solutions at every interface between the drug, container and delivery device and save significant amounts of time and money.

The number of biological therapies in development to treat chronic diseases has risen steadily over the years. The fact that many of these therapies are designed for home delivery by patients or caregivers via subcutaneous injection, combined with the increasing complexity of longer acting formulations, larger injection volumes and longer injection durations, has raised the bar for seamless injection delivery technology. Patients today receive these drugs inside prefilled injection devices, together called combination products. These combination products include auto-injectors, wearable injectors, and prefilled syringes.

To bring a drug-device combination product to market, pharmaceutical companies must select and assemble multiple components that work together optimally to deliver the drug formulation safely and effectively. These components include, but are not limited to:

- A primary container consisting of a syringe barrel, stopper, plunger rod and backstop
- A secondary delivery system such as an auto-injector or wearable injector
- An add-on needlestick safety guard.

Drug makers and their contract manufacturing partners have the option of sourcing these components from a variety of suppliers. However, pharmaceutical companies who purchase components separately take on additional risks that can be significantly reduced by selecting an integrated system instead.

RISKS OF USING SEPARATE COMPONENTS

Broadly, the risks addressed by system integration include the delivery system not functioning as intended, such as primary container breakage, inconsistent

> "For combination products to perform most effectively, special attention must be paid to component interfaces throughout the product development and delivery process, from the early design phases to manufacturing strategy and execution."

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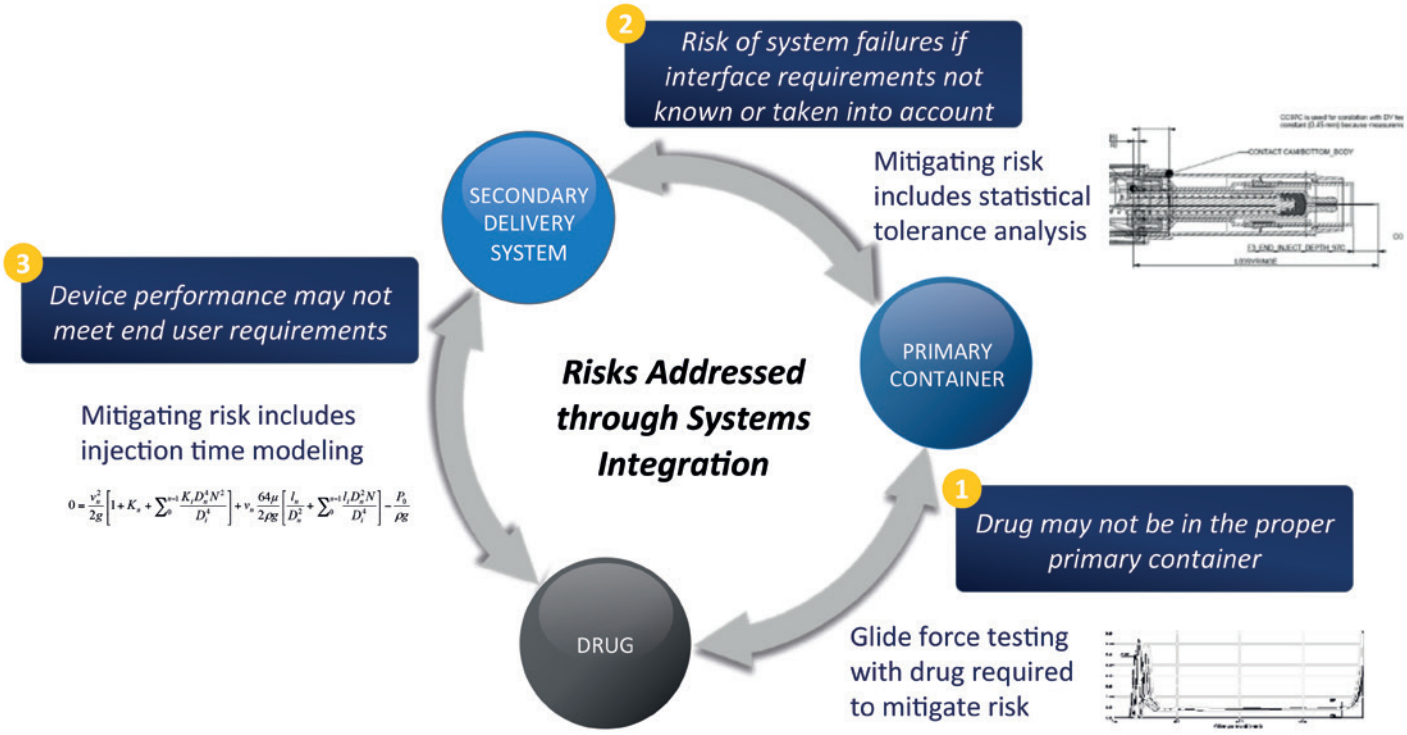

Figure 1: Risks addressed by well managed systems.

system performance and incompatibility with key container components (Figure 1). When realised, these risks bring issues such as an increase in project management complexity and time, a potential delay to launch and unforeseen problems post-launch, amongst others. Moreover, problems may not be revealed until late in development, or possibly after commercialisation when the combination product has already been manufactured in large quantities, and reached the hands of patients. Consequences can range from high scrap rates and waste during the filling or assembly process to a loss of costly drug and a delay of therapy in the care setting.

These risks and the costs associated with them, whilst real, may not be immediately obvious to the pharmaceutical company.

ADVANTAGES OF SYSTEM INTEGRATION

Assurance Through Expertise

For combination products to perform most effectively, special attention must be paid to component interfaces throughout the product development and delivery process, from the early design phases to manufacturing strategy and execution. BD is a leading provider of primary containers globally and offers secondary delivery systems, including needlestick safety systems, wearable injectors and auto-injectors, for a complete combination product solution.

Due to its legacy of developing and providing billions of prefillable syringes and components to the pharmaceutical industry every year, BD has the experience, analytical tools and lab test capabilities to optimise the components of combination products to operate cohesively. As a result, pharmaceutical companies can benefit from delivery system interfaces that have been properly managed well in advance of product assembly and launch.

BD designs its secondary delivery systems to integrate with the well established primary containers most pharmaceutical manufacturers are already accustomed to using in their auto-injectors, wearable injectors and safety systems. This not only provides convenience, but also enables more flexibility in device selection before manufacturers make downstream decisions about device features and functionality.

For example, BD integrates its best-in-class BD Hypak™, BD Neopak™ and cannula technologies into their self-injection systems, providing multi-platform flexibility across a range of dose volumes. BD's wearable injector, BD Libertas™, is the leading model of BD systems integration, designed from the bottom up, with an array of proven BD components, including BD Neopak™ technology and cannula.

BD also offers a leading brand of passive needle guards through its BD UltraSafe Passive™ and BD Plus™ Needle Guards. Unlike most add-on safety devices, BD UltraSafe Passive™ and BD Plus™ Passive Needle Guards are designed to work with BD prefillable syringes. "Because BD develops both components, we can test compatibility long before a pharmaceutical customer has the opportunity to test the components together with a specific drug," said Sarah Baer, Global Strategic Marketing Leader.

"It's widely known that BD offers world-class primary containers for combination product development. Our customers are also increasingly coming to understand our investment and full capabilities in delivering exceptional secondary delivery devices. They understand the benefits of working with BD to manage the increasingly complex combination product world," added Bernard Egoyan, Vice-President BD Medical – Pharmaceutical Systems.

> "The most significant time and cost savings come from avoiding potentially delayed launch timelines."

Solutions at Each Interface

BD's integrated systems offer solutions to the complexities of combination products at every interface between the drug, primary container and secondary delivery system. Consider a few examples of this:

- At the interface between the drug and primary container, BD leverages its expertise and capabilities in glide force testing to ensure the drug is in the appropriate primary container to meet the manufacturer's needs.
- Between the primary container and the device, BD provides statistical tolerance analysis to specify interface requirements that minimise the risk of system failures.
- Between the drug and secondary delivery system, BD employs injection time modelling to improve overall device performance.

THE VALUE OF INTEGRATION

Risk Mitigation

System integration provides value to pharmaceutical companies and patients at several levels. A well integrated system anticipates and mitigates system performance risks early in development. BD performs system validation and design verification testing on established reference systems, challenging system performance at the limits of process capability. The outputs of this process are provided in summary report documentation.

BD can also anticipate where problems can arise throughout the development process and how to troubleshoot them effectively. Because BD produces both primary and secondary systems, they have a unique appreciation of nuances in meeting ISO standards that can help customers.

Visibility across secondary system platforms results in product designs that reflect detailed component specifications to ensure system integration between BD prefillable syringes and BD secondary systems, both during development and after manufacturing scale-up through commercialisation. Internal experts share learnings from implementation experience across project teams. Moreover, quality commitment is maintained at the component and system (including primary container) level, which forces tighter specifications and reduced variability in system performance. This drives a high degree of accountability for BD, as the pharmaceutical sponsor can hold a single party accountable for performance of the total delivery system.

"BD creates and manufactures to specifications that are so tight, pharma can accurately predict performance and put components together successfully with less risk of waste," explained Janice Adkins, Associate Director, Marketing.

Finally, BD conducts human factors engineering testing on its most advanced products across a range of representative users to confirm that the integrated devices are safe and user-friendly as a system. While pharmaceutical companies will conduct their own testing with the actual formulation, this early testing of the system increases confidence in the usability of the combined components and reduces the risk of unforeseen issues.

Time and Cost Savings

BD's system integration has been designed to facilitate significant time and cost savings. On a case by case basis BD provides data at the system level, incorporating the primary container, which creates a more readily usable format for the critical step of combination product registration filing. And as BD continuously improves their manufacturing processes and product designs the "fit" between primary and secondary containers is proactively verified and tracked, and potential problems are resolved to avoid performance issues that may ensue.

BD's leading primary container technology designed for biologic drugs, BD Neopak™, ensures a fit with many secondary systems, including BD handheld auto-injectors, wearable injectors and passive safety devices. This enhanced fit supports greater choice and flexibility for pharmaceutical companies to serve diverse patient groups, therapeutic areas and markets with the appropriate delivery format. Furthermore, a single prefillable syringe technology that integrates with a broad range of secondary delivery systems can minimise the costs associated with managing multiple component interfaces and suppliers.

The most significant time and cost savings come from avoiding potentially delayed launch timelines. BD's integrated approach is focused on ensuring that every system component, including the barrel,

Figure 2: The range of BD's fully integrated devices.

Figure 3: BD Physioject™ auto-injector.

Figure 4: BD Intevia™ auto-injector.

stopper, needle, needle shield, primary container and secondary delivery system, functions cohesively. This approach is intended to develop a seamless delivery system that performs as designed and meets the rigorous regulatory requirements for safety, effectiveness, functionality and usability.

"BD ensures that our components will work together. There are no surprises that the primary container selected doesn't work or fit perfectly with the device," commented Justyna Dudaronek, Manager of Technical Services.

End-to-End Services Add Value

Based on BD's experience in designing and integrating components into systems and extensive collaboration with drug developers, BD has developed a range of end-to-end services it offers to customers. These services are designed to help their pharmaceutical partners choose the correct components and system for their application, to assess and offer solutions to any potential challenges or sensitivities, and to help produce the necessary data packages needed to demonstrate the safety and performance of the integrated combination product. These include:

- Analytical and bioanalytical chemistry capabilities
- Formulation services
- Functional and performance testing
- Clinical/human factors consultancy
- Combination product documentation support and testing
- Process consultancy
- Regulatory customised support.

For example, testing for performance feasibility may include *in vivo* testing, demonstrating that a range of injection volumes or flow rates is feasible. Combination product support occurs throughout the development process, from matching the right set of components with the formulation in Phases I and II, to validation testing of the system in Phases II and III.

Only BD offers this breadth of capabilities in combination with the entire system of components (Figure 2) to enable customers to anticipate and resolve challenges before they become issues from a system interference perspective.

BD'S FULLY-INTEGRATED DEVICES

Auto-Injectors

BD Physioject™ is a disposable auto-injector that fully integrates with the BD Neopak™ 1 mL glass prefillable syringe or the BD Hypak™ for biotech 1 mL glass prefillable syringe (Figure 3).

BD Intevia™ is an auto-injector platform technology specifically designed for high-viscosity drug delivery. BD Intevia™ supports biotech's evolving needs for high dosages, whilst offering integration with BD Neopak™ technology and BD Hypak™ for biotech, offering manufacturers the flexibility to accommodate formulation changes (Figure 4).

Wearable Injector

BD Libertas™ is a pre-assembled, fully-integrated, mechanical wearable injector designed to deliver 2-10 mL doses of high viscosity biologics. It was purposefully designed to work as an integrated system with BD Neopak™ technology and fits within current manufacturing assembly technology, both providing high performance and prefilled convenience for patients (Figure 5).

Safety Systems

The BD UltraSafe™ family of products are add-on passive needle guards for prefillable glass syringes, offering versions for both cut flanges and small, round flanges. BD UltraSafe Passive™ and BD Plus™ Needle Guards are market-leading safety solutions for prefillable glass syringes. BD conducts a multi-phase set of compatibility tests to ensure primary container integration (Figure 6).

Figure 5: BD Libertas™ wearable injector.

Figure 6: BD UltraSafe Passive™ and BD Plus™ Needle Guards.

"BD's integrated systems offer a means to incorporate already existing world-class technologies with novel secondary delivery device solutions to provide complete products that meet the evolving needs of pharmaceutical manufacturers."

EXAMPLES OF CHALLENGES ADDRESSED WITH INTEGRATED SYSTEMS

Drawn from years of experience with customers, the following are examples of real-world challenges faced with non-integrated components from different suppliers (Figure 7) and the corresponding solutions offered by integrated systems – auto-injector examples used are BD Physioject™ and BD Intevia™.

Cap Removal Malfunction & Wasted Drug

Limitation of a non-integrated system: When patients remove the cap from an auto-injector, the rigid needle shield (RNS) may not always be pulled from the needle. The result could be an uncapping motion that damages the needle and the drug delivery device. In this case, the device becomes unusable and the patient may fail to receive their important and expensive medication.

For the pharmaceutical company this issue may produce complaints, drug wastage and negative quality perception. Although some companies may recognise this issue during development and may resolve it by switching to a different auto-injector, others may not observe it until after scale-up and launch.

Integrated system solution: With BD's integrated auto-injectors, the caps are designed to integrate with and reliably remove the RNS so that the needle is not damaged. Knowing that even minor changes such as replacing mould tools can affect RNS dimensions, design and manufacturing updates are routinely and proactively assessed by BD for their impact to cap/RNS integration. BD designs for system performance to help manufacturers avoid project delays and post-launch issues.

Needle Extension Variability

Limitation of a non-integrated system: Needle extension (depth) is not always well-controlled or understood when the auto-injectors and prefillable syringes are combined. The range of specifications for each component can result in an unexpectedly wide variation when the tolerances are stacked.

As a result, unexpected clinical outcomes may occur when bridging from syringe injection to auto-injection. The implications of this issue are that pharmaceutical companies may have to repeat clinical studies or perhaps even re-design the auto-injector or prefillable syringe. Either case could result in product launch delays.

Integrated system solution: Injection depth was thoroughly characterised and controlled during the development of BD Physioject™ and BD Intevia™, through close work with

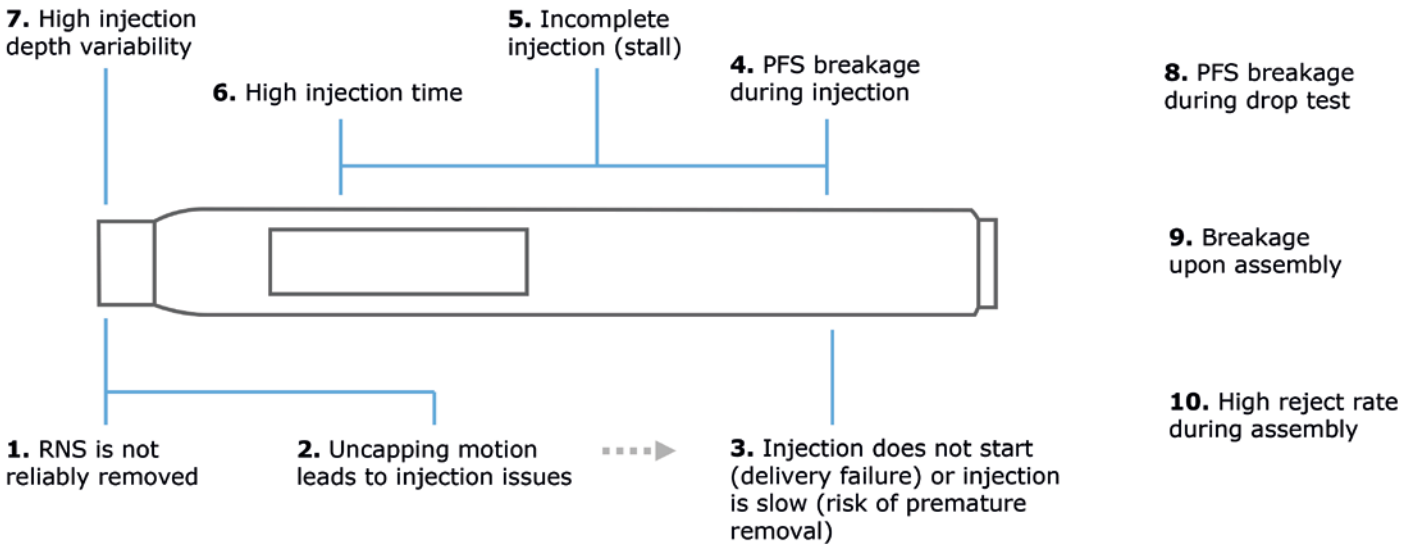

Figure 7: Most common challenges encountered with non-integrated components from different suppliers for auto-injectors.

the prefillable syringe team, to evaluate needle length variability and methods of controlling this dimension.

With the BD Physioject™ system, BD has addressed needle depth variability and conducted clinical studies to show how injection with BD Physioject™ compares to injection with a syringe alone. These studies provide evidence of more predictable clinical outcomes with BD's integrated system.

According to Fabien Dubuc, Platform Leader for Auto-Injectors with BD Intevia™, the team went a step further to optimise the system. They set a goal to eliminate the variability of requiring a skin pinch upon injection, simplifying the process for the patient. BD's ability to tightly control variability of components enables consistent targeting of the subcutaneous space. Preclinical studies have demonstrated that, without the use of a skin patch, BD can reliably control injection depth, greatly improving the injection experience.

Primary Container Defects

Limitation of a non-integrated system: Like needle extension, component dimensional variability (e.g. prefillable syringe variability) is not always well accounted for in the design of the auto-injector assembly process. Higher reject rates and possible primary container breakage during assembly may occur as a result.

Integrated system solution: With BD's clear vision on detailed, proprietary prefillable syringe component specifications, critical dimensions to assembly which incorporate both BD Physioject™ and prefillable syringes are accounted for within the assembly process design. In an ISO 11608 drop test (1 m drop) study comparing BD Physioject™ with one of the most commonly marketed disposable auto-injectors, BD Physioject™ outperformed the comparator auto-injector in terms of prefilled syringe breakages and successful complete injections (Figure 8).

BD provides guidance for system assembly, ensuring that the process works smoothly with both the secondary delivery system and primary container, reducing the need for troubleshooting or other workarounds.

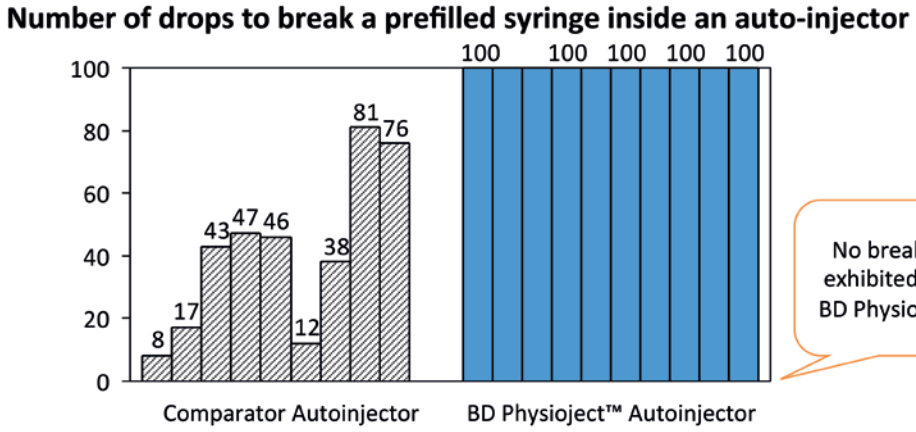

Figure 8: Comparison of auto-injectors with 1.0 mL prefilled syringes, filled with water. The same type of syringe was used inside all auto-injectors tested. Each bar represents one auto-injector. Auto-injectors were dropped a maximum of 100 times, or until prefilled syringe exhibited breakage. All BD Physioject™ samples confirmed intact by X-ray analysis. (BD internal study.)

ABOUT THE AUTHOR

Theresa Bankston, PhD, leads the Technical Services group for BD Medical – Pharmaceutical Systems that is responsible for providing technical support, solutions and services around delivery systems for injectable drug therapies. She has over 15 years of combined experience in the pharmaceutical and medical device industries. Her areas of expertise include process chemistry and engineering development, analytical method development and drug-container integration science. Theresa received her BS in Biochemistry from Florida State University and her doctorate in Chemical Engineering from the University of Virginia (NH, US), and a Bachelors' degree in Psychology from Boston College (MA, US).

BD LIBERTAS™ EXAMPLE

Another example of where a systems integration approach adds value is the tolerance stack-up analysis conducted to design the BD Libertas™ wearable injector for high-scale production.

For example, to establish the axial clearance between the primary container and device flow path, an analysis of design parameters and geometric tolerances on nine dimensions was performed to ensure the resulting device's functional performance.

This approach to development enabled identification of critical inputs from a systems performance perspective and yielded a database of system specifications. This database houses hundreds of geometric tolerance stack-up chains that comprise system specifications and enabled a comprehensive understanding of how the device components, as a well integrated system, result in a high performing combination product: the BD Libertas™ wearable injector.

CONCLUSION

With a long history and expertise in combination products, BD is applying its knowledge to current needs in product development. The growing complexities and regulatory rigour of combination products has called for increasingly innovative delivery systems. BD's integrated systems offer a means to incorporate already existing world-class technologies with novel secondary delivery systems to provide complete systems that meet the evolving needs of pharmaceutical manufacturers.

Combined with BD's continuous process and service improvements, BD integrated solutions are designed to mitigate system performance risks, facilitate cost savings and prevent launch timeline delays to help pharmaceutical companies succeed in bringing their drug-device combination products to market and achieve commercial success.

BD Intevia™ and BD Libertas™ are products in development; some statements made are subject to a variety of risks and uncertainties. The combination products and the claims are subject to regulatory approval.

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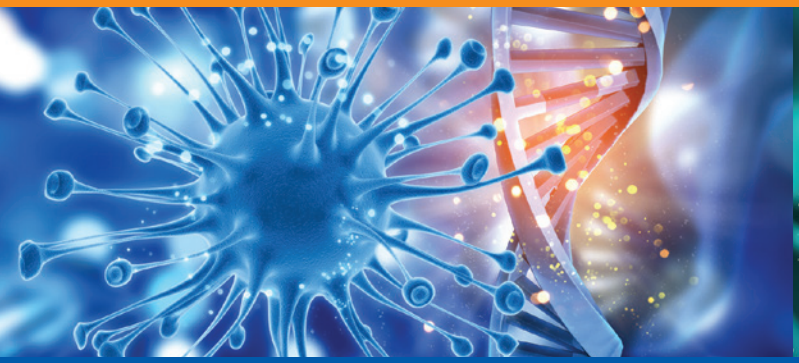
- Extractables and Leachables



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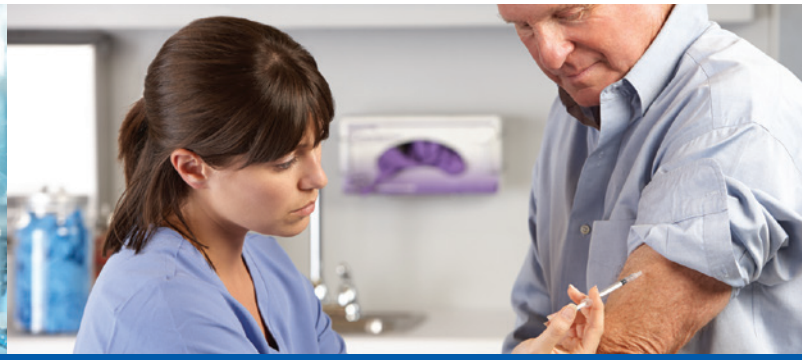

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THE UNIVERSE OF PRE-FILLED SYRINGES & INJECTION DEVICES

The new business reality for prefilled syringes centres around self-injection delivery systems adapted to the needs of individual patients, a fact which will certainly have a clear and decisive impact on the pharmaceutical market. At the same time, these new products will require new approaches to addressing the needs of regulators.

The US FDA has in recent years expressed concerns about errors related to self-administration by patients, necessitating more attention to human factors analysis during the development cycle.[1] Lifecycle management during manufacturing will also be critical to the success of self-administered injection devices. But how can manufacturers of prefilled devices learn more about the latest developments in this area as well as gain a sense for the larger business environment and regulatory picture?

This year's *Universe of Pre-filled Syringes and Injection Devices* will examine these increasingly important issues. In the opening keynote presentation, Pfizer's Simon Wilson and Amgen's Sheldon Moberg will look at the issues of evolving perspectives on connectivity and patient-centric solutions respectively. The talks in this session will cover outcomes-based adaptive reimbursement. Such arrangements between payers and pharma have been made for multiple self-injected drugs. The subsequent drug delivery implications will also be discussed. Following up on this, there will be a review on the payer's view of value of drug delivery devices on the second day. Results

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of conversations with payer executives will be presented on how to improve population health with the assistance of drug delivery technology.

The conference will be distributed in three tracks, each one addressing a highly in-demand topic of discussion. One track will address marketing and business development for prefilled syringes. The first session in this track will cover lifecycle management, featuring a case study on how an off-patent IV drug was filed in a SC version using a patch pump. A second case study from Japan will describe the impact of a third-generation digital auto-injector for a growth hormone franchise. The second day of the track will start with a session on market trends and reimbursement. Delegates will receive an update on the latest overall market trends followed by presentations on reimbursement. The final presentation of the session will review the evolving payer perspective on the value of drug delivery devices. The last session will focus on business strategies.

The conference will also feature an exhibition, with more than 100 exhibitors in a 7,500 m² hall, and an extensive education programme with focused training courses.

The Universe of Pre-filled Syringes and Injection Devices takes place on November 7-8, 2017, at the Vienna Center, Vienna, Austria. For more information visit the event web page, and don't forget to download the Event App, available for Android and Apple devices.

PDA looks forward to welcoming you in Vienna next month!

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Elcam
Drug Delivery Devices

A REVIEW OF REUSABLE AUTO-INJECTORS FOR BIOLOGICAL & BIOSIMILAR DRUGS

In this article, from the perspective of the growing biologics and emerging biosimilars markets, Menachem Zucker, PhD, Head and Founder of E3D – Elcam Drug Delivery Devices (a sister company of Elcam Medical ACAL), showcases the company's mechanical and electronic auto-injector platforms, both of which are reusable devices with disposable cassettes.

A GROWING NEED FOR BIOLOGICS & BIOSIMILARS

When generic drugs began to be introduced 30 years ago, they revolutionised the pharmaceutical industry. Now, many ask if biosimilars will have the same impact. Since the approval of the first biosimilar drug in 2015 this approach is becoming ever more prominent in drug development. Healthcare Recruiters International (San Francisco, CA, US) suggest a figure of US$250 billion (£185 billion) in drug cost savings[1] if 11 bio-similar drugs are approved by the US FDA. The same source claims that biosimilars have been lowering healthcare costs globally since 2006 with no known safety issues. Another report, by SNS Telecom (Dubai, UAE), claims that by the end of 2020 approved biosimilar drugs will account for nearly $22 billion in revenue.[2] According to Dyadic (Jupiter, FL, US) the market for therapeutic biological drugs will soar to $287 billion by 2020.[3] These numbers are only a first indicator of the clear demand for, and true potential of, biologicals and biosimilars.

Both biological drugs and biosimilar drugs are typically fragile proteins, calling for administration by injection. Auto-injectors therefore increase the therapeutic value of the drug. When these drugs are prescribed for people with chronic diseases – such as multiple sclerosis, diabetes or growth hormone disorders - requiring daily doses (sometimes multiple times a day) for treatment success, then reusable auto-injectors are the sensible solution. Reusable auto-injectors increase safety and ease of use, they reduce the volume of storage and waste footprint (and are thus more environmentally friendly) and they are also significantly more cost effective.

> "The disposable cassette design can be customised to incorporate standard glass prefilled syringes from different manufacturers, including dual-chamber syringes. A vial adapter is also currently in development, which will enable drug reconstitution and mixing."

GENERATIONS OF REUSABLE AUTO-INJECTORS

E3D (a sister company of Elcam Medical) specialises in the development and production of high-quality, patient-compliant auto-injectors. The company sees its products as the next step in effective care. E3D offers two generations of reusable auto-injectors, which are currently under development.

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Figure 1: E3D Flexi-Q-mMU, reusable auto-injector.

Mechanical Multi-Use Auto-Injector

The E3D Flexi-Q-mMU comprises a reusable driving unit and a disposable cassette (Figure 1). The cassette is cost effective and can be used with standard prefilled syringes (PFS) and vials (using an adapter).

The Flexi-Q-mMU reusable auto-injector is designed with patient compliance in mind. The product is easy to use (with just one additional preparation step when compared with a fully disposable injector). All the patient has to do is:

1. Insert cassette into the driving unit
2. Remove safety cover
3. Press against skin
4. Press the INJECT button.

A two-step mechanism for enhanced safety was designed: drug delivery can only take place when both the skin sensor and the INJECT button are activated. This way only when the auto-injector is pressed to the skin (and when the patient is ready) can the button be pressed and the injection take place.

Safety is further enhanced as the patient will have two indications for the end of injection. Firstly, they will hear a click when the injection is completed and, secondly, the patient can monitor the process through the injection window.

The needle is hidden during the entire injection process. It only emerges when the auto-injector is touching the skin and the INJECT button is pressed. Injection is a quiet process and injection speed/time can be pre-set by the pharma company at assembly to further reduce patient anxiety, needle phobia and perceived pain. As soon as the patient lifts the injector from the skin the needle shield is lowered and the cassette jumps partly out, ready for disposal.

The disposable cassette design can be customised to incorporate standard glass PFS from different manufacturers, including dual-chamber syringes. A vial adapter is also currently in development, which will enable drug reconstitution and mixing.

The reusable injector is an environmentally friendly product on a number of levels (see Figure 2). The disposable cassette reduces the storage footprint for both manufacturing and delivering the product. The storage volume is also reduced at the patient's home, as is waste. In fact, the disposable cassette's waste footprint is four times (4X) smaller than that of a disposable injector. Due to its smaller size, the amount of plastic used is also reduced, the benefits of which in terms of production costs and the environment are clear.

Using a disposable cassette rather than a disposable auto-injector reduces the

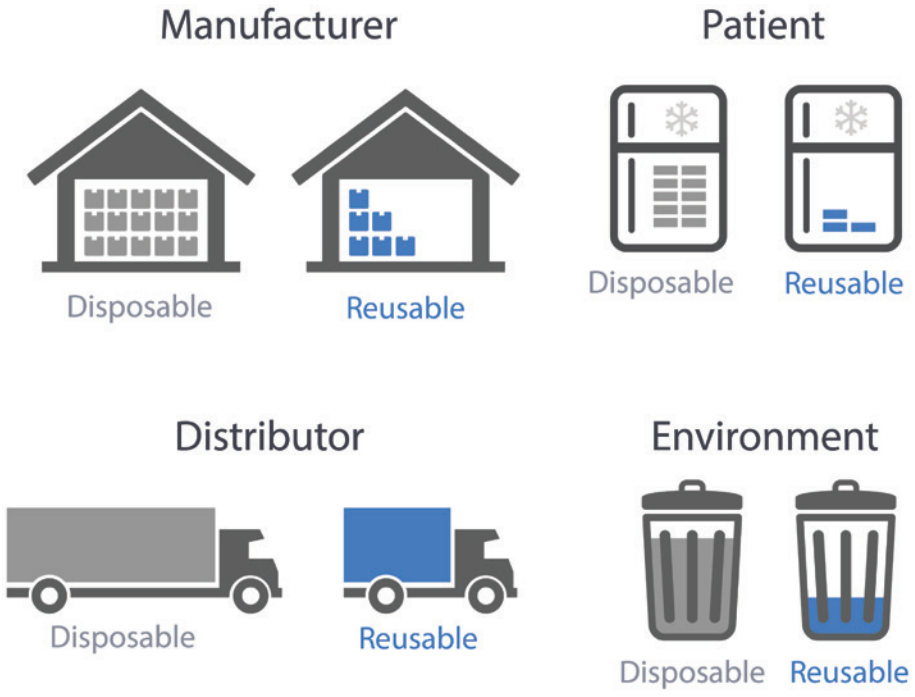

Figure 2: Footprint and environmental impact.

cost per injection. The cost ratio is 1:5, meaning a reusable auto-injector results in a saving of approximately 80%. The reusable unit is good for three years (approximately 1000 uses) and is easily disposed of. It thus has a negligible effect on the environment and operation costs.

Electronic Multi-Use Auto-Injector

E3D has taken all the advantages of reusable auto-injectors for effective care mentioned above another step further with its electronic version, the Flexi-Q-eMU-P (Figure 3). The electronic version works with PFS and E3D also offers a version that is suited for cartridges (Flexi-Q-eMU-C).

With Flexi-Q-eMU-P, self-injection is made even easier. The LCD screen provides the patient with a large display where each stage of the injection process is presented with clear instructions in real time. The patient is further empowered for effective care with reminders and injection history (Figure 4).

The disposable cassette also includes an RFID component, on which the pharma company can encode the expiry date, anti-fraud barcode, various permissions and definitions and, of course, the drug name and dose. If the drug has expired or is fraudulent the injector will warn the patient, and will not allow the injection to proceed.

The needle within the disposable cassette is protected and hidden at all times in this version as well. In the electronic version, injection is stopped as soon as the patient lifts the injector from the body (even if injection is not completed – so no drug is lost – but the cassette becomes void). Partial injections are recorded into the electronic log.

With a specialised mobile app (Figure 5), the data regarding injecting habits and patient compliance with the prescribed treatment programme can be enhanced and its delivery made even easier. The auto-injector can automatically send patients, as well as doctors and family members, reminders, logs and injection data.

Figure 3: Flexi-Q-eMU-P, electric reusable auto-injector and disposable PFS-based cassette.

> "Time, quantity, drug type and whether a full or partial injection was delivered are all recorded and sent from the auto-injector via a wireless connection to the cloud, per the definition of the drug company at the filling stage of production."

This is especially useful for patients who are prone to forgetting their injection schedule.

Time, quantity, drug type and whether a full or partial injection was delivered are all recorded and sent from the auto-injector via a wireless connection to the cloud, per the definition of the drug company at the filling stage of production. The pharmaceutical company may also make use of injection data in order to improve its future products.

A five-question survey following the injection can be defined as optional or mandatory, helping to gather additional data regarding the injection process, patient symptoms and their reaction to the drugs in real time. This information is especially important for the physician follow-up and its collection has never been easier.

Further advantages of the electronic product include measuring drug temperature before injection is permitted and injection with a motor for better control of injection

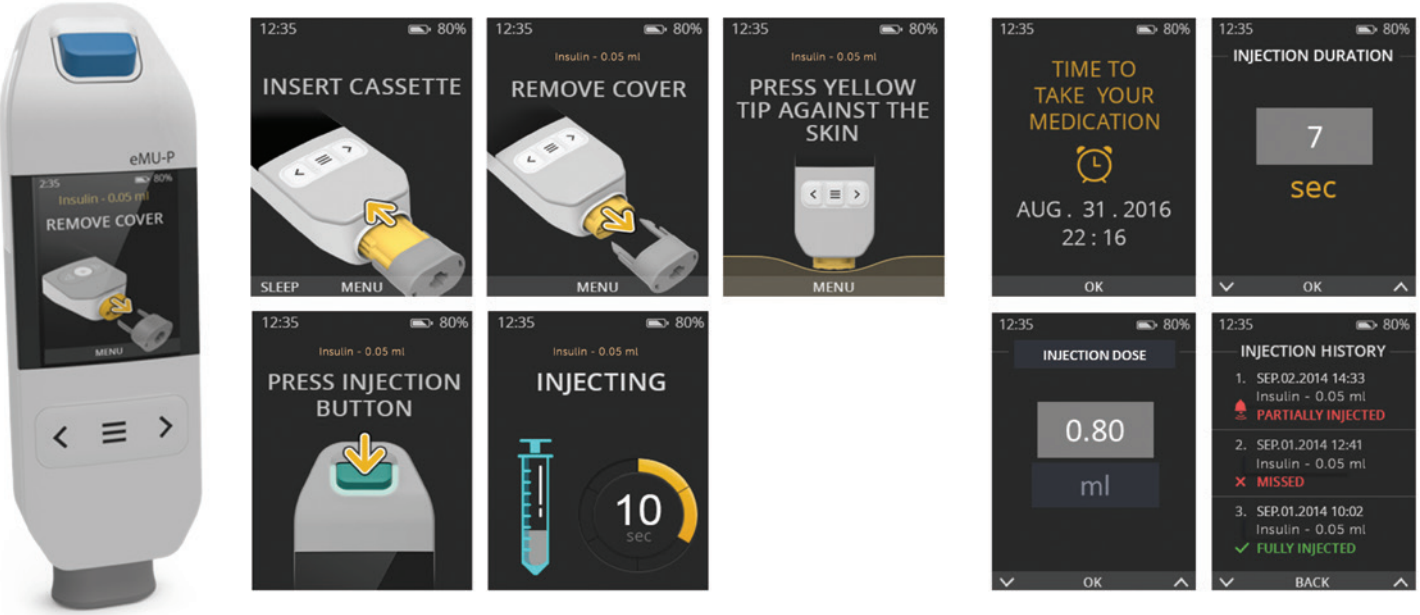

Figure 4: Injection stages and instructions on screen, reminders, data and history display.

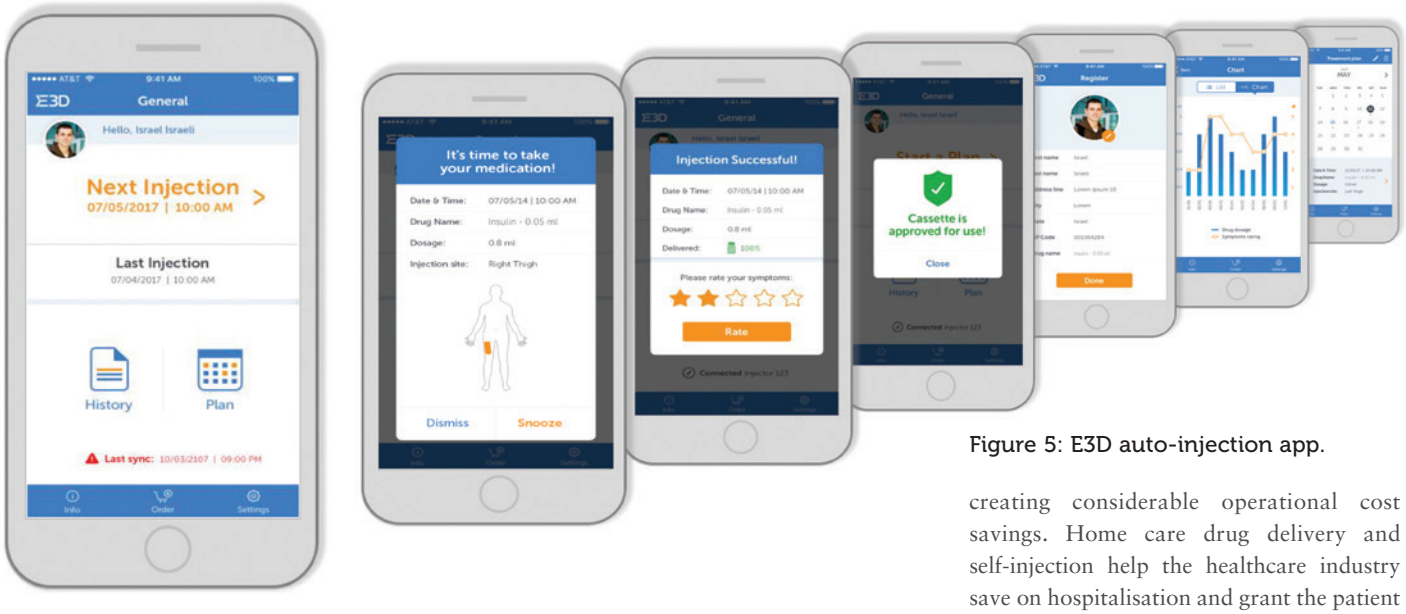

Figure 5: E3D auto-injection app.

speed and reduced pain. Out-of-date cassettes cannot be used. Drugs with high or low viscosity (or anything in between) can be all injected using the same platform.

The product can also be customised for marketing and commercialisation. The front panel is available in different colours and designs for branding purposes, as well as for fun. A music feature can be enabled for targeting younger users.

AUTO-INJECTOR SUPPLY CHAIN

At E3D we know that flexibility and customisation are keys to success (we even named our product line FLEXI). We know that the selection of drug delivery devices depends on several factors, including formulation, primary package, dosing and safe, effective usage. Our products are designed to suit varying needs so that each drug company can find the auto-injector best suited to its requirements.

E3D provides drug companies with all the components and machinery required to complete the assembly of the disposable cassette with the drug PFS (or cartridge), branding and labelling, all in accordance with the company's own requirements. The drug know-how and production thus remains fully under the pharmaceutical company's control.

E3D provides:

- Reusable auto-injector units
- Disposable cassette components
- Automatic final assembly machine for the cassette with the drug PFS (or cartridges)
- Software for electronic labelling (RFID chip on cassette).

Our products are designed in accordance with our belief that drug companies will have a growing need for auto-injectors that are customised to their products, their brand and to their user's needs and treatment programmes.

PHARMA GROWTH ACCORDING TO DRUG DELIVERY MARKET TRENDS

Three of the most significant demands driving the growth of drug delivery system development, in addition to increasing the commercial value (and lifecycle) of the drug, are:

- Demand for improved patient compliance and quality of care
- Growing awareness of production costs, both financial and environmental
- Self-administered drug therapy (another step towards precision medicine and telemedicine).

E3D reusable auto-injectors, of both generations, answer these trends. The products are designed to provide each patient with effective care according to their own specific treatment programme. By making the product safe and easy to use, reducing needle phobia, ensuring delivery of the full dosage and enabling better therapy follow-up, the quality of care, patient safety and patient compliance are all increased.

Reusable auto-injectors reduce both the storage and waste footprint, for both manufacturers and patients, thus reducing environmental impact. Disposing of only the cassette and not the entire injector reduces the cost per injection significantly, creating considerable operational cost savings. Home care drug delivery and self-injection help the healthcare industry save on hospitalisation and grant the patient enhanced independence via self-treatment.

The electronic generation of reusable auto-injectors takes these traits even further. By enabling full supervision of the amounts of drug used, injection logs, reminders to patients, reports to family members and physicians, every participant in the entire healthcare system can become more involved (even at a distance), thus providing enhanced and effective care.

The software enables control of dosage and other therapeutic factors, customising them to personal patient needs after a specific follow-up of injection logs and analysing the therapeutic results attained. This is just a step away from precision (or personalised) medicine. Adjustments can be made by patients, doctors or both, depending on parameters predefined by the drug company. This means that the highest quality treatment can be easily administered from a distance.

Throughout the development process for its auto-injectors, E3D conducted formative usability tests involving patients form various groups (gender, age, illness, disability, etc). Issues such as auto-injector shape, convenience and ease of use, location of buttons, size of display and ideal ratio between injector width and display size were tested and optimised. After integrating the test recommendations into the product design, repeated tests resulted in high satisfaction with regards to holding the injectors, display size and ease of use.

At E3D we develop and manufacture our products according to required regulations and relevant standards. With our sister company Elcam Medical's know-how in injection and moulding, plus its automated assembly capabilities, and by embracing

their business culture of partnering with clients, we can provide drug companies with the exact products they need.

ABOUT THE COMPANY

E3D is a sister company of Elcam Medical ACAL, developing and manufacturing auto-injectors and patch pumps for biologic and biosimilar drugs, utilising the moulding injection and assembly know-how, engineering and technologies of Elcam Medical as well as its well-established quality assurance and quality control. E3D believes in a growing need for customised auto-injectors that enhance the therapeutic and commercial value of drugs and their lifecycles. Customisation and flexibility are at the core of its product development.

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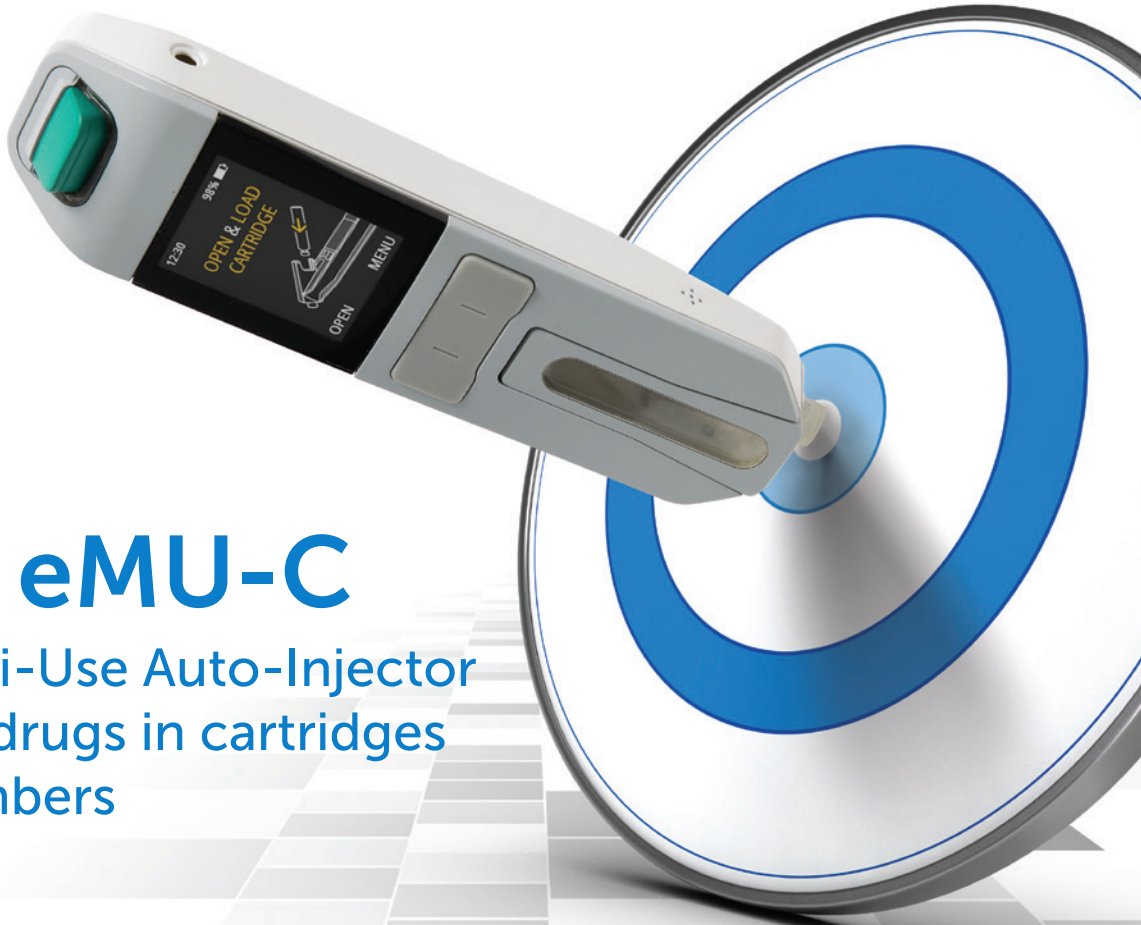
ABOUT THE AUTHOR

Joining Elcam Medical ACAL in 2002, **Menachem Zucker** served as Vice-President of Business Development, Marketing and Sales. In 2010, he initiated the E3D activity and since then serves in the role of Vice-President and Head of E3D. Previously the Chief Executive of Opgal Medical (Israel), he led the development of simulation products for cardiac surgery. He also founded a company for catheterisation closure devices. Dr Zucker holds a PhD from Imperial College London, which he obtained in 1990.

ON drugDELIVERY

2017/18 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Nov 2017	Pulmonary & Nasal Drug Delivery	DEADLINE PASSED
Dec 2017	Connecting Drug Delivery	Nov 13th 2017
Jan 2018	Ophthalmic Drug Delivery	Nov 20th 2017
Feb 2018	Prefilled Syringes & Injection Devices	Dec 22nd 2017
Mar 2018	Skin Drug Delivery: Dermal, Transdermal Microneedles	Jan 20th 2018
Apr 2018	Pulmonary & Nasal Drug Delivery	Feb 19th 2018
May 2018	Injectable Drug Delivery: Devices Focus	Mar 19th 2018
June 2018	Connecting Drug Delivery	April 23rd 2018
July 2018	Novel Oral Delivery Systems	May 21st 2018
Sept 2018	Wearable Injectors	July 23rd 2018
Oct 2018	Prefilled Syringes & Injection Devices	Aug 27th 2018
Nov 2018	Pulmonary & Nasal Drug Delivery	Sept 24th 2018
Dec 2018	Connecting Drug Delivery	Oct 29th 2018



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PROFITABLE PACKAGING & MODULAR THINKING FOR INDUSTRY 4.0

In this article, Christoph Hammer, Chief Executive Officer, Dividella, discusses the financial reasoning behind the selection of packaging equipment, taking into account real current and potential future requirements (paying particular attention to Industry 4.0 concepts), and highlighting the advantages of taking a modular approach, such as the solutions offered by Dividella and its sister companies.

Marketing and financial departments analyse and calculate, depending on market conditions and potential in a given country, basic indicators which are later introduced into their company's development strategy and further investments in production. Naturally, packaging is a key consideration when devising a production investment scheme.

Before defining a process and selecting equipment, it is important from the start to select the packaging material itself. It must be determined:

- in which form the packaged product will be most reliably protected
- what is most convenient and physically available for use by the end-user
- whether there will be a guaranteed indicator of initial opening
- if the protection from children is in accordance with GMP standards
- whether the package will be ecologically and easily developed
- if the information on the package itself about the product and its usage conditions will be adequate
- if it is cost-effective, which depends upon several other factors such as complexity, quality and quantity.

However, everyone knows that acquiring new equipment is connected with a serious investment and it must always be justified. An important parameter in deciding about purchasing new packaging equipment is the existing or estimated volume of production. If discussing volumes from 100,000 to one million packages per year it makes sense to talk about the advisability of using manual labour, whereas for volumes of more than one million packages per year, then it is clearly reasonable to talk about the semi-automation of the packaging line.

The principle of the semi-automatic line of work lies in the creation and sealing of packages occurring automatically, whilst product insertion is done by hand. Switching to a semi-automatic system allows small investments to guarantee the replication of quality, increased quantity, decreased staffing expenses and increased production efficiency.

"Each of these modules is becoming increasingly relevant to questions of how the pharma industry can generate sustainable competitive advantages within the Industry 4.0 concept, which leverages the very latest information and communications thinking to generate innovation and progress."

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A most important factor regarding Dividella's packaging machines is that they are based on a modular platform. This modularity makes Dividella's platform seamlessly scalable and customisable to an individual production line's needs (Figure 1).

MODULARITY

Modular design has always been a core characteristic of Dividella's NeoTOP cartoners and top-loading machinery, enhancing service life, upgradeability and flexibility to minimise the total cost of ownership (TCO). Similarly, an integrated range of complementary packaging modules allows clients to adopt more space- and cost-effective solutions to reduce the total cost of package (TCP).

It's no coincidence that Dividella is itself part of a modular ecosystem of related skills and competences within the Medipak Systems group, each highly expert in their respective core areas and able to collaborate to provide complementary modules of innovation and specialised capability. Each of these modules is becoming increasingly relevant to questions of how the pharma industry can generate sustainable competitive advantages within the Industry 4.0 concept, which leverages the very latest information and communications thinking to generate innovation and progress.

A modular approach to Industry 4.0 allows Dividella to offer cutting-edge solutions in smart packaging, smart devices, condition monitoring and predictive analytics, plug and produce Internet of Things (IoT) functionalities and enterprise manufacturing intelligence (EMI).

The Modular Philosophy

A module is a self-contained unit or item, performing a defined task or purpose, which can be linked with other modules to form a larger system. The modular approach has three key advantages:

- Easy to configure to an exact purpose
- Easy to upgrade and expand
- Easy to analyse, allowing for quick identification of bottlenecks and areas for further investment.

However, modularity is not without challenges, i.e. interconnection, interoperability and compatibility. For modularity to work to best effect, it is vital that each module connects properly with neighbouring modules, that each module forms its own discrete "centre of excellence" without needlessly duplicating the functions of others and that each module can match the capabilities of the system.

Modularity in Top-Loading

Modular design and construction allows Dividella's NeoTOP family of TOPLoader machines to form a continuous upgrade path from manual packaging of small lots, up to 100,000 units per year, to fully automated high speed production of more than 24 million packages annually.

The NeoTOP machine family ranges from NeoTOPx, designed for semi-automated packaging of small batches of blisters, ampoules, vials, syringes, injectors and similar products, through to the NeoTOP 804 and 1604, designed for fully automated, high-speed production of very large lots. Across the range, there is consistent sharing of specialised modules that add specific capabilities, such as tailored in-feeding.

Modularity in Packaging

Dividella's TOPLoading packaging solutions for pharmaceutical products follow a similarly modular philosophy, emphasising a component-based approach to design, assembly and regulatory compliance. These features include provision of flat blanks for cartons and partitions allowing printing on all sides, 100% mono-material packaging, safe automated erecting of packs and a safer loading process, enabling 100% verification after loading.

This approach offers a variety of advantages for pharma companies and their customers, influencing the complete production and logistical process, having a positive effect on both TCO and TCP. It also allows Dividella to incorporate innovative concepts like the folding "wing" format, extended fifth panel flap, integrated partitioning, external tamper-evident wafer seals, use of 100% recyclable material and space-saving designs that minimise footprint and logistics costs.

In turn these deliver further cost-saving benefits that include:

- Cold-chain storage and distribution improvements
- In-package damage reduction
- Packing/processing efficiency
- Cost-saving mono-materials.

> "A module is a self-contained unit or item, which itself performs a defined task or purpose, but which can be linked with other modules to form a larger system."

Figure 1: Modularity and scaleability is built into every aspect of Dividella's packaging and cartoning products and services.

Pharma 4.0 Modularity

Dividella is working in tandem with its fellow Medipak Systems group companies to find solutions to the question of how the pharma industry can generate sustainable competitive advantages with the aid of Industry 4.0 concepts. These solutions include:

Smart Packaging: Smart packaging takes product personalisation and security to a new level, envisaging packs that communicate with the patient and with the machines in the production process. Using digitally encoded data within the package can revolutionise information and service options for providers and end-users, such as:

- digital/audio patient information leaflets
- digital tamper-proof protection
- digital health management
- intake reminders
- automatic repeat orders
- individualised product tailoring during production.

Smart Devices: Smart control devices provide the right information at the right time and place, enabling operators or production managers to more easily operate and monitor a machine or system. By means of the mobile, "extended" human machine interface (HMI), the operator gains significant freedom of movement and can thus perform tasks more efficiently, resulting in higher quality and hugely simplified changeover, setup or maintenance.

Condition Monitoring & Predictive Analytics: Condition monitoring and predictive analytics can reduce downtime and optimise deployment of personnel and resources by collecting data in real-time whilst interpreting it more meaningfully to detect critical incidents before they occur and schedule preventative maintenance.

Plug & Produce: Plug & produce lays the basis for IoT functionalities by using standardised interfaces to allow vertical integration between MES, automation and control systems. Like connecting an electronic device via a USB interface, it should be possible in the future to link a line, system or machine to the network simply and straightforwardly.

Enterprise Manufacturing Intelligence: EMI can improve product quality (process stability) and productivity (process efficiency) by translating production data into usable information for decision making. By analysing these data the customer can, in turn, improve process stability and efficiency, which naturally feeds back into increased product quality and productivity. Production can be supervised in virtually real-time and can be continuously verified.

FLEXIBLE, SCALABLE PACKAGING SOLUTIONS

The modular and readily scalable nature of Dividella's packing equipment means that our customers can begin at an extremely simple level, possibly even starting without a machine and just receiving an identical carton pre-erected by Rondo, our sister company. The next level is a module that erects the carton automatically, and product loading is done manually. Companies can then scale this up to a fully automated machine, depending on various factors such as production volumes and product lifecycle. Dividella also has a manual product inserting module, because with very small lots it's sometimes not worthwhile to fully automate the process. The main steps in the pharmaceutical product packaging process are summarised in Figure 2.

If the pharmaceutical production plans are sufficiently ambitious and the expected production volume is in the range of three to five million packages per year, then it is impossible to avoid automated packaging lines. Such production volumes are difficult to ensure merely with staff packagers, and the human factor will bring the replication of quality into doubt. The employment expense will also be considerable.

Let's examine, as an example, the pharmaceutical market in India. Even under the conditions of quite low salaries (on average, a worker in a pharmaceutical manufacturing company earns €1200 (£1050) per year), production modernisation and the replacement of manual labour by machine labour results in positive economic performance, and investments in quality European equipment pay for themselves in five to seven years (based purely on the replacement of manual labour and decreased TCP). If we shift focus to Europe the economic benefits are even greater, due to factors such as the higher cost of staff, with packaging lines breaking even within one to five years.

With volumes from five to 24 million pharmaceutical packages per year, production may only be done by fully automatic, high-speed packaging lines. The return on investment for such equipment will, in the long run, lead to covering the production volume, decreasing the cost of the packaging materials and, of course, decreasing the expenditures on staff, which, depending on the country, allows for savings from hundreds of thousands to millions of Euros per year.

CONCLUSION

It can be seen that when assessing options for packaging pharmaceutical products there are several questions which must be thoroughly considered. Dividella's modular, scalable solutions to these questions provide companies with flexible, cost-effective answers to the important questions. Dividella can help product and delivery device manufacturers make decisions on this subject in a competent, well-informed and reasonable manner.

Figure 2: Main steps in the pharmaceutical packaging process.

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- Latest technology for small to large batches
- New functions allow innovative pack styles
- 100% momomaterial packaging for sustainabilty
- Very fast format line clearance and change over
- Large format range
- Highest OEE possible

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KÖRBER

DEVELOPING DEMONSTRATORS TO INCREASE PATIENT CONFIDENCE & REDUCE ANXIETY

Using Noble's recent partnership with BD to develop trainers for BD's UltraSafe™ needle safety technology as an example, Joe Reynolds, Research Manager, Noble, discusses the importance of training devices for the successful onboarding of patients beginning to use self-injected therapeutics, and how Noble's training devices are designed to be faithful to the look and feel of the real product.

According to recent research, the global prefilled syringe market is estimated to reach US$22.5 billion (£16.8 billion) by 2025. Drivers in the market's expansion include technological advancements in drug delivery and the growing use of prefilled syringes for delivering biologic and large molecule medications.[1]

Whilst these medications can significantly improve patients' quality of life, the WHO estimates that 50% of patients diagnosed with chronic conditions do not take their medications as prescribed.[2] While myriad factors influence patient adherence and outcomes, demonstrators and education can positively influence patient acceptance of, and adherence to, treatments using prefilled syringes, safety systems and other forms of drug delivery.

Through advancements in usability and human factors engineering, the overall understanding of patient adherence and the value of both device demonstrators and onboarding education has greatly improved. While Instructions for Use (IFU), package inserts and other content-based collateral are effective, it is estimated that only 12% of patients have the health literacy needed to understand and manage their treatment using these materials alone, resulting in training gaps that can adversely affect the use of prefilled and safety syringes by patients and other stakeholders.[3]

Through experience, Noble has found that confidence and anxiety are two key variables that influence a patient's perception toward drug delivery devices and their overall therapy. The onboarding period (or the first 30, 60, 90 days of treatment) is where these attitudes and usage behaviours are first established, and become key predicators of long term adherence and outcomes (Figure 1). During the onboarding phase 45% of patients skip or avoid injections due to needle anxiety or fear,[4] which can lead to avoidance behaviours and, ultimately, the discontinuation of treatment.

> "All device demonstrators are tested to guarantee that needle simulation and plunger speeds accurately mimic those of real drug delivery devices."

DEVICE DEMONSTRATORS REDUCING NEEDLE ANXIETY

Needle anxiety is a common adherence barrier for patients who use prefilled syringes and other injection-based delivery systems. To help patients overcome the emotional barriers of self-injection, novel needle simulation technologies have been developed to fully mimic the deformation, puncture and insertion force characteristics

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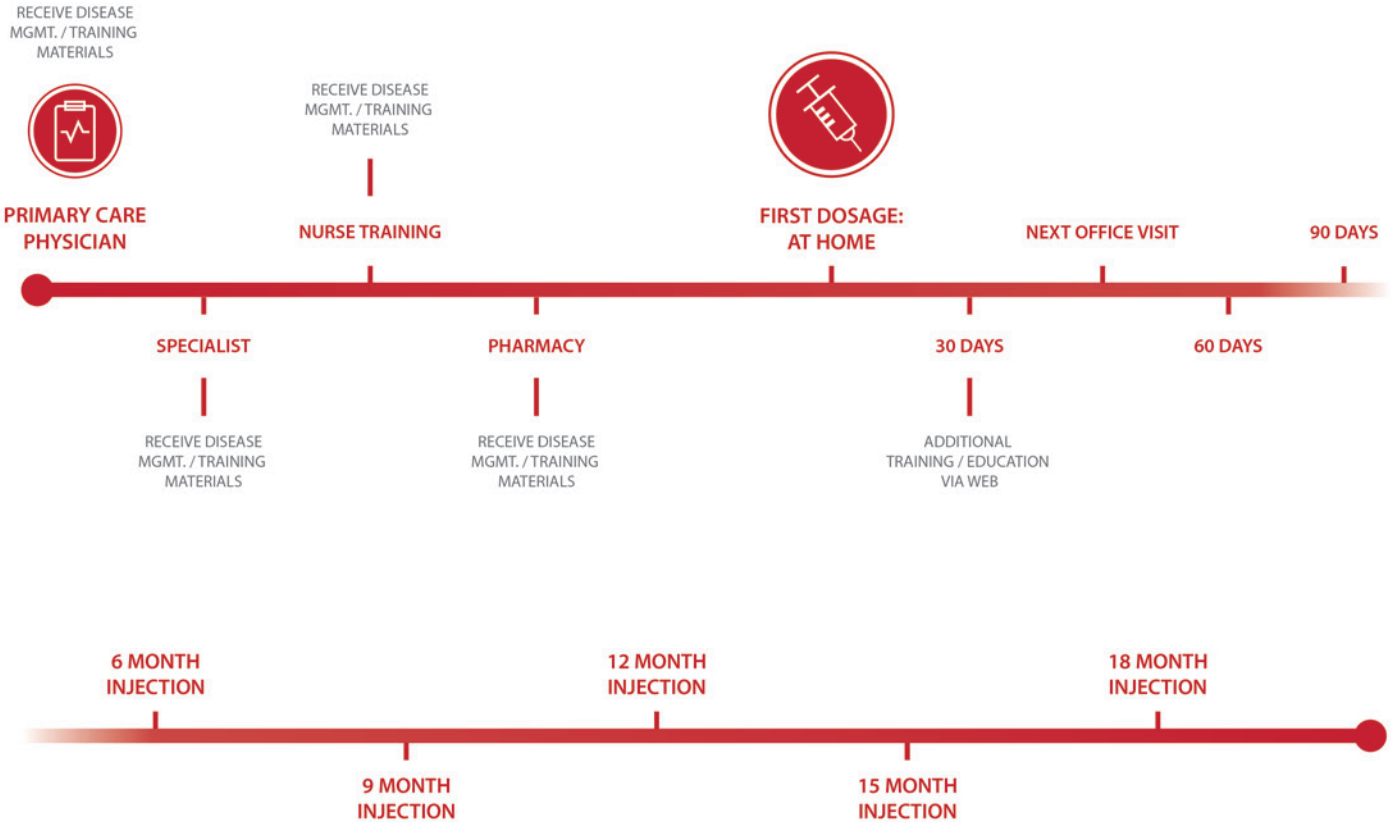

Figure 1: Timeline showing onboarding, including initial and subsequent injections at different dosing frequencies.

> "A study announced by Noble revealed that demonstration devices that incorporate needle simulation technologies result in a greater reduction in patient anxiety compared with traditional training."

of syringe needles. When applied to prefilled syringe training, these proprietary technologies allow patients to learn the force and technique required to insert a needle into subcutaneous tissue safely. A study announced by Noble revealed that demonstration devices that incorporate needle simulation technologies result in a greater reduction in patient anxiety compared with traditional training.

COLLABORATIONS THAT FOCUS ON PATIENT SUCCESS

As the pharmaceutical market continues to grow, so too does the need for injection devices that support both the complex properties of molecules and the needs of the end-user performing the injection. By providing a best-in-class user experience, pharmaceutical manufacturers can ensure that patients have access to resources that promote meaningful outcomes and build confidence in their ability to self-manage treatments and use drug delivery devices.

Noble recently announced its collaboration with BD to provide advanced patient onboarding solutions, including demonstration devices. Through the ongoing collaboration, Noble will leverage its onboarding solutions to develop novel demonstrators based on the BD UltraSafe™ technology (Figure 2), thereby improving the patient experience and confidence. Noble's market expertise and BD's passive needlestick safety devices allow for the full customisation of drug delivery devices and access to dedicated onboarding systems. BD has been an early innovator in developing safety-engineered solutions for the market, partnering with numerous customers to ensure product success.[5]

Figure 2: Noble is collaborating with BD to develop novel demonstrators based on the BD UltraSafe™ technology.

Partnerships and collaborations like this one provide the expertise needed to develop optimal treatments from start to finish. In a recent market survey conducted by Noble, 89% of patients reported that it was "very important" to have the most realistic demonstrating device possible. By having a deep understanding of complex device engineering and patient needs, companies are better able to create positive and impactful onboarding solutions for patients. User-centric companies, like BD and Noble, have the patient in mind from when they begin the onboarding process all the way to the end with administration of treatment.

One example of how this collaboration benefits patients is the BD UltraSafe Plus™ passive needle guard. The overall design of the product was validated by performing handling studies with both nurses and self-injecting patients. The user study confirmed that the BD UltraSafe Plus™ passive needle guard was intuitive and easy to use with a 100% activation success rate for all 500 injections.[6] Noble's device demonstrators will compliment BD's prefillable syringe safety systems and help instil another level of confidence during the onboarding process by providing hands-on experience that fully mimics the actual device. Demonstration devices, like those produced by Noble, have become the foundation of effective education and onboarding strategies by allowing patients and healthcare professionals to safely learn how to use prefilled syringes and other forms of drug delivery.

DEMONSTRATORS FOR PREFILLED SYRINGE SYSTEMS

Noble's prefilled syringe demonstrators simulate the attributes of real prefilled syringes and are available off-the-shelf or as customised platforms that include proprietary technologies. With the ability to be customised, brands can include capabilities like audio, tactile feedback, sensors, syncing and error detection. They also offer customisable options for syringe angle training that can be custom-fit to shape and design, colour, and 45° or 90° angularity.

These demonstrators are custom developed to mimic both standard prefilled syringes and those with safety systems. A few key features (also shown in Figure 3) include:

- Plunger speed simulation – Noble's device demonstrators replicate viscosity and volume, and are designed to help patients become familiar with break-loose and glide forces.
- Resettable Safety Mechanisms – Designed for repeated use, demonstrators are intended to replicate the device safety and shielding systems with the capability for users to reset the mechanisms for repeated use.
- Replication – Demonstrators should be designed true to form and function and able to simulate all aspects of the patient experience including design form, colour adjustments, window size and actuation force.
- Needle Tip Simulation Option – Demonstrators should also offer the option to exhibit realistic injection simulation designed to simulate the "feel" and "forces" involved with an injection.

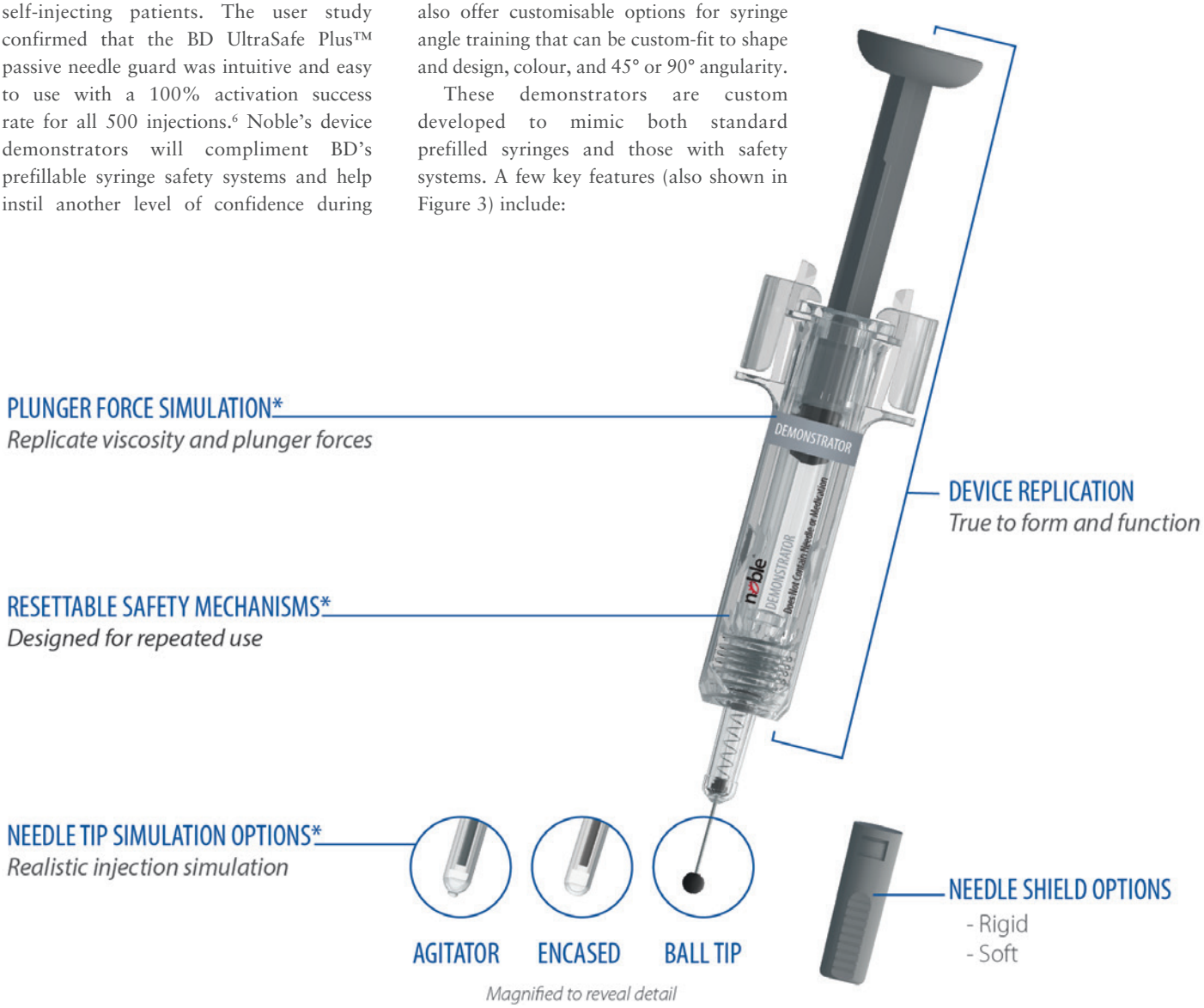

Figure 3: Noble offers a variety of innovative features designed to simulate BD UltraSafe™ with the goal of familiarising and preparing patients to self-inject.

BEST PRACTICES IN QUALITY

Noble adheres to a strict quality control process to ensure patients are provided with best-in-class demonstration devices. All device demonstrators are tested to guarantee that needle simulation and plunger speeds accurately mimic those of real drug delivery devices. By setting high quality standards when designing medical demonstrator devices, companies are able to prioritise user needs and translate those needs into effective onboarding solutions.

The industry will continue to evolve, giving patients opportunities to gain confidence in their treatments, overcome adherence barriers and, ultimately, achieve an improved quality of life. Through partnerships and collaborations that put the patient at the centre, like the relationship between Noble and BD, patients will have a better onboarding experience for treatment all the way to the last step when they administer their own medication. Industry leaders and partners who know the power of incorporating human factors into engineering and experiential training inspire the industry to innovate in design and onboarding practices, providing patients with better overall treatment options.

ABOUT THE COMPANY

Noble is a full-service, user-centric, advanced drug delivery training device and patient onboarding company. Noble works closely with the world's leading drug delivery device original equipment manufacturers and pharmaceutical companies to develop educational and training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes.

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ABOUT THE AUTHOR

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

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Nemera

COMPLEX DEVICES, SIMPLE PATIENT CARE

Adrien Tisserand, Global Category Manager – Parenteral, Nemera, explains how the recent granting of German Pharmaceutical Drug Manufacturing Authorisation for Nemera's facility in Neuenburg enhances the company's offering to industry, before going on to discuss the Safelia® auto-injector and Safe'n'Sound® safety device platforms.

GROWING INDUSTRIALISATION CAPABILITIES

Nemera is known for collaborating with its customers in the development and manufacture of multiple market reference devices for parenteral usage.The company engages at all stages of the design process, from concept generation to large-scale manufacturing. Its service offering includes:

- First class, clean-room manufacturing
- Cutting-edge development processes
- Industry-leading injection and assembly capabilities
- Expertise in programme management for project success
- A scalable approach for reduced lead-time and costs.

DRUG HANDLING VIA AN INNOVATIVE SUPPLY CHAIN

To provide flexibility and convenience to its customers, Nemera has integrated pharmaceutical drug handling capabilities, providing the company with the ability to assemble a prefilled primary container together with a combination device.

Specifically, in September 2017, Nemera's manufacturing facility in Neuenburg, Germany (Figure 1) received Pharmaceutical Drug Manufacturing Authorisation. This certification under the German Medicinal Products Act (Arzneimittelgesetz, AMG) approves the manufacturing plant for handling, assembling, sterilising and storing pharmaceutical drugs and medicinal products for auto-injectors.

The authorisation is an important achievement for Nemera, reflecting the company's commitment to quality in developing and manufacturing drug delivery devices. It confirms that Nemera meets the highest standards, ensuring quality manufacturing and testing of therapeutics. It is a crucial regulatory step and allows Nemera to provide its customers with a complete set of services, including additional support for the development and manufacturing of pharmaceutical combination products and drug delivery devices.

"Achieving this pharmaceutical drug manufacturing approval highlights our commitment to ensuring the safety of our drug delivery devices for the benefit of patients. It is also represents confirmation that our quality systems and processes consistently meet regulatory requirements and patient expectations," commented Christian Meusinger, Nemera's Vice-President of Quality.

The Neuenburg plant has been manufacturing high quality products since 1953. Covering more than 20,000 m^2,

> "The certification under the German Medicinal Products Act approves the manufacturing plant for handling, assembling, sterilising and storing pharmaceutical drugs and medicinal products for auto-injectors."

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Figure 1: In September Nemera's Neuenburg facility received German Pharmaceutical Drug Manufacturing Authorisation.

the plant features Class 8 clean-rooms and employs more than 400 members of staff to guarantee production 24 hours a day, seven days a week. The plant produces billions of injection moulded parts and assembled devices every year. Recent key quality management achievements include:

- Short reaction times
- Detailed and comprehensive root cause analysis
- Reduction of scrap rates
- Elimination of inefficiencies.

LEADING EXPERTISE IN DEVELOPING & MANUFACTURING PARENTERAL DEVICES

Being granted the German Pharmaceutical Drug Manufacturing Authorisation has strengthened Nemera's offering to its customers considerably. The platforms Nemera will now be able to handle, assemble, sterilise and store pharmaceutical drugs for include Safe'n'Sound®, a customisable passive safety device for prefilled syringes, and Safelia®, an innovative two-step auto-injector platform.

Safe'n'Sound®

Safe'n'Sound® is a single-use safety device to protect patients and healthcare professionals from accidental needlestick injuries. It is activated passively with one hand, suitable for low fill-volumes and higher viscosity formulations, robust against shocks and vibrations and compatible with all scales of assembly line, from manual to fully automated.

It is also compatible with both prefilled ISO standard glass syringes and PLAJEX plastic syringes, fitting 1 mL "long" and 2.25 mL long staked syringes with a maximum needle length of half an inch (12.7 mm).

Ergonomically designed, Safe'n'Sound® is intended for naive users, experienced users and healthcare professionals alike. It features a large thumb pad for ease of use, clear visibility of the tip for easy inspection of the drug and a rounded shape for increased labelling surface.

Safe'n'Sound® is a highly customisable platform (Figure 2), able to respond to pharma and user needs. There are, for example, the options of an extended finger flange, coloured plunger rod, a "soft touch" thumb pad and a one-handed, subcutaneous rigid needle shield (RNS) removal feature.

Safelia®

Nemera's new generation two-step auto-injector, Safelia® (Figure 3), has been designed to improve the patient self-injection experience and to deliver a variety of drug products in glass syringes. These range from more fluid formulations to the most challenging drugs, such as viscous, sustained-release, concentrated formulations and products for subcutaneous and intramuscular injection (including larger volumes). To be competitive, new generation auto-injectors have to be able to deliver highly viscous formulations, in larger volumes.

The Safelia® auto-injector:

- Administers a large range of formulations and injection volumes; by design the platform can adapt to handle both fluid and highly viscous formulations, taking care specifically of biologics, sustained-release formulations and sheer-sensitive molecules, of up to 2.25 mL injection volumes
- Improves the patient experience, with the possibility to reduce needle gauge, reduce injection time and slow down the needle penetration inside body tissues (giving the possibility of a delayed retraction for viscous injections especially).

The injection speed profile of Safelia® can be tailored to minimise injection forces. This injection force control should prevent the initial injection peak force, and allow a better drug absorption, and could also lead to a lower pain perception.

Figure 2: The highly customisable Safe'n'Sound® single-use safety device.

Figure 3: 1 mL and 2.25 mL versions of the Safelia® auto-injector.

CONCLUSIONS

Parenteral drug administration exposes patients and healthcare professionals to many hazards. To ensure adherence and users' safety, reliable and easy-to-use devices are needed.

With decades of experience in developing and manufacturing some of the most complex and innovative parenteral drug delivery solutions, Nemera is the ideal partner for a successful product launch.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology & generics industries.

Nemera's services and products cover several key delivery routes:

- Parenteral (auto-injectors, pens, safety devices & implanters)
- Ophthalmic (multi-dose, preservative-free eyedroppers)
- Nasal, buccal, auricular (pumps, valves and actuators for sprays)
- Inhalation (pMDIs, DPIs)
- Dermal and transdermal (airless & atmospheric dispensers).

Within the injectables field specifically, Nemera's experience in drug delivery devices include:

- Insulin Pens (more than one billion insulin delivered to the market)
- Auto-injectors for pharma and military usage
- Customised plastic syringes for human and animal usage
- Safety devices for prefilled syringes
- Implanters (devices for delivering sustained-release formulations).

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development, and contract manufacturing.

ABOUT THE AUTHORS

Adrien Tisserand is Category Manager at Nemera in charge of the parenteral range of proprietary products including Safe'n'Sound®, the passive safety device platform for prefilled syringes. Adrien joined the company in 2013. He previously worked for Janssen: Pharmaceutical Companies of Johnson & Johnson in the strategic marketing division. He holds three diplomas: a Bachelors in International Business from HUBS (Hull UK), a Masters in Marketing from Universidad Rey Juan Carlos (Madrid, Spain) and a Masters from Kedge Business School, France.

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PRODUCT SHOWCASE: Aptar Pharma's Premium Portfolio

Aptar pharma

NEW STANDARDS FOR QUALITY AND CLEANLINESS

For over 50 years Aptar Pharma's injectables specialists have led the way in developing innovative elastomer solutions. Their commitment to continuous improvement has resulted in elastomer formulations that feature best-in-class extractables and leachables profiles.

As the pharmaceutical market continues to develop ever more sensitive drugs, including biotherapeutics, the need for improved regulatory requirements increases. Aptar Pharma has risen to the challenge, delivering the highest standard of cleanliness in elastomer components. Aptar Pharma's focus for both the last 12 months and the foreseeable future is quality: in R&D, customer insight and product solutions.

> "PremiumCoat™ sets the standard for film-coated stoppers with an unrivalled reduction in particulates: achieving a market-leading Particulate Count Index of 1.3."

Aptar Pharma was the first company to provide a Drug Master File (DMF) for the Ready-to-Sterilise (RTS) process, as well as the first company to provide Ready-to-Use (RTU) stoppers to the market – a quality standard now seen as the norm. With future commitment to quality in mind, Aptar Pharma has developed the Premium portfolio of injectable components.

Figure 1: PremiumCoat™ stoppers feature a homogenised ETFE coating to provide an unrivalled reduction in particulates.

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True experts love a challenge

Aptar Pharma
Taking on injectable complexities

Isn't our industry all about taking on challenges and pushing boundaries? Imagine just how dull life would be if we never tried to be better? Settling for the perceived standard is essentially settling for second best, and no-one can afford to do that.

Rest assured, taking on a complex injectable challenge doesn't have to be a risk. For over 50 years, our injectable specialists have led the way in developing innovative elastomer solutions. Their commitment to continuous improvement has resulted in elastomer formulations, which today feature best in class extractables and leachables profiles.

But we know that isn't enough. As the pharmaceutical industry continues to develop more sensitive and expensive drugs, we need to go further. That's why we have developed the Premium portfolio of injectable components.

To find out more about how we can help you address your next injectable challenge, call **Adam Shain**, Director, Global Business Development at Aptar Pharma on **+1 908-458-1782** or email **adam.shain@aptar.com**

Delivering solutions, shaping the future.

Aptar pharma

"Aptar Pharma will introduce the latest developments in its Premium Portfolio when it exhibits at CPhI Worldwide in October."

THE PREMIUM PORTFOLIO

The Premium portfolio delivers cleaner components to satisfy the ever-increasing demands of the pharmaceutical industry for inert stoppers; particularly in the delivery of more sensitive and expensive drugs, including complex proteins.

PremiumFill® is a RTS process, prior to container filling, with specifications guaranteed to Aptar Pharma's highest quality of production, resulting in lower embedded particles, improved particulate cleanliness, and an overall reduction in defects.

All PremiumFill® manufacturing is in-line, reducing the risk of contamination during transport around the plant, thus avoiding adding intermediate storage steps in a classified manufacturing area.

PremiumCoat™ sets the standard for film-coated stoppers with an unrivalled reduction in particulates: achieving a market-leading Particulate Count Index (PCI) of 1.3, compared with the historic standard of 2.9. The coated stopper features a fluorinated polymer film (ETFE), which is applied during the manufacturing process. This approach delivers a homogenised coating, which is the established best practice method, to create the most robust and effective barrier between the drug and the stopper (Figure 1).

PremiumVision™ is a guaranteed quality commitment using an in-line, automated vision system. PremiumVision™ is designed to further validate against critical defects.

MARKET BENEFITS OF THE PREMIUM PORTFOLIO

The challenge to deliver higher standards of cleanliness in elastomer components is driven both internally and externally. As ever more complex and expensive drugs are developed, there is an absolute need to ensure that a stopper's integrity is guaranteed. The Premium Portfolio's commitment to lowering particulates provides for the highest standard level of guaranteed specification for laminated stoppers in the market today, meaning even greater levels of reassurance for the customer.

PREMIUMCOAT™

There are several key advantages of PremiumCoat™, most notably its aforementioned 1.3 PCI and Aptar Pharma's deep experience in delivering gamma-irradiated stoppers. For several years Aptar's injectables specialists had focused solely on developing elastomer formulations with extremely low extractables profiles, to the point where they are the cleanest available on the market today.

Whilst non-coated stoppers are still the component of choice for many drug formulations, there is an increasing need for the additional level of reassurance provided by coated stoppers. PremiumCoat's homogenised ETFE coating results in a barrier which is both more effective and easier to inspect with automated vision systems. The process also ensures that only the area that comes into contact with the drug is treated, guaranteeing closure with the vial.

The Ready-to-Sterilise product, PremiumCoat™ is designed for organisations that have sterilisation facilities in place. It is compatible with steam sterilisation and uses Aptar Pharma's proprietary washing process. The Ready-to-Use version comes already gamma radiation sterilised, providing the customer with convenience and flexibility. This approach leads to a reduction in the number of human operations as well as improved productivity, as the stoppers may be used immediately and can be directly used in RABS or isolators. There are significant economic advantages too in terms of a reduced investment in equipment required, negated maintenance costs and reduced stock levels.

PREMIUM PORTFOLIO EXHIBIT AT CPHI

Aptar Pharma will introduce the latest developments in its Premium Portfolio when it exhibits at CPhI Worldwide in Frankfurt in October. In addition to exhibiting at CPhI, Arnaud Fournier, Aptar Pharma's Senior Business Project Manager, will be delivering a Pharma Insight Briefing entitled "Setting New Standards for Coated Stoppers". His presentation will take place on day two of CPhI.

ABOUT THE COMPANY

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

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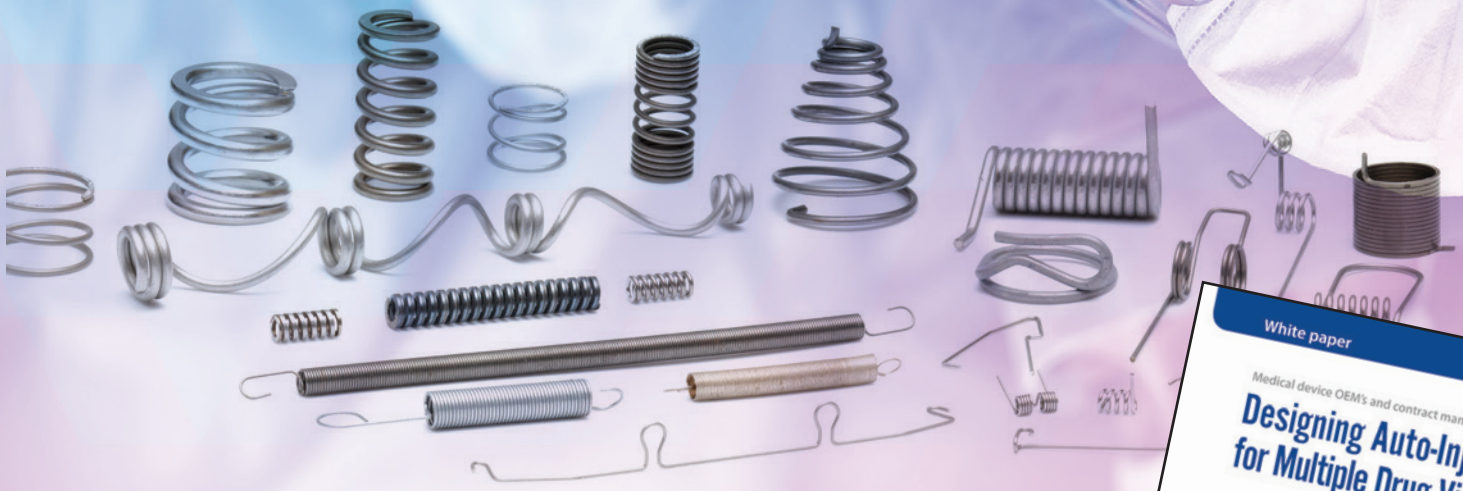

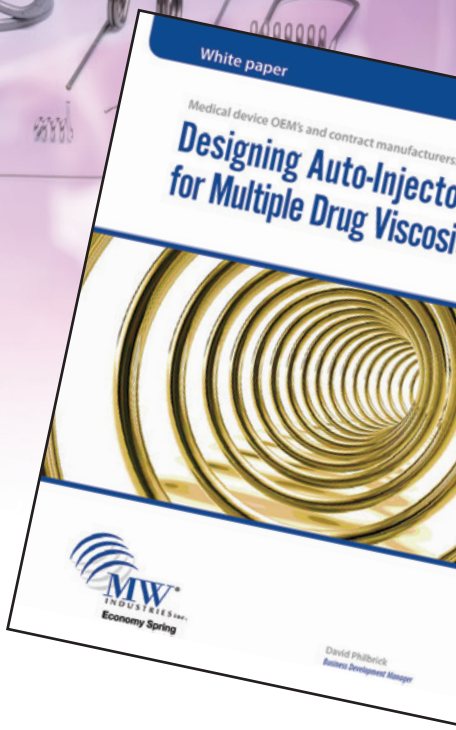

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