PREFILLED SYRINGES & INJECTION DEVICES

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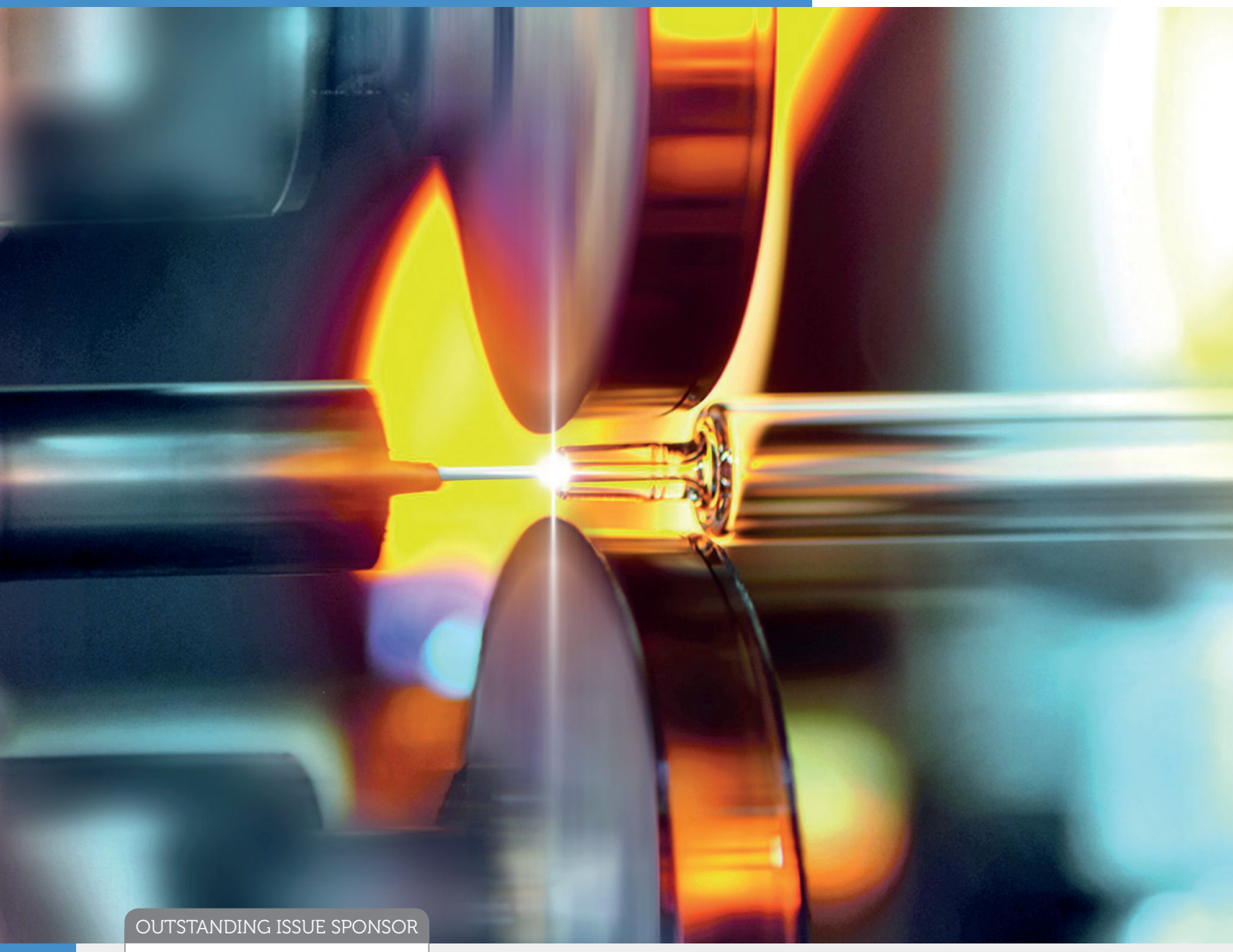

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ONdrugDelivery Issue N° 83, February 5th, 2018

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.

EDITORIAL CALENDAR

Mar 2018	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Delivery
May	Injectable Delivery: Devices Focus
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery Systems
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Delivery
Dec	Connecting Drug Delivery
Jan 2019	Ophthalmic Delivery
Feb	Prefilled Syringes & Injection Devices

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ON drugDELIVERY

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SHL GROUP

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INJECTING HIGH VOLUME, HIGH VISCOSITY DRUGS

SHL has extensive experience in the parenteral arena. In this article, SHL details its latest offerings in the world of biologics, as well as its partnership with QuiO, a speciality digital healthcare start-up, to develop injectables in the connected healthcare space.

"As diseases are split up into sub-categories, the patient groups naturally become smaller. Therefore, to maintain returns on investment, higher prices and/or decreased R&D costs must be implemented."

The rising trend towards biologics in the pharma industry has opened the gates for the development of very specific molecules targeting the diseases right at their core. Due to their effectiveness, the market for biologics and biosimilars is expected to grow at an annual rate of over 8%.[1] We now see several disease areas, historically dominated by a few blockbuster products, splitting up into a number of different sub-diseases, each with their own tailored treatments.

Upon first inspection, this appears to be a huge win-win scenario, but it comes with a number of challenges. As diseases are split up into sub-categories, the patient groups naturally become smaller. Therefore, to maintain returns on investment, higher prices and/or decreased R&D costs must be implemented. At the same time, there is a focus on patient convenience and self-treatment has become the gold standard in subcutaneous injections. Also worth noting is a strong trend towards less frequent administration and, as a result, increasingly large dosing.

With autoinjectors delivering higher doses of proteins subcutaneously, there is the major consideration of injection duration. A duration of 10-15 seconds has historically been regarded as the maximum acceptable threshold for autoinjection – patients typically prefer to not hold a device in place for any longer.

The complex molecular structure of biologics also poses a technical challenge. Biologics have a propensity towards destabilising or aggregating in a prefilled syringe or other primary package over the course of their shelf life. They often need to be delivered in higher concentrations to have an effect, and with increasing concentration the viscosity of the product increases exponentially.[2] From a formulation point of view, higher viscosities could cause problems with the drug's syringeability (i.e. the ease with which the formulation can be pushed through a needle).[3] At the patient level, the force and needle bore size needed to administer a viscous injection may result in increased discomfort and user anxiety.

"Benefitting from two decades of experience, SHL's technologies are able to deliver any formulation for subcutaneous and intramuscular injections effectively and efficiently."

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Figure 1: Bertha® is a disposable autoinjector that can safely deliver drugs with viscosities of up to 60 centipoise.

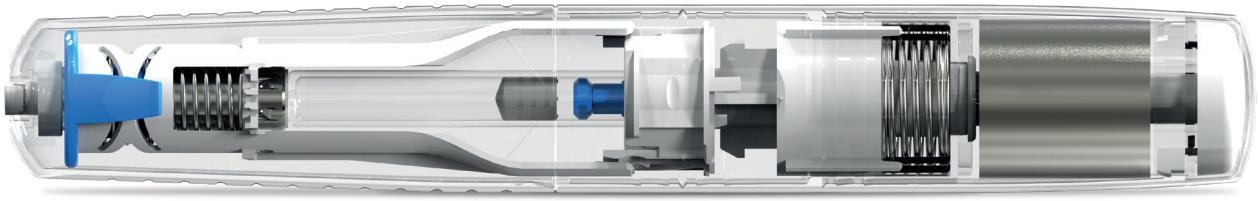

Figure 2: The Rotaject® technology uses a constant force technology that allows the delivery of highly viscous formulations of up to several hundred centipoise.

THE SHL APPROACH

Benefitting from two decades of experience, SHL's technologies are able to deliver any formulation for subcutaneous and intramuscular injections effectively and efficiently. We believe that an advanced drug delivery solution can save time and money in drug formulation without compromising patient comfort.

SHL's offerings are patient-friendly autoinjector solutions for many different types of formulations, including:

- High volume
- High viscosity
- Unstable formulations requiring separation and reconstitution of drug and diluent.

Our most requested specifications are available in preconfigured devices that offer a faster developmental timeline compared with bespoke products, giving clients a much shorter path to market with their innovative and novel therapies.

For higher viscosity drug preparations, SHL's Bertha® (Figure 1) provides the safe and reliable delivery of up to 60 centipoise. Bertha® is a disposable, fixed-dose autoinjector that is compatible with either a 1.0 mL or 2.25 mL prefilled syringe.

Made for higher viscosities, Bertha® was designed with a particular focus on human factors, as complex formulations can be harder for a patient to inject independently. Bertha® features a continuous clicking mechanism, visual feedback ribbon and viewing window for easily understandable and immediate feedback. Its larger design provides the user with a sense of security during the injection process, and its proprietary rounded needle cover helps to prevent accidental activation when the user is seeking the desired injection site.

For viscosities of up to hundreds of centipoise, SHL's market-proven Rotaject® (Figure 2) technology offers safe and dependable support. Rotaject® can solve some of biologics' most daunting challenges with its clock-spring technology, ensuring that the full dose is pushed by a constant force. This technology allows for high viscosity drugs to be delivered safely and comfortably, within seconds.

For dosing in higher volumes, SHL's Molly® family of autoinjectors (Figure 3) can deliver up to 2.25 mL. Molly® 2.25, the highest volume variant, features the same simple two-step handling, ergonomic cap and automatic locking needle cover features of its predecessors. Its enhanced anti-roll feature prevents unwanted rolling for enhanced safety.

The Molly® family is developed with a range of spring options that can be adapted to suit a variety of drug characteristics. Their intuitive features and compact design make them less intimidating and more appealing to the patient. They are also designed with a unique power pack that offers robust functionality whilst using significantly fewer components. For pharmaceutical companies, this means that the timeline and investment required to integrate a Molly® autoinjector into development can be dramatically reduced. At the same time, Molly® still offers customisation flexibility, meeting the requirements of various drug specifications and branding.

SHL's cartridge-based solutions, with a maximum fill volume of 3.0 mL, can safely deliver drugs in higher volumes. The Maggie®, for example, uses a 3.0 mL standard ISO cartridge. The VSDI®+NIT® autoinjector, compatible with 1.5 mL to 3 mL cartridges, allows precise dosing variations, customised to client needs.

Cartridges offer a broad range of options for fulfilling various drug characteristics and therapeutic needs, widening the scope of container choices, including for both single- and dual-chamber therapy solutions. However, because their needles are not pre-attached, they do pose a challenge in terms of avoiding contamination and preventing needlestick injuries. SHL addresses this problem with Needle Isolation Technology (NIT®), a unique safety solution where the needle is pre-installed in the device. In one

Figure 3: The Molly® family of devices (from left to right): Molly 1.0 mL FNS, Molly 1.0 mL RNS and Molly 2.25 mL.

simple 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, and we mitigate the risk of metal contamination.

For the drugs we handle, and for sensitive biologics in particular, SHL evaluates the leachability of syringes and primary containers on a case by case basis, in order to establish the optimal packaging for ensuring product stability.

Meanwhile, all of SHL's offerings are developed in close partnership with biopharmaceutical clients to increase patient acceptance and safety throughout the injection process. Our in-house design team works with clients to develop devices based on both human factors studies and input from a range of stakeholders and experts on how the patient understands the device.

CONNECTED THERAPEUTICS

In recent years, SHL Group has integrated connectivity with its devices to enhance patient adherence, one of the most important factors affecting therapeutic outcome. Combining our own expertise with that of active partnerships, SHL is working on a number of initiatives in the digital space to bring innovation to the healthcare market.

Last year, SHL Group entered into a strategic partnership with QuiO, a New York-based digital healthcare start-up, to support even the most viscous and/or high volume biologics. QuiO is developing a range of smart add-ons for SHL's devices, including SHL's solutions for drug formulations with higher viscosities or volumes. QuiO is also developing a universal, reusable smart injector that will be compatible across all common primary containers, enabling drugs along a sweeping range of viscosity levels to be administered subcutaneously.

QuiO-connected devices can record injection performance and transmit that information to ConnectedRx®, a fully integrated cloud-based platform that is the first solution designed specifically for connected therapeutics.[4] ConnectedRx® gives patients analytics and communication tools so that they can monitor their health metrics, and it can be paired with services like QuiO Coach™, which provides high-touch interventions and patient onboarding.

ConnectedRx® can also automatically collect dose-level data and share it as desired with stakeholders, including physicians and payers. Through the software, clinicians can track patient data indicating health status and medication adherence outside the clinic; they can also receive alerts for identifying patients in need of attention and are provided with tools for co-ordinating, performing and tracking interventions.

On the platform, payers and pharmaceutical clients can gain invaluable business intelligence derived from de-identified data measuring patient experience, adherence and health outcomes. These analytics can help them identify opportunities to improve adherence and to participate confidently in value-based contracts.

Integrated with ConnectedRx®, SHL's injectors offer the unique opportunity of time-tested yet leading-edge delivery solutions that factor in the complexities of higher volume and higher viscosity drug preparations. Amid rapid growth in the biologics space, SHL's delivery technologies enhance product differentiation for clients, as they support the realisation of protein-based therapies by making at-home administration comfortable, simple and safe, ultimately leading to better clinical outcomes.

ABOUT THE COMPANY

SHL Group is a world-leading solution provider in the design, development and manufacturing of advanced drug delivery systems. The company works with leading biotechnology and pharmaceutical companies to develop drug delivery devices, including compact disposable autoinjectors, reusable pen injectors and complex inhaler systems.

SHL has been investing significantly into R&D, allowing us to enhance our broad pipeline of next-generation drug delivery devices. In particular, it has initiated several forward-thinking initiatives, exploring new technologies and future developments, including comprehensive connectivity offers.

Developing these projects in-house allows SHL to customise existing platforms in our pipeline or develop completely new bespoke devices based on the unique requirements of our customers. With locations in Taiwan, Sweden, the US and mainland China, SHL experienced engineers and designers develop product enhancements and breakthrough drug delivery solutions for clients globally.

Figure 4: ConnectedRx® is the first solution designed specifically for connected therapeutics.

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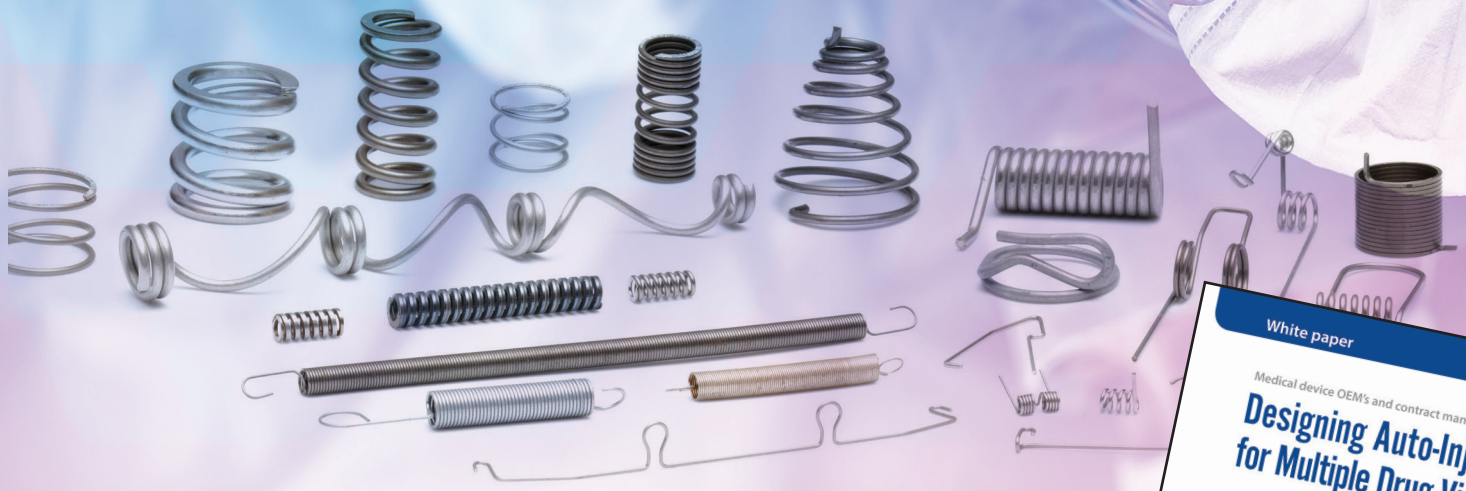

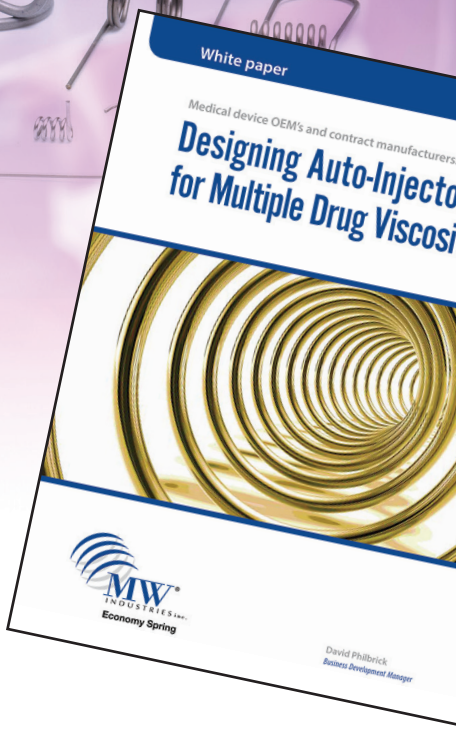

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A PATIENT-CENTRIC APPROACH TO THERAPY MANAGEMENT

Life after being diagnosed with a chronic illness is difficult. Here, Karl Hewson, User-Centred Design Engineer, and Uri Baruch, Head of Drug Delivery, both of Cambridge Design Partnership, discuss the challenges presented by chronic illness, and look ahead to a better future of patient-centric treatment, personalised to each individual's needs.

Average life expectancy is longer than ever before. However, this increased longevity often goes hand in hand with an increase in health issues. We're more likely to fall prey to the so-called diseases of ageing – problems such as cancer, diabetes and heart disease. In a similar vein, younger patients suffering from chronic conditions, such as rheumatoid arthritis, face the burden of living with their illness for many more years than previous generations. Add to that the effect on their families and the increased workload for healthcare professionals and the scale of the problem becomes clear.

The patient "journey" is tough. Going from the initial identification of symptoms, through consultations with various medical professionals to reach a diagnosis is often a traumatic experience. But, in many ways, that is only the start of the journey. Once treatment has been prescribed, a patient with a chronic condition suddenly has to take on the burden of the day-to-day responsibility of managing their disease – sometimes with little or no support system to fall back on. The symptoms of their disease also often exacerbate the problem, causing significant physical or cognitive difficulties, as well as the emotional challenges of coping with the life-changing diagnosis.

> "There is growing pressure for device functionality to be as simple as possible – sometimes down to just two steps for device operation. But, at the same time, there is a demand for more and more complex features."

> "Once treatment has been prescribed, a patient with a chronic condition suddenly has to take on the burden of the day-to-day responsibility of managing their disease."

A patient's age also presents its own challenges. A diagnosis later in life often requires patients to relearn, adapt or even sacrifice many of the activities and routines which have become a key part of their daily lives. In addition to the symptoms and physical challenges arising from the illness, the patient may also have to face the added complexity of a mental health issue. A diagnosis during childhood, on the other hand, can be easier for the patient – but may be more challenging for the parent who is responsible for initially managing the condition, administering therapy and eventually training their child to manage the condition themselves.

Pharmaceutical therapy regimens can vary significantly in frequency and complexity but even the simplest routine, such as swallowing a tablet at the right time, can prove difficult for some patients. Memory problems, for example, might make it difficult for an elderly patient to reliably take their medication at the right time, thus leaving them at risk of accidentally under- or overdosing.

When a drug delivery device is involved, technical complexities are added to the cognitive burden. Inhalation devices often require conflicting techniques – the use of a dry-powder inhaler, for example, requires a vastly different technique from a pressurised metered-dose inhaler. The correct inhalation rate might be fast or slow, and the device may or may not need to be shaken prior

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to use. Similarly, injection devices often require careful preparation and an understanding of where and how to inject, whilst avoiding accidental needlestick injury. For more complex treatments, such as those for HIV or cancer, multiples of different drug therapies and devices may be required, in addition to treatments being received for comorbidities.

A PATIENT-CENTRIC APPROACH

In other sectors, such as transport and the consumer industry, we're seeing technologies emerge which greatly simplify our daily routines. Smart homes can now detect whether or not a person is at home and switch the central heating and lighting on or off accordingly. We can remotely switch on our smart ovens or record our favourite TV programme from the office so everything is ready for when we get home. We're even able to get our sound system to play our favourite track using a simple spoken request. Our cars have evolved to keep us safer on the road, systems ranging from anti-lock brakes and self-dipping headlights through to corrective steering to prevent lane drift and automated speed and breaking control reduce our physical and cognitive burden when driving, thereby decreasing the risk of human error.

So how could assistive technologies help patients with chronic illnesses and complex therapy regimens? One approach is to look at the areas where patients are commonly making mistakes, leading to harm or poorly controlled symptoms. Medical device manufacturers today follow a risk-based approach to design laid down by regulatory bodies such as the US FDA and the MHRA. This approach helps to ensure patient safety, within the context of administering a drug. It looks at the design of the therapy administration and tries to simplify it to ensure patients or carers are informed through an ever-growing list of information sources – ranging from standard "Instructions for Use" to online therapy websites offering training videos and detailed instructions. Some new devices even offer phone apps and augmented reality features.

There is also growing pressure for device functionality to be as simple as possible – sometimes down to just two steps for device operation. But, at the same time, there is a demand for more and more complex features: more elaborate patient injection prompts on the device and automated functions such as needle insertion, reconstitution and connectivity. It's a delicate balancing act, even before you take into account the fact that patients really just want to forget about their illness and get on with their busy lives.

That's why a patient-centric approach is crucial: one size does not fit all. Diagnoses and treatments need to be designed, or at least customised within safe limits, for each patient and their lifestyle. Diagnosis is already moving towards point-of-care diagnostics, as well as at-home diagnostics. In Japan, for example, where there is already a high prevalence of electronic toilets, companies are working on the automated collection and analysis of urine samples. Imagine the potential benefits from early detection of a variety of medical conditions.

On the therapy side, personalised therapy has made headlines; CAR-T cell therapy from Novartis has achieved approval and further developments are in the pipeline for Roche and others. These go hand in hand with cheaper, faster DNA sequencing, which companies such as 23&Me are using to offer DNA insights, whilst also building a large pool of human DNA metadata that can help customise the therapies of tomorrow.

LIMITING FACTOR

So, we are well on the way to detecting diseases earlier and understanding their make-up better, as well as having keener insight into patients themselves. In the near future, this will allow us to really personalise therapies, not just to specific diseases but to individual patients. The limiting factor is the manufacturing and delivery of these personalised therapies. Manufacturing is currently geared towards large-scale production and can't cope with a complete shift to individually personalised "therapy on demand". Several organisations are working on solutions to tackle this issue, moving away from large-scale manufacturing of identical therapies into a situation where each batch is patient specific. The aim is to be able to manufacture, on demand, a batch of medication for a specific patient based on their disease state and genomic make-up.

> "Personalised therapy has made headlines; CAR-T cell therapy from Novartis has achieved approval and further developments are in the pipeline for Roche and others."

> "We are on the way to detecting diseases earlier and understanding their make-up better, as well as having keener insight into patients themselves."

That future is still some way off – but the technology is already here to transform the lives of patients juggling complicated treatment regimens and bring down costs for healthcare providers. A radically new approach is possible by combining state-of-the-art technology with user experience and human factors expertise, all within the framework of current medical device regulation.

A NOVEL APPROACH TO DRUG DELIVERY

This new generation of treatment could, for example, transform the world of autoinjectors. We could do away with the need for rheumatoid arthritis patients to worry about storing their drugs in the fridge, warming them up to the correct temperature for injection, preparing their autoinjector for use, and disposing of the device safely. A smart base station could reduce the patient's task to the simple action of picking up a reusable autoinjector from the base station when prompted to do so, injecting themselves and then returning the device to its cradle. After injection, the base station could automatically collect the needle and cartridge ready for safe disposal, also alerting the patient when supplies are running low, and possibly even automatically reordering if required. Such technology could be adapted to cope with multiple users and different medications, either in the home or at a small clinic, for example. Fingerprint recognition technology could be used to identify the correct user each time, with a childproof lock to prevent accidental use.

The technology is here now – all it takes is a little imagination.

JOHN A. MERHIGE, CREDENCE MEDSYSTEMS

John A Merhige is Chief Commercial Officer at Credence MedSystems, leading the business development, sales and marketing activities. Previously, he was Vice-President, Market Development at Sanofi BioSurgery. Mr Merhige came to Sanofi upon its acquisition of Pluromed in 2012, which he joined in its early stages. Prior to Pluromed, he founded Prelude Devices and previously he gained general management and commercial leadership experience at Ford Motor Company and Avery Dennison. Mr Merhige graduated from Dartmouth College (Hanover, NH, US) earning a BA, a BE in Mechanical Engineering, and a Masters in Engineering Management from Dartmouth's Thayer School of Engineering and Tuck School of Business.

Here, in conversation with ONdrugDelivery Magazine, Mr Merhige discusses Credence's Companion Safety Syringe System, new advances in the product development pipeline, customer/market driven feedback from user studies and exciting developments planned for 2018 that will take the company on to the next major phase in its growth.

"With our staked syringe, the staked Companion, the drug companies will receive sterile syringes with the needle mounted, just like they do today, in three-inch tubs, just like they do today."

Q It has been a couple of years since we last spoke (see Issue 67 (June 2016), pp 34-35) and there are exciting new developments to discuss. But before that, could you bring new readers up to speed? Introduce Credence MedSystems, tell us about the Companion Safety Syringe range, and explain how the Companion enables Innovation Without Change.

A Credence MedSystems was founded in early 2013, so we're into our fifth year. We're located in the San Francisco Bay area, right in the heart of Silicon Valley, which is the home of technical innovation. This location has been a big part of the fabric of who we are as a company. Our mission is to provide innovation in injectable drug delivery to our pharmaceutical manufacturing customers.

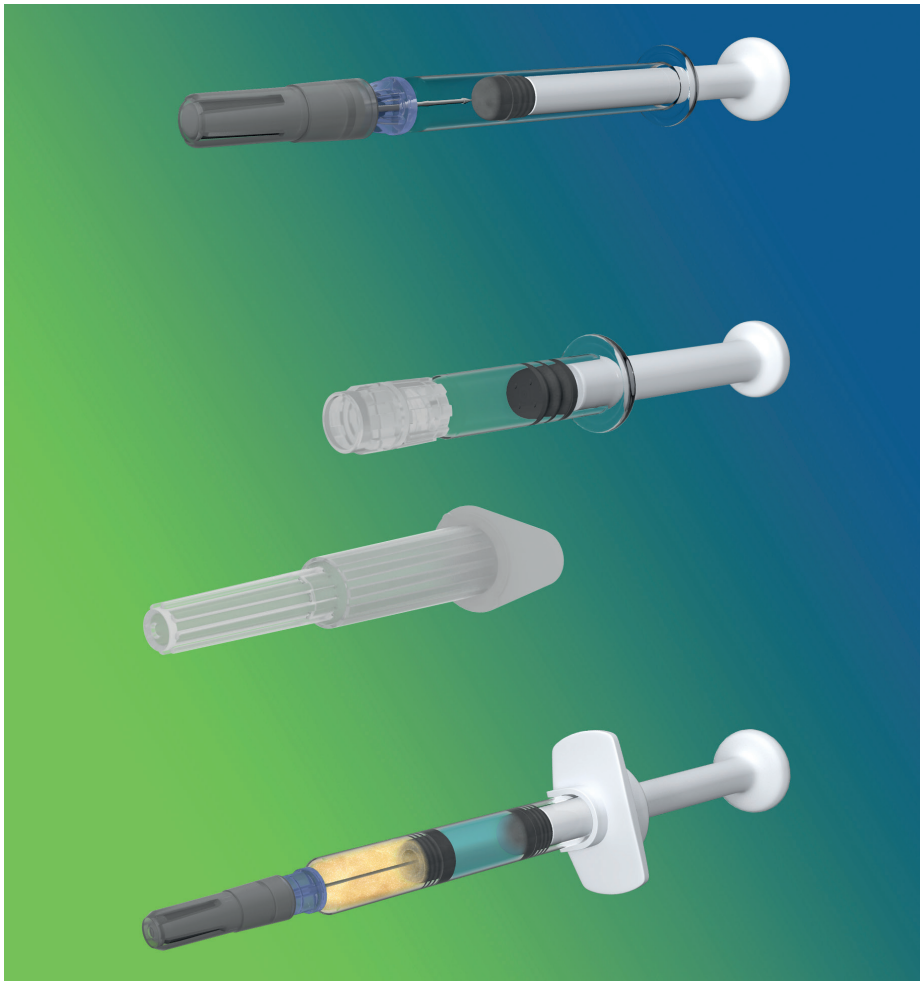

Figure 1: The Companion platform. The Companion staked needle syringe (top), the Companion luer lock syringe (middle), and the dual-chamber device for reconstitution (bottom).

I think one of the points I made last time we spoke, and it is just as important today, is that we have a great team of people. They're experienced, they love what they do, they care deeply about the impact our work has on patients and caregivers in terms of protecting them, enabling successful injections and compliance with prescription regimens. This is the core of what we do. But equally important, we like and trust each other and, when you're in that kind of environment, coming to work is easy because everyone is supportive of the mission and everyone is going in the same direction. It's a special place to work.

You asked about Innovation Without Change and that is our core philosophy. I would expand upon the question a little because Innovation Without Change is not just about our product line. It's also about how our business model achieves Innovation Without Change. We have shaped the business model and the design and development of the products on that core concept of maximising the innovation that is delivered but minimising the disruption to our customers when they implement the technology.

It always makes sense to start with thinking about the end user – whether a healthcare provider or self-injecting patient – and the experience they have when using our devices. Across the Companion platform (see Figure 1) we provide a very consistent experience. At its most basic, the user performs an injection, they hear and feel a click when the dose is fully delivered, and then the needle disappears. It is retracted back into the plunger rod and the barrel of the syringe (Figure 2).

That experience sounds like needlestick safety, and certainly passive and integrated needle safety is an element of it, but the Companion goes well beyond that. The protection element encompasses needlestick safety of course. Reuse prevention, so that needles cannot be shared across users, is also important. But that element of protecting the patient also goes to the integrity of the drug as well. For example, our devices don't use glue to attach the needles. Removing glue from the system removes the risk of unwanted interaction with the drug product. It also enables flexibility in silicone minimising techniques. We also have options that remove any contact with stainless steel or with tungsten.

Beyond protection, with the Companion users have a familiar-looking syringe in their hand. It doesn't look disrupted by the technology because all of the technology is integrated into the syringes. That consistent experience across the product line provides an enhanced user experience that extends further than injection safety into ease of use with the goal of enhancing patient compliance.

> "The goal has to be that proper use of the device occurs on the first untrained attempt. We talk about ensuring the proper use by design. It's a high standard but it is the standard."

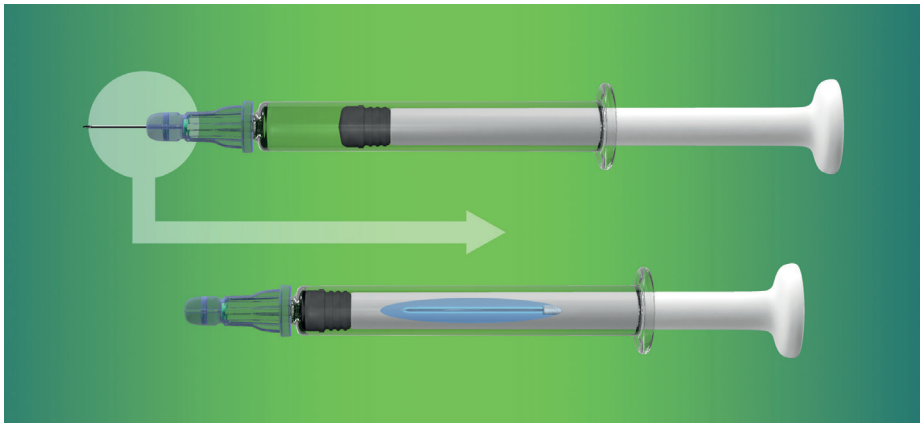

Figure 2: After the user performs an injection, they hear and feel a click when the dose is fully delivered, and then the needle is retracted back into the plunger rod and the barrel of the syringe.

Protecting the caregiver and patient, protecting the integrity of the drug and improving compliance are a big part of what we do. And this is all wrapped up into the Innovation part of Innovation Without Change.

So, turning to the Without Change part of Innovation Without Change; this is about product design and business model as I mentioned earlier. Using existing primary package components, existing syringe barrels, stoppers and other closure components, from trusted suppliers to the industry, preserves the prior work that the drug companies have done in validating their products and primary packaging components. It preserves their sourcing strategy. It preserves their processes and filling procedures. Because we've designed the product line in a certain way, and because our business model is one of assimilation into the supply chain as opposed to disruption to the supply chain, it allows our pharma partners minimised disruption to, and preservation of, their existing processes.

We have a grand vision to set a new standard for syringe-based drug delivery that includes, but goes well beyond, needlestick prevention.

Q When pharma manufacturers are presented with the concept of Innovation Without Change, how do they react?

A It's a really good question. Naturally, we talk to a lot of people – inside and outside the industry. Those outside the industry often ask why "without change"? Don't you want to change things? Don't you want to disrupt with this technology. And of course we do in that sense. Disruptive technology is wonderful. But if you cannot implement that technology then it is just left on the shelf. So people within the industry truly appreciate the idea of minimising disruption to existing processes.

Another thing that really hits home is that different companies have different drivers that lead them to our platform. For some it's needlestick safety legislation and reuse prevention guidance from the WHO. For others it's more of a classic marketing driver – it's the ability to differentiate their drug-device combination products using a device, to earn loyalty from their users and to promote compliance.

We're working with the syringe manufacturers so that, for example, with our staked Companion, the drug companies will receive sterile syringes with the needle mounted, just like they do today, in three-inch tubs, just like they do today. We're also working with some of the leading contract manufacturers and that provides a further risk reduction for pharma. Why

rebuild a manufacturing footprint when there are experts who can do the manufacturing? They produce the Companion products under our design controls and under our lot release but they are perfectly suited to build our products because while the design is innovative, the manufacture is pretty straightforward. So the ability to readily outsource production of the Companion to contract manufacturers is another risk reduction for pharma, because they can trust the supply chain.

Overall, when we explain the concept of Innovation Without Change it really does resonate with people in the industry.

Q The parenteral delivery devices field is both growing and changing very rapidly. Things are moving forward apace. Can you talk about how demands from the market, first specifically the market in terms of the industry and regulators, are changing and how those changing demands are driving the development of Credence's Companion products?

A We try hard to make sure the market is guiding our product development. Let me make a couple of points on this. First, as the molecules coming through pharma pipelines become more complicated it has a trickle down all the way through to the delivery device and the manufacturing of the delivery device. Take molecules that are sensitive to glue, or to tungsten, or aggregate when in contact with too much silicone oil. We touched on how we address that – we remove glue from the system and there are benefits there.

Another consequence of these complex molecules coming through development is that many of them either cannot be formulated to be stable in a ready-to-inject solution over the shelf-life of the product or, if they can, it is very time consuming and costly to achieve. This gives rise to the need for point-of-care reconstitution, of a lyophilised/freeze-dried drug powder with a diluent. You've got to have an easy-to-use device to enable these products to be administered at the correct dose, without contamination, without exposure to needles. So we've put a lot of work and made a lot of progress with a dual chamber reconstitution system that is removing user steps. You don't have to twist and turn and purge an air bubble. The user picks it up, pushes on the thumb-pad, the drug is mixed, they perform the injection, and the needle retracts (Figure 3). We have a version where there is no needle, so it's suitable for IV administration.

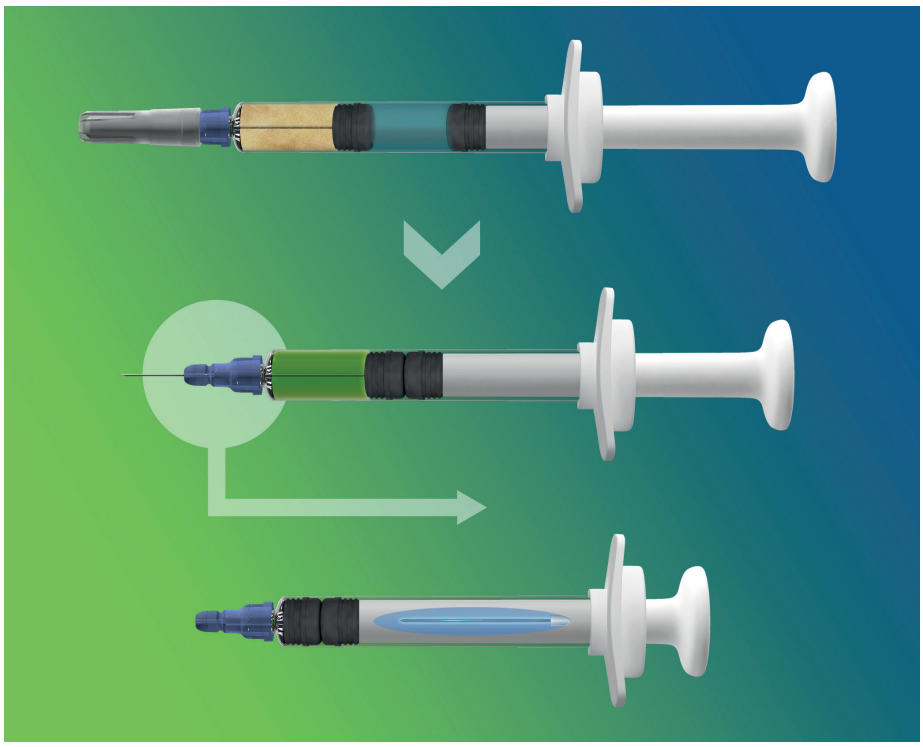

Figure 3: Steps of the Companion dual chamber device for reconstituting lyophilised products.

Because we have simplified, and simplified and simplified, we're getting to a point where this dual chamber system can be housed in an autoinjector. So we're reaching a stage where the user experience of injecting a lyophilised product is largely the same as injecting a stable solution. The implications of this are tremendous. The reliability of delivering a fixed dose by a trained professional or a self-injector is there. Now pharma can say "well maybe we don't have to get this stable in liquid formulation before we go to market and deliver a therapeutic benefit to the patient and gain market share. Maybe we can go to market sooner with a viable product, and spend fewer development dollars." As we look at the transfer of healthcare from a formal setting to the home, this becomes even more important. So our dual chamber system is an area of intense focus for us, and it has achieved really fantastic traction and made substantial progress. You can't just have a "cool device" – you need a device and robust process that go together. We have formed some really valuable partnerships with contract fillers and lyophilisers and this is helping us bring a complete solution to the market. Again, it goes back to assimilating with the existing supply chain, and using the expertise that already exists out there. Innovation Without Change is not just some marketing line. It really runs deep and informs everything we do.

"Because we have simplified, and simplified and simplified we're getting to a point where this dual chamber system can be housed in an autoinjector. So we're reaching a stage where the user experience of injecting a lyophilised product is largely the same as injecting a stable solution."

Let me tell you about another thing we've been working hard on. Compliance is a major problem. It's very much in the news and we are talking about a problem of the order of economic magnitude of US$300 billion in the US, twice that globally. It's a cascading effect. The patient doesn't take their drug according to the prescription regimen, they get sick and end up having to go into a clinic, a hospital or emergency room, which is expensive, to recover from what was a wholly preventable situation.

So we have been working hard on developing a smart syringe. A lot of people are working on connected health but we feel we have a pathway to a product that works in the economic range that makes a connected single-use prefilled syringe possible. So we're working on a device that collects the right data, improves compliance, but is also addressing the economic challenges out there.

Our location in Silicon Valley is a factor. We're in the middle of everything going on here and we are bringing a Silicon Valley approach to the pharma industry. It is this approach that has allowed us to do things that others have not thought of despite the fact they've been in the market for decades.

As I said, we let the market guide our development. We work hard to stay focused on advancing our products – in particular our staked Companion and other Companion products – but we also continue to build a platform with the breadth required to respond to market needs.

Q Continuing on the theme of the rapidly evolving market, but this time the market in terms of the end-users – patients and healthcare professionals – again how is the development of Credence Companion products responding to and being driven by these changing demands?

A All of us involved in developing delivery devices have multiple masters. There is of course the primary customer – the pharmaceutical company. There are the regulators. But it is all ultimately guided by the user.

We perform extensive user studies, our customers perform extensive user studies. First users guide development, then they verify that we're going in the right direction and then they also inform our lifecycle strategies. So it is about the user, always.

A critical point that we've digested is that we cannot rely on training. Training is important and there are companies out there that do a great job on training tools, such as Noble. Training is critical but you cannot rely on the user being trained the way you envision them to be trained. The goal has to be that proper use of the device occurs on the first untrained attempt. We talk about ensuring the proper use by design. It's a high standard but it is the standard.

How are we achieving this? There are fundamental, technical things we've worked on such as the force profile of the injection. We've made amazing headway in smoothing out the force profile and reducing the force of activation when the needle retracts. We've reduced that peak force by almost 50% in the last few months and that is a real feather in the cap of our design team.

Additionally, we realise that we have a small device – the Companion looks like a normal syringe and therefore doesn't have much surface area for on-device guidance, but there are other things you can do. We've made a version of the Companion where the plunger rod is transparent so you see the inner workings of the plunger rod that house a portion of the retraction mechanism. This cues the use that there is something else going on. Then we've coloured certain components. Green means "go" so we have a pre- and post-injection guidance depending on the different positions of a green component before and after injection. We've also incorporated clicks. These approaches combine to motivate proper use the first time the device is used, and then reinforce it on the second and third use, and so on. I would say that if we're thinking about what the greatest user input has been, the most significant user impact on the device design in the past 12 months or so, then it has been on this topic.

Q What is the latest news from Credence? What have you been up to and, in particular, what are the latest insights from Credence's interaction with users? How do they like the Companion products?

A So I've touched on the dual chamber syringe for reconstitution, and its progress towards a size where it can be incorporated within an autoinjector. And I've also mentioned the work on a smart, connected Companion. But there's a lot more!

I wish I could share some of the user studies that our customers have performed but, of course, that is confidential. What I can say is that we hear consistently an overwhelming user preference for our technology over both existing solutions out there in the market today as well as solutions in development. That is something we are very proud of and has helped lead to the traction we have with our pharma customers.

What is driving this positive response from users? Well certainly the passive safety and the "cool" and "wow" factor of the needle retracting at the end of the injection. But equally it's the end-of-dose cues, it's the familiarity of using a device that looks like a "normal" syringe and is comfortable. The use steps are the same as the steps users have used in the past.

"We have been working hard on developing a smart syringe. A lot of people are working on connected health but we feel we have a pathway to a product that works in the economic range that makes a connected single-use prefilled syringe possible."

Also, the consistent experience across the platform comes up as a positive. There are different drugs, different routes of administration, different requirements, different user populations. Getting this consistent user experience allows the drug companies to have and provide that to their users. Familiarity.

You also asked what we have been up to. So, after a lot of hard work over a long period, we are on the verge of having great news to report regarding a major deal with a top pharma company. It's very slightly premature right now to talk about it in detail. But it's a great accomplishment for the company. We're very excited. It's a point of inflection for the business where we will move to the next stage. While we've had many collaborations at various stages, this is the first one that really moves us on to the next level.

Q As 2018 starts to really get underway and gather momentum, what does Credence have planned for the year ahead in terms of milestones for the company and Companion product development?

A We constantly preach to ourselves that we have to maintain depth and focus, but also we have to be broad enough. By this I mean that, for example, you cannot develop a syringe that only works for a product demonstration, or works when you're making a thousand units per month. It's got to work when you're making a hundred million units or more per year. That depth of design, that prerequisite, is a very important priority. This ties-in with the news about a partnership that

> "The news is, we are scaling. We are going from making products on a pilot manufacturing line and moving toward commercial industrialisation of our Companion syringe product. For the business, it becomes a jumping-off point, an inflection point, to build that capability. That is our focus for 2018, by a mile!"

I just mentioned. The news is, we are scaling. We are going from making products on a pilot manufacturing line and moving toward commercial industrialisation of our Companion syringe product. For the business, it becomes a jumping-off point, a point of inflection, to build that capability. That is our focus for 2018, by a mile!

Fortunately from day one we have been designing a product that is able to be scaled, both in terms of reliability at full-scale manufacturing volumes, and in terms of the economic considerations and challenges in the market. From the outset we've been eliminating components, reducing parts and fine-tuning so that we have a manufacturable product at high volumes at a cost point that meets the pricing needs of the market and still returns to the company a profit margin that the company and our investors need to see. This is going to be a busy year but a very fulfilling year. We're ready for it!

ABOUT THE COMPANY

Credence MedSystems is an innovator in injectable drug delivery devices, offering its pharma partners a simplified path to commercialisation of best-in-class delivery systems. The Companion Safety Syringe System was born from Credence's philosophy of Innovation Without Change, allowing customers to impress and protect end-users while preserving it's existing processes, sourcing strategies and preferred primary package components. The Companion is available in luer needle, staked needle and dual chamber reconstitution configurations. Across the platform, the user performs the injection, receives end-of-dose cues and then the needle automatically retracts into the syringe, preventing reuse.

CREDENCE MEDSYSTEMS

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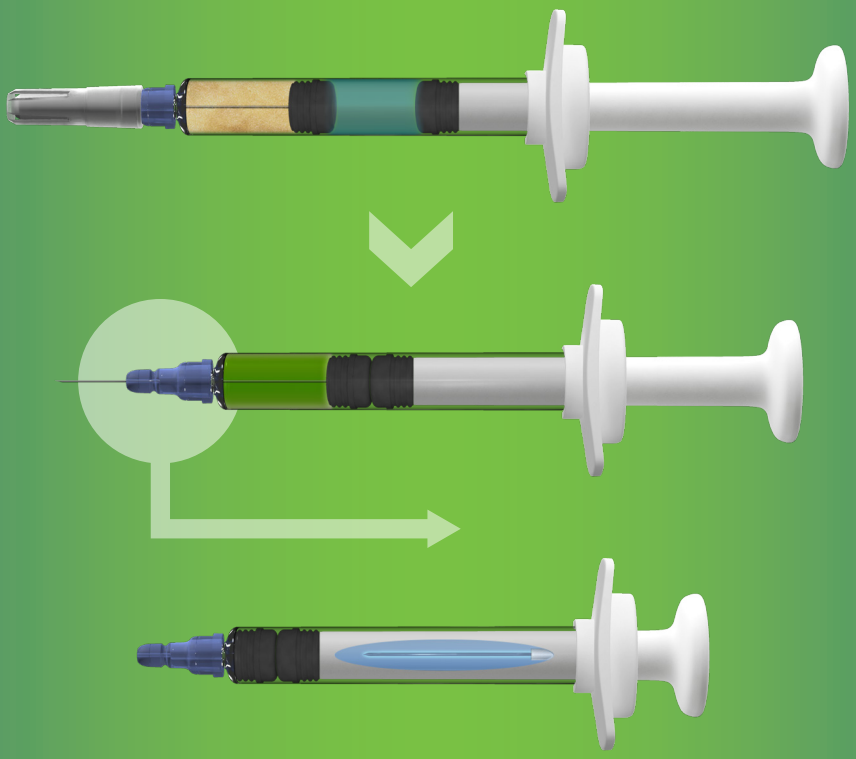
THE CREDENCE COMPANION

IMPRESS | PRESERVE | PROTECT

DUAL CHAMBER



IMPRESS

ENHANCED user experience
FAMILIAR syringe techniques
CONSISTENT platform-wide experience
CLEAR end-of-dose and safety cues

INNOVATION WITHOUT CHANGE

Credence MedSystems, Inc. - +1-844-263-3797 - www.CredenceMed.com
This product has not yet been evaluated by FDA

CREDENCE MEDSYSTEMS

GERRESHEIMER

PREFILLABLE SYRINGE DEVELOPMENTS TO MEET BIOTECH DRUG NEEDS

Claudia Petersen, Global Director Business Development at Gerresheimer MDS, looks at the technological advances being made to ensure prefillable syringes are compatible with protein-based, biotech-derived drugs. She reviews the various options available to tackle the three main syringe components – glue residuals, tungsten residuals and silicon oil particles – as well as outlining advances in safety.

The global biopharmaceuticals market accounted for US$160 billion (£116 billion) in 2014, and it is expected to grow with a $CAGR_{2015–2020}$ of 9.6%, outpacing the overall global pharmaceutical market growth. Many biotech-derived drugs have to be administered by injection using vials, cartridges or prefillable syringes as primary packaging containers. The specific needs of these protein-based drug product formulations pose new challenges to existing primary packaging solutions.

Some of the trends which are affecting the injectable device market are:

- A shift to self-medication to increase patient convenience and save costs, linked to an increasing demand for easy to use delivery devices such as autoinjectors and pump systems.
- Increased regulatory scrutiny and quality requirements for patient safety.
- Increased focus on understanding and anticipating user needs (continuous exploration of the patient experience, patient adherence/compliance).

In addition to this, there are some trends which are affecting biopharmaceutical manufacturing specifically:

- Increased flexibility is being requested from suppliers.
- More biological product applications are being made, but often for small indications which results in smaller batch sizes with high – and specific – quality demands. This is supported by the growing market for biosimilars/biogenerics.
- As a result, more automation, monitoring and process control during production means higher quality packaging materials are needed.

> "More biological product applications are being made, but often for small indications which results in smaller batch sizes with high – and specific – quality demands."

For syringes, these trends can be grouped into four different areas which each require different innovative primary packaging solutions as well as continuous production process improvements (Figure 1).

Regarding the biocompatibility of a prefillable syringe system, three main topics have kept the industry busy in recent years.

- Glue residuals
- Tungsten residuals/oxides
- Silicone oil particles.

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Biocompatibility	• Glue residuals • Tungsten oxides • Silicone oil partides	▮ Clearject™ Plastic Prefilable Syringes ▮ Metal free cone bore forming ▮ Low tungsten process ▮ Baked on RTF® siliconization
End user safety	• Screw cap closures • Needle stick prevention • Breakage resistance	▮ Gx TELC® ▮ Gx InnoSafe® (safety syringe) ▮ Modern glass forming technology
Device compatibility	• Specific dimensional requirements for device applications like auto injectors	▮ Modern glass forming technology ▮ State of the art proprietary camera system
Total Cost of Ownership	• Low cosmetic defects • Secure supply chain • Low particle load	▮ State of the art proprietary camera system ▮ No glass-to-glass contact during forming and ready to fill processing ▮ Washing machine after glass forming

Figure 1: Global pharma injectable packaging market trends.

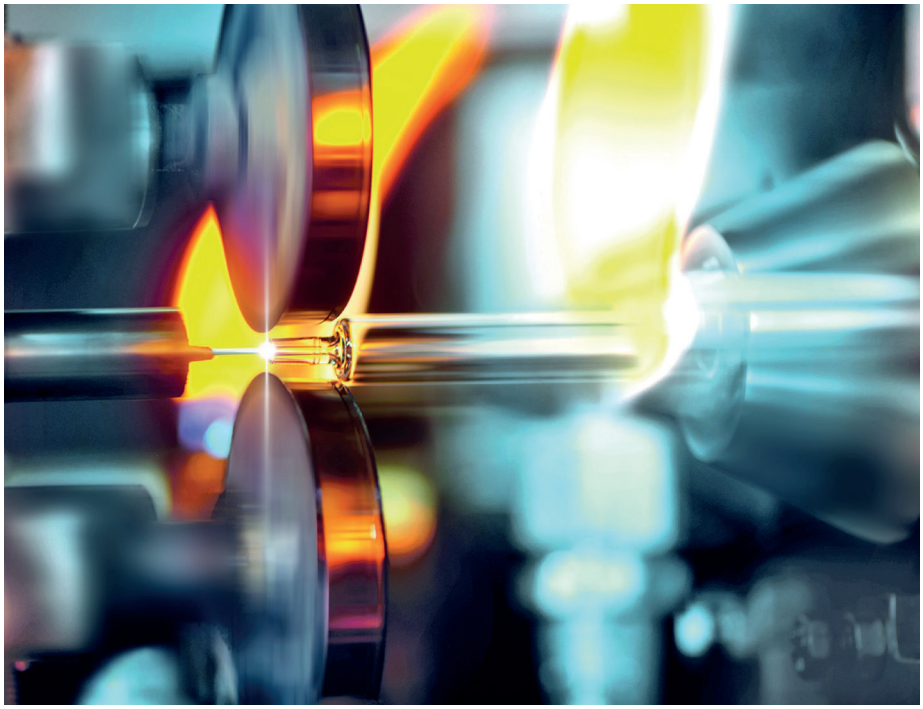


Figure 2: Cone bore forming step.

GLUE RESIDUALS

To fix the metal cannula inside the syringe bore, an organic, UV-activated, methacrylate-based glue is the industry standard. However, glue residuals may l each into the drug product solution and interact with the protein.[1] The level of glue residuals can be controlled by using optimised curing process conditions. After implementation of this process improvement, product specifications with methacrylate in the picogram range per syringe have been realised.

TUNGSTEN

Tungsten pins are used to form the bore in the syringe luer cone (Figure 2). Tungsten is the pin material of choice, offering a range of advantages. It is a heavy metal that melts at 3422°C, with the highest tensile strength at ≥1650°C, and the thermal expansion is very similar to borosilicate glass. These features make tungsten a preferred contact material for the forming of glass syringes. The glass forming temperature of borosilicate glass is around 1200°C.

The downside is that tungsten pins always leave tungsten residuals inside the syringe cone. This can be either tungsten oxides, caused by the high temperatures used for glass forming, or abrasive particles. For many proteins this does not pose a problem, but there have been several reported incidences when tungsten residuals did interact with proteins causing protein aggregation.[2]

As a result, regulatory bodies like the US FDA asked pharmaceutical companies to define tungsten limits for their drug products. In *Guidance for Industry – Immunogenicity Assessment for Therapeutic Protein Products*, the FDA recommends that a dedicated leachables and extractables laboratory assessment for packaging components is performed. Spiking studies are also suggested to assess the risk of tungsten-induced protein agglomeration.

Also the PDA TR No. 73 (Parenteral Drug Association Technical Report) *Prefilled Syringe User Requirements for Biotechnology Applications* recommends performing spiking studies to determine the effect of tungsten.

As the sensivity of different proteins to tungsten residues varies a lot, there is no fixed tungsten limit defined. Also the achievable low tungsten specifications for luer cone and staked-in needle syringes vary drastically due to the size of the pin used to form the bore.

On the syringe manufacturing side, there are several ways to counter this problem:

1. All syringe suppliers offer so-called “low tungsten” syringes. This can be achieved either by improving the glass forming conditions and/or adding an additional

> The future may see further developments for alternative syringe coatings or silicone oil-free solutions, especially as modern syringe production technologies provide continuously higher qualities in terms of cosmetic defects."

washing step after glass forming, thus lowering the tungsten load.
2. Tungsten pins can be substituted with other metal pin materials.
3. Metal-free, glass syringe cone-bore forming can be done using ceramic pins instead of tungsten pins.
4. Injection-moulded, plastic polymer syringes made from cyclic olefins can be used.

Metal-free glass syringe cone-bore forming

The best way to avoid any problems with tungsten residues is to replace the tungsten pin with a non-metal one. This can be achieved using ceramic materials, which require some adjustments in the glass-forming process. We have identified a ceramic material with optimal properties that shows nearly no abrasion and does not leave any new residues behind. This allows us to offer tungsten-free (below the detection limit), "ready-to-fill" (RTF) syringes. In the first step, this process was qualified for luer cone syringes and can be combined with other specialties such as baked-on siliconisation.

SILICONE OIL

As a lubricant, silicone oil is required to enable the plunger stopper to glide inside the syringe barrel. However, silicone oil particles, especially in the sub-visible range, are also known to be able to induce protein aggregation.[3] In addition, silicone particles increase the overall particle load inside a syringe and are difficult to differentiate from protein particles. The overall particle load is of specific importance in the field of ophthalmic applications, with the most stringent particle requirements for parenterals defined by USP 789 "Particulate matter in ophthalmic solutions" and especially with regard to protein formulations. Also sub-visible particulates in the 2–10 µm range should be characterised and quantified.

Baked-on Siliconisation

The so-called baked-on process (Figure 3) enables syringe suppliers to lower the amount of free silicone oil particles significantly by fixating a certain amount of the silicone oil emulsion on the inner walls whilst still maintaining functionality. Figures 4 & 5 show particle measurements derived from a recent study comparing oily (0.5 and 0.8 mg/syringe) and baked-on siliconised syringes. WFI and a Tween 80 0.03% solution were chosen as model liquids. The samples were stoppered (fluoropolymer-coated plunger stoppers) and the number of silicone oil particles was determined according to EP 2.9.19 after one day of storage, three months storage and after three months under stress conditions to simulate a transport situation. Results shown are for the "after three month under stress" conditions.

It is obvious that baked-on siliconised syringes (BoS) syringes show much lower particle loads compared to oily siliconised syringes in both cases for all particle classes examined.

For RTF syringes, baked-on siliconisation is an off-line process using a specific oven. The amount of free silicone oil inside a 1 mL long baked-on siliconised syringe is no higher than 0.1 mg. Also in this case, fixed and diving nozzles are used for siliconisation to ensure an even silicone oil distribution in larger syringes which enables Gerresheimer to specify USP 789 compliance if necessary.

When selecting the appropriate syringe it should be remembered that plunger stopper siliconisation contributes heavily to the overall silicone oil particle load. It is therefore recommended to choose silicone oil-free or crosslinked, siliconised, fluoropolymer-coated plunger stoppers, offered by several suppliers.

Gx® RTF baked-on needle syringe

Baked-on siliconisation has only been

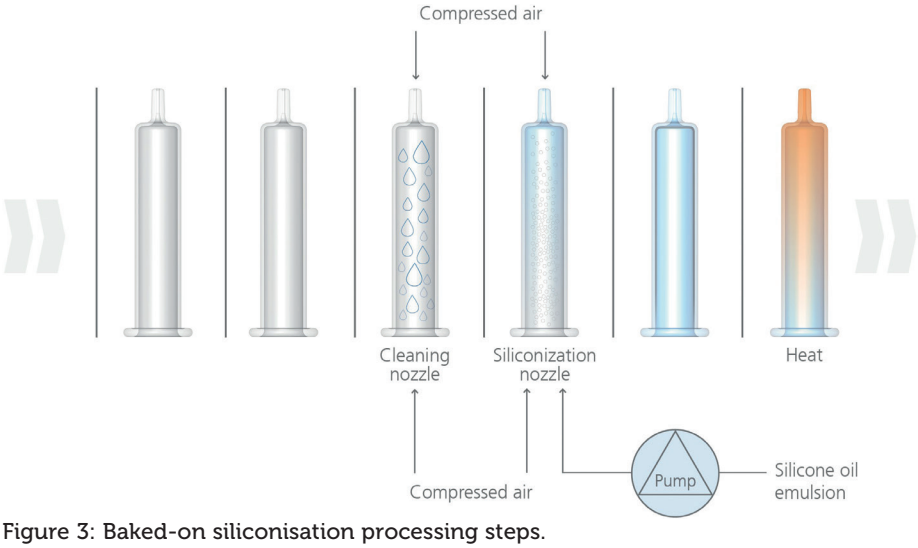
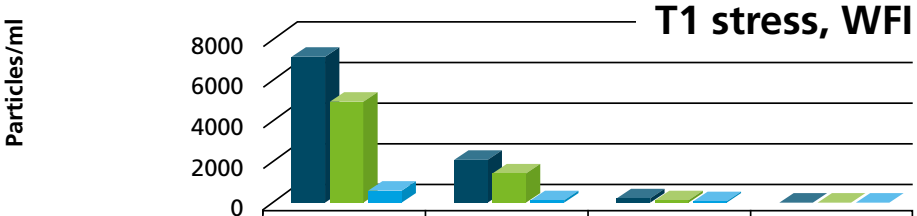
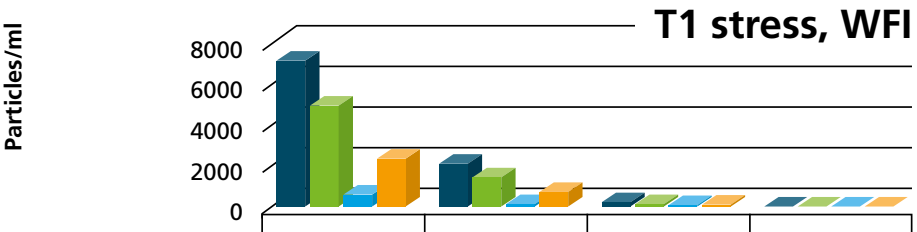


Figure 3: Baked-on siliconisation processing steps.



	≥2 µm	≥5 µm	≥10 µm up to 25 µm	≥25 µm up to >50 µm
WFI 0.8 mg	7153	2040	185,6	2,4
WFI 0.5 mg	4906	1334	123,0	1,4
WFI BOS	585	105	6,5	0,2

Figure 4: Sub visible silicone oil particles ≥ 2 µm WFI solution.



	≥2 µm	≥5 µm	≥10 µm up to 25 µm	≥25 µm up to >50 µm
WFI 0.8 mg	7153	2040	185,6	2,4
WFI 0.5 mg	4906	1334	123,0	1,4
WFI BOS	585	105	6,5	0,2
WFI CJ	2344	713	85,4	3,2

Figure 5: Sub-visible silicone oil particles ≥ 2 µm Tween 80 0, 03% solution.

applicable to luer cone syringes, as the high temperatures during the baking process negatively impact the organic glue used for the fixation of the cannulas inside the syringe cone. Using an additional process step, which involves atmospheric plasma to remove potential silicone oil residuals from the inside of the syringe bore and provides a defined surface for the subsequent cannula gluing process (Figure 6).

Using low temperature plasma flame at atmospheric pressure inside the syringe bore converts any residual silicone into nearly carbon-less layers. This conversion is accompanied by a 50% layer thickness reduction and requires no aggressive or contaminant primers. The already siliconised inside barrel of the syringe is shielded to avoid any impact of the plasma on the surface.

Baked-on, siliconised, staked-in needle syringes are therefore the optimum choice for sensitive protein therapeutics.

END USER SAFETY – GX INNOSAFE

Next to biocompatibility, end user safety is also a major trend. The use of staked-in needle syringes is very convenient/user friendly but always bears the risk that healthcare workers may stick themselves after injection and thereby infect themselves. To avoid this, a needlestick safety and prevention act was put in place in the US in 2000, which was followed by similar regulations in Europe in 2013. Since 2000 all staked-in needle syringes sold in the US have to be equipped with a needlestick prevention feature. So far most of these safety devices have to be assembled on the filled syringe during secondary

Figure 6: Luer cone bore plasma cleaning for baked on staked in needle syringe.

packaging operations.

Recently, to tackle this problem, a safety syringe called the Gx® InnoSafe was launched. In this second generation safety syringe, the safety feature is an integral part of the RTF syringe and looks similar to a rigid needle shield. Syringes are supplied sterile using standard RTF packaging (nest & tubs). The safety system is very intuitive and fully passive, meaning it does not require any activation step by the end user. For the pharma company, it has the advantage that no additional assembly step after filling is required. The slim design also allows the use of a small blister and thereby more cost-efficient secondary packaging and storage (Figure 7).

PLASTIC PREFILLABLE SYRINGES

Glass as a primary packaging material has many advantages, like gas tightness, transparency and high chemical inertness. For the production of glass prefillable syringes only borosilicate glass Type 1 is used (either 51 or 33 extension). Nevertheless there are also some drawbacks, especially with regard to breakage. Sensitive areas for breakage are the finger flange and cone area.

Plastic prefillable needle syringes made from cyclic olefins have now been available for a few years (Figure 8, next page). They are break-resistant, have the same transparency as glass and allow for a much higher grade of customisation. Furthermore, no glue is used to fix the cannula inside the syringe bore and no tungsten pin is required for forming, causing tungsten residuals. ClearJect with needle syringes (Figure 9, next page) are siliconised using highly viscous DC MD 12500 silicone oil to reduce specifically the amount of sub-visible particles compared to conventional oily siliconisation. The syringes are supplied with standard rigid needle shields, plunger stoppers, back stops and plunger rods.

Also in this case the appropriate plunger stopper selection is important regarding the final total silicone particle load. Figure 10 shows results from the same particle study as Figures 4 & 5 extended by ClearJect with needle syringes (CJ). The silicone oil amount per syringe was 0.8mg. A significant reduction compared to glass syringes can be observed, especially for particles below 10 µm. This provides another reason to recommend the use of these syringes for silicone oil particle-sensitive protein therapeutics.

CONCLUSION

Considering the complexity of modern biopharmaceutics there is no "one-size-fits-all" solution for all protein formulations. The container closure system has become a decisive factor for sustained market success, with autoinjectors and injection pumps being

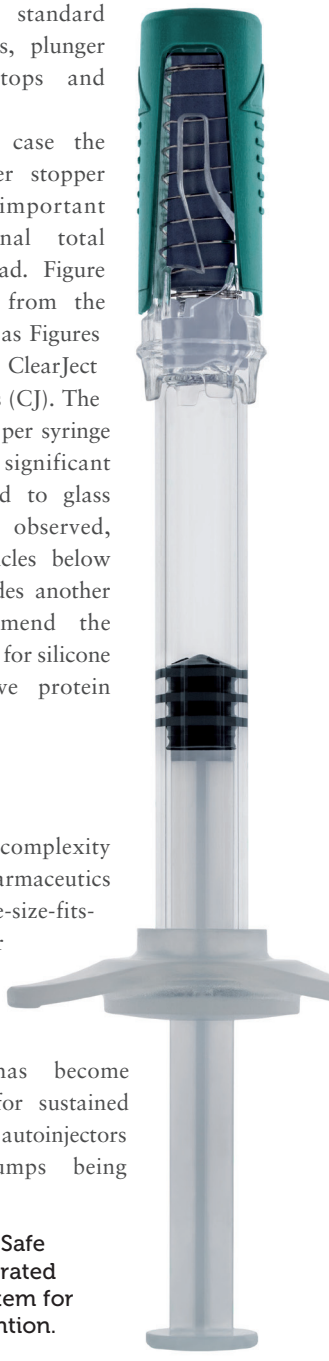


Figure 7: Gx® InnoSafe syringe with integrated passive safety system for needlestick prevention.

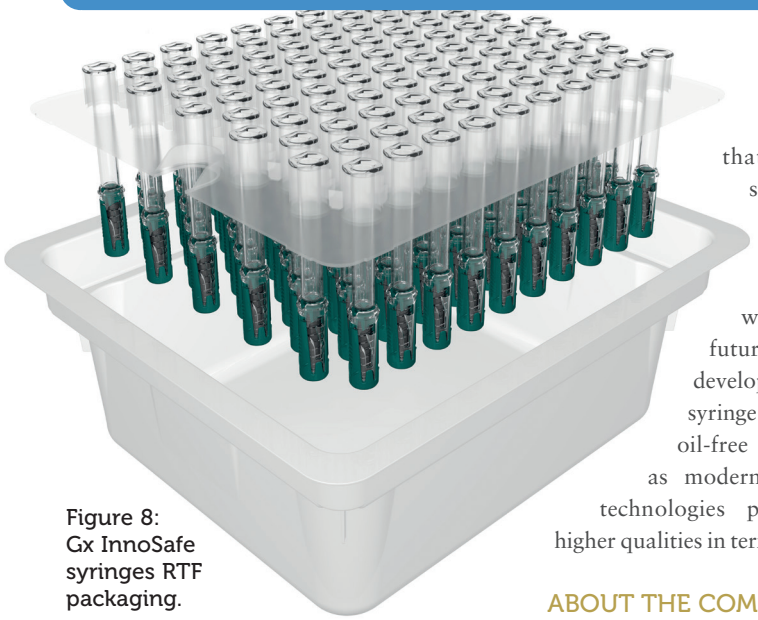


Figure 8: Gx InnoSafe syringes RTF packaging.

growing areas of interest. This demands an even earlier involvement of packaging specialists in the drug product development process to avoid development risks.

It is recommended that the packaging supplier should be consulted early on in the development process to determine what is feasible. The future may see further developments for alternative syringe coatings or silicone oil-free solutions, especially as modern syringe production technologies provide continuously higher qualities in terms of cosmetic defects.

ABOUT THE COMPANY

Gerresheimer is a leading global partner to the pharma and healthcare industry. With its specialty glass and plastic products, the company aims to contribute to health and wellbeing. Gerresheimer operates worldwide and its approximately 10,000 employees manufacture products in local markets, close to its customers. With plants in Europe, North America, South America and Asia, Gerresheimer generates revenues of around €1.4 billion (£1.2 billion). The comprehensive product portfolio includes pharmaceutical packaging and products for the safe, simple administration of medicines: insulin pens, inhalers, prefillable syringes, injection vials, ampoules, bottles and containers for liquid and solid medicines with closure and safety systems, as well as packaging for the cosmetics industry.

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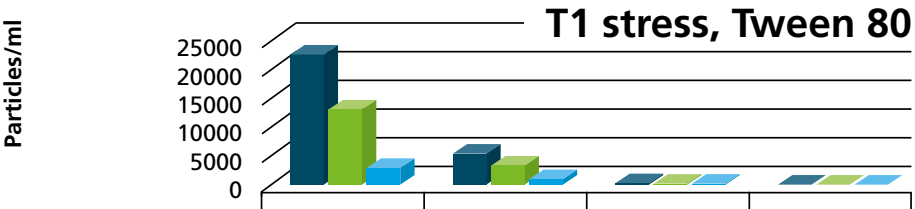
Figure 9: Gx RTF ClearJect with needle syringe using common syringe accessories.



	≥2 µm	≥5 µm	≥10 µm up to 25 µm	≥25 µm up to >50 µm
Tween 0.8 mg	22089	5287	412,5	7,7
Tween 0.5 mg	12839	3327	318,1	4,6
Tween BOS	3023	1061	165,5	1,1

Figure 10: Sub-visible particle load ClearJect with needle syringes.

ABOUT THE AUTHOR

Claudia Petersen studied bioprocess engineering at the Technical University of Berlin from from 1990 to 1996. In 1998, after two years' post-graduate work in the field of oncology research she joined Life Sciences Meissner & Wurst, where she became a lead validation engineer mainly on projects for biopharma customers. From 2000 to 2007 Mrs Petersen held different positions at West Pharmaceutical Services' European Technical Support and Marketing department, becoming Senior Manager Biotechnology, before starting as Director Business Development for the Tubular Glass Division at Gerresheimer. Since Dec 2014, she is the Global Director Business Development for the Gerresheimer Medical Systems unit.

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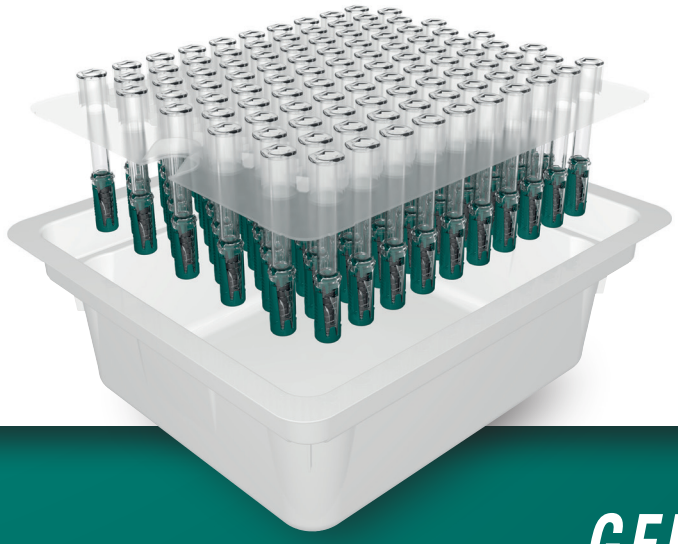

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DEVELOPMENT OF PLATFORM INJECTION DEVICES – ADDRESSING HUMAN FACTORS AT AN EARLY STAGE FOR DIFFERENT USER GROUPS

In this article Orfeo Niedermann, Business Development Director, and Jakob Lange, PhD, Account Director, both of Ypsomed Delivery Systems, provide insights into the development of platform products that offer pharma companies low risks and shorter timelines at an attractive cost. The authors then describe how Ypsomed addresses the issue of human factors engineering testing with broad user populations for platform products, using the examples of the YpsoMate autoinjector and UnoPen pen injector platform products.

With the large number of new biologic and biosimilar products launching, the demand for subcutaneous self-injection devices for biopharmaceuticals continues to grow and develop. These devices, including autoinjectors, pen injectors and new large volume patch injectors, are designed for ease of use and improved patient adherence. Timeline and cost pressures are driving both big and small pharmaceutical and biotech companies to source these state of the art devices quickly, and at low risk, for both clinical trials and commercial launch. This has boosted the demand for platform products that can be easily customised to both drug- and marketing-specific requirements, whilst having been thoroughly tested and documented beforehand to minimise project risks and shorten time to market.

PLATFORM PRODUCTS: LOW RISK AND SHORT TIME TO MARKET

Ypsomed has built up a comprehensive offering of platform products that meet key customer needs and are specifically designed to be modified into customer-specific products. The platform products enable flexible customisation, while minimising project risks and shortening time to market. With this approach, described in Figure 1,

> "Driven by patient needs, market intelligence and new technology, the development of novel platform products also requires significant investments in manufacturing capacity."

Ypsomed decouples the development of new platform products from the customer project, thereby moving the risks associated with platform development and installation of manufacturing infrastructure in-house. Each customer commercial product is derived from an existing platform product that is based on proven technology.

Driven by patient needs, market intelligence and new technology, the development of novel platform products also requires significant investments in manufacturing capacity. Ypsomed supports its partners not only by customising its injection systems to market demands, dosing needs and the primary container, but also by increasing its installed manufacturing infrastructure to match customer capacity

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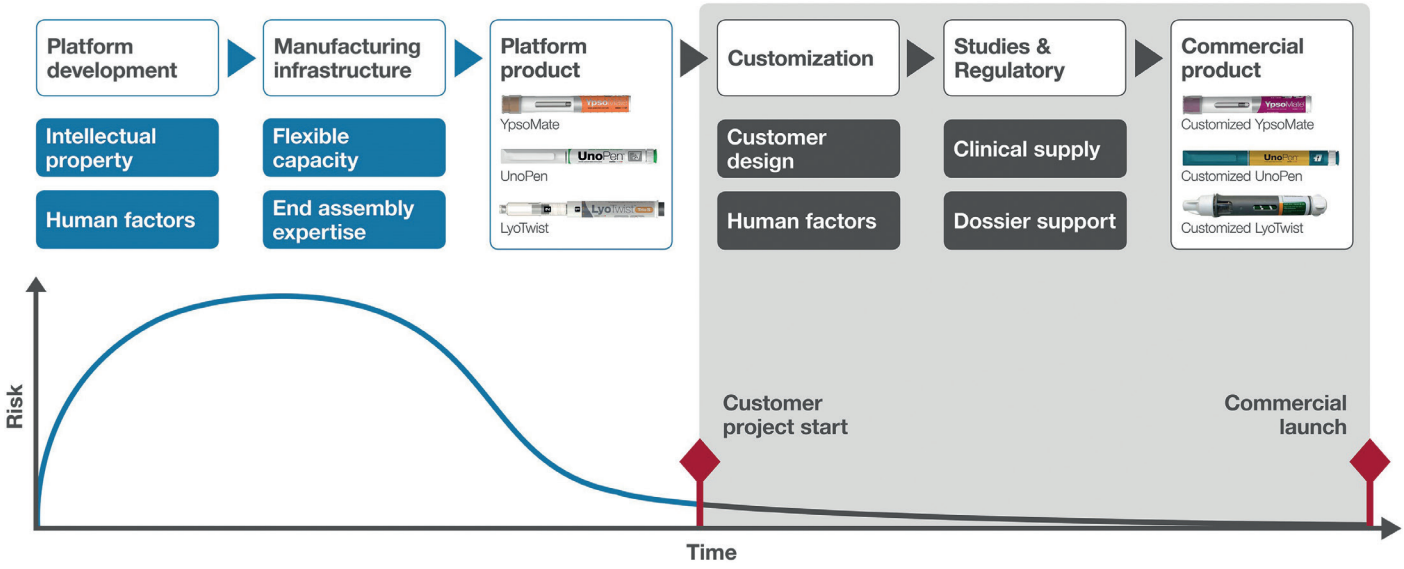


Figure 1: Ypsomed's platform-based product strategy lowers risk and shortens timelines during customer projects.

requirements. Today, Ypsomed offers one of the broadest ranges of self-injection platforms and supports its customers in selecting the ideal device for their specific application.

PERFORMING USABILITY STUDIES WITH PLATFORM PRODUCTS

Successful development of safe and reliable medical devices requires the application of usability evaluation throughout the design cycle, and documented usability testing is an important part of the information required by regulatory authorities in order to grant marketing authorisation. Usability evaluation during device development is typically divided into three parts:

- **Early formative testing:** Conducted in the early development stages to collect feedback from users at various stages of the design process in order to iteratively refine the design, the packaging and its instructions for use (IFU).
- **Late stage formative testing:** Carried out to gain certainty that the device is suitable, and therefore likely to successfully pass design validation.
- **Summative testing:** Performed at the end of development in order to provide objective evidence that the intended use has been met and that the device can be safely and reliably used by the intended patient population.

With the move from development of customer- and indication-specific devices to device platform products used across a wide range of therapies and indications, a new approach to formative usability work, involving user groups with a broad range of user requirements, is necessitated. This raises the question of how to set up a usability engineering programme in line with regulator expectations, without a known specific user population. Ypsomed adopts a two-tiered approach:

- First, the platform device undergoes formative testing with a broad user population, recruited to reflect more general user backgrounds and abilities rather than those of a specific indication.
- Second, the device is customised for a given application and subjected to further formative testing, followed by design validation with the corresponding specific user population.

> "With the move from development of customer- and indication-specific devices to device platform products used across a wide range of therapies and indications, a new approach to formative usability work, involving user groups with a broad range of user requirements, is necessitated."

Figure 2: UnoPen™ and YspoMate® product platforms. Use steps summarised in Box 1.

UNOPEN AND YPSOMATE LATE STAGE FORMATIVE STUDIES

To illustrate Ypsomed's approach to platform usability, two late-stage formative studies of the UnoPen pen injector and the YpsoMate autoinjector platform devices

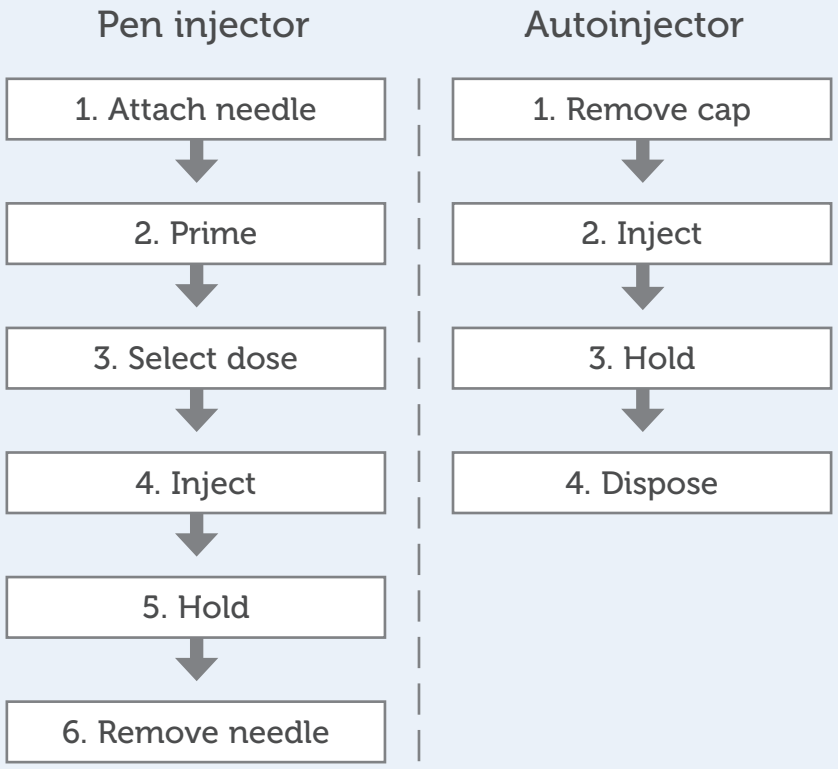
Figure 3: User with impaired dexterity with YpsoMate® autoinjector in formative study.

(Figures 2 and 3) have been performed and published.[1,2] Both studies were conducted with broad user populations, defined to represent user requirements across a range of indications. Specifically, the studies were designed and carried out with the goal of understanding whether the platform device and its IFU were suitable for users in all intended applications, and whether the device would be likely to pass summative usability tests for specific indications.

UnoPen is a disposable, multiple variable dose pen injector holding a 3 mL cartridge. The device is fully manual and similar in design to insulin pen injectors currently on the market. The UnoPen operates according to the principles of "dial-to-dose" and "push-to-inject". It is designed for ease of use, with a geared dosing mechanism to provide reduced injection force and a dose scale with large, easy to read numbering.

YpsoMate is a single dose, single use two-step autoinjector intended for the subcutaneous self-injection of drugs in the context of various treatments requiring relatively infrequent (weekly, bi-weekly or monthly) injections of a single fixed dose. The device contains a 1 mL long prefilled syringe and features automated delivery of the drug into the subcutaneous tissue once triggered by pushing the device onto the skin. The handling steps for each device are summarised in Box 1.

BOX 1: HANDLING STEPS FOR THE UNOPEN™ PEN INJECTOR AND YPSOMATE® AUTOINJECTOR.



Participants and Procedures

As both device platforms are used across different medical indications and patient groups, no specific indication was used to define the user groups to participate in the studies. Rather, relevant user requirements were selected which can reasonably be expected to be found in a wide range of applications. Ideally, any user population for subsequent products would be a subset of the user properties thus defined. Table 1 presents the different defined user groups for the two studies. The different user groups reflect differences in the abilities of potential end users.

For both studies, participants were recruited through market research agencies and scheduled to attend individual sessions. As part of each session, the participants provided personal information, studied the IFU and performed simulated injections into an injection pad. For the pen study, no training was provided and the participants performed a distraction task between the two injections. In the autoinjector study, in addition to the self-study of the IFU, the device was demonstrated to the participants

Definition (abbreviation)	Characteristics
Healthcare professionals (HCP)	Healthy qualified user
Caregivers (CG)	Healthy lay user
Diabetics with retinopathy (DR)	Impaired vision
Diabetics with neuropathy (DN)	Impaired tactile perception
Patients with arthritis (AR)	Impaired dexterity
Adolescents (AD)*	Lay user of 12-18 years of age

Table 1: User groups as defined for the two studies. *Only included in the pen study

> "Both devices could be safely and efficiently used by all user groups, with overall success rates in performing injections above 95%, and high reported degrees of confidence and comfort in using the devices across all user groups."

followed by a distraction task directly after which the two injections were performed. These differences in procedure correspond to the expected use scenarios for the two device types.

In both studies, the outcome was recorded as:

1. Injection success rate.
2. Participant feedback on device handling.
3. Observed deviations from IFU procedure and user errors.

Results and Conclusions

The injection success rates for both devices/studies are summarised in Figure 4, while the self-reported data on confidence and comfort is presented in Figure 5.

Both devices could be safely and efficiently used by all user groups, with overall success rates in performing injections above 95%, and high reported degrees of confidence and comfort in using the devices across all user groups. The number of user errors observed for the pen was in line with previous studies, and higher than for the autoinjector, reflecting the differences in handling complexity between the devices. For the pen, experienced users sticking to their habits rather than not understanding or misinterpreting the IFU was the main reason for user errors. For the autoinjector, virtually all observed use errors concerned the holding time after injection, with users typically making the error of holding for less than the required time.

The observation that both devices could be safely and efficiently used by all tested user groups provides confidence that the device and IFU will pass future summative testing in specific applications, which has since been corroborated by a significant number of customers for both YpsoMate and UnoPen.

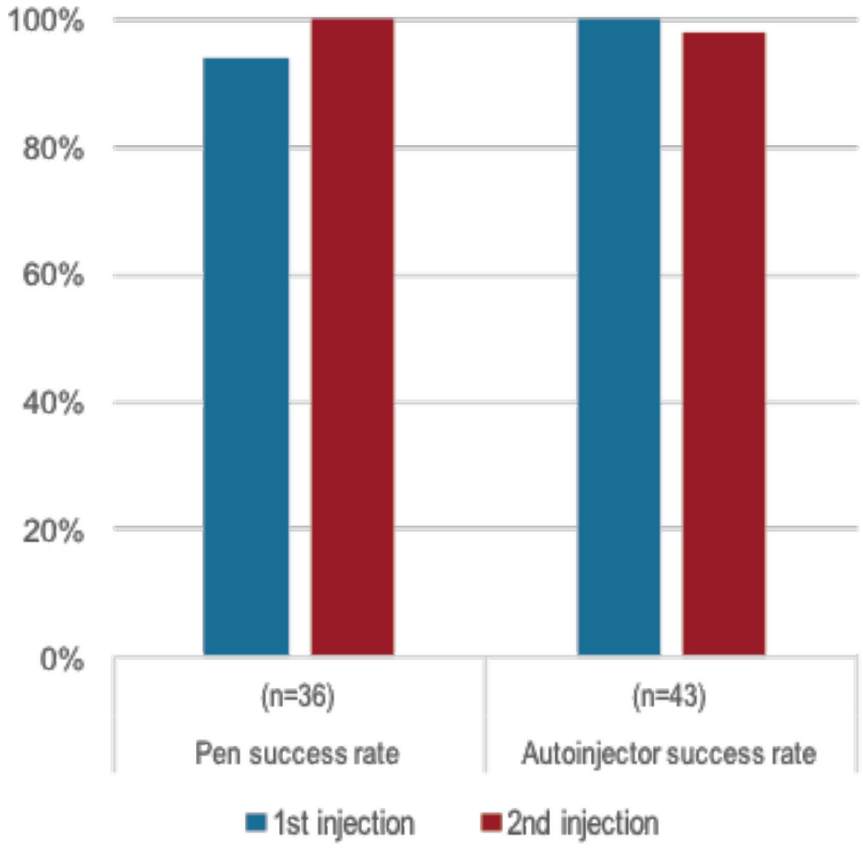


Figure 4: Injection success rates for the two devices from each study.

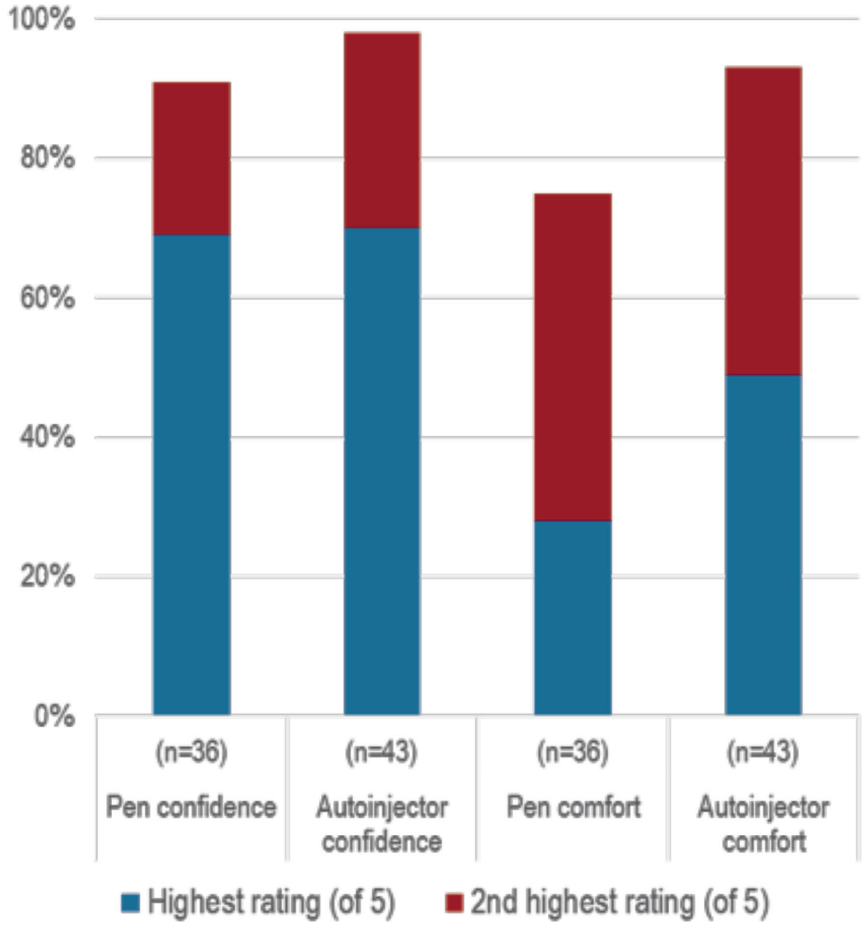


Figure 5: Participant self-reported confidence and comfort in use of the two devices from each study.

REINFORCING THE SUCCESS OF PLATFORM PRODUCTS

The move from long, costly and risky bespoke device development to customisation projects based on established platform products is very well received in the market, providing pharmaceutical and biotech companies with state of the art devices quickly, at low risk for their clinical and market needs. First customer product versions have received approval in regulated markets and initiated commercial marketing.

With Ypsomed's innovative approach to conducting usability work on device platform products, using broad user populations, it becomes possible to build a solid foundation for the usability activities conducted as part of product customisation in customer projects. Although indication-specific summative work will always be required for submission and approval, the basis provided at the platform level reduces the amount of additional work required and significantly de-risks the later stages of the human factors engineering process.

ABOUT THE COMPANY

Ypsomed is the leading independent developer and manufacturer of innovative autoinjector and pen injector systems for self-administration. The customisable platform products cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pens, ready to use prefilled wearable bolus injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on pen needles and infusion sets complement the broad self-injection systems product portfolio.

As a pioneer with more than 30 years of experience in the development and manufacturing of innovative injection and infusion systems, Ypsomed is strategically developing of a range of smart devices and services, supported by unique in-house capabilities in electronics, software and connectivity. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters and processing them to facilitate self-management of diseases.

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 and supply devices for global markets including US, Europe, Japan, China and India.

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ABOUT THE AUTHORS

Orfeo Niedermann is Business Development Director with Ypsomed Delivery Systems. His responsibilities at Ypsomed include business development activities in the US, Europe, Japan and China as well as product strategy for Ypsomed's range of YpsoMate autoinjector devices. He has spoken at numerous international conferences and authored or co-authored a number of articles.

Mr Niedermann studied mechanical engineering at the Swiss Federal Institute of Technology in Zurich, Switzerland (MSc ETH) and management in Bern (MBA BFH). Before joining Ypsomed in 2005, he was in the packaging machinery industry in various positions including engineering, project management, sales and R&D management.

Jakob Lange is an Engineer and Materials Scientist by training, with an MSc in Chemical Engineering from the Royal Institute of Technology in Stockholm, Sweden and a PhD in Polymer Science from the Swiss Federal Institute of Technology in Lausanne, Switzerland. He has written and published more than 30 peer-reviewed papers on medical devices, packaging materials and polymers and is a regular contributor to technical and scientific conferences.

After previous positions with Nestlé in Lausanne, Switzerland and GE Healthcare Biosciences in Uppsala, Sweden, Jakob joined Ypsomed in 2006, where he has held different positions within Marketing and Sales as well as in R&D Project Management. Currently he has the role of Account Director in M&S Delivery Systems, overseeing a team of Product Managers with focus on managing customer relationships in device development projects, as well as for marketed device products.

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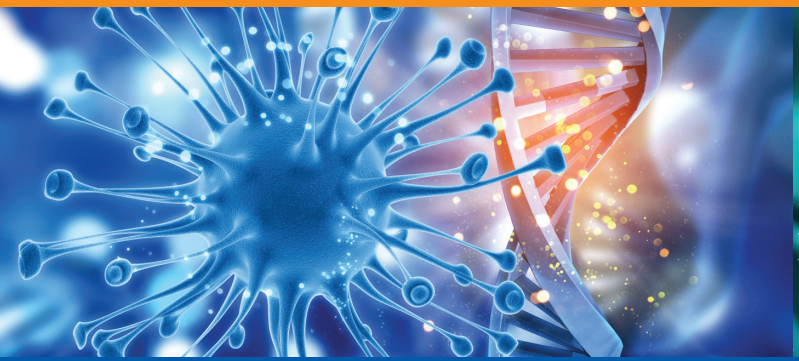

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RECONSTITUTION DEVICES: MIXING, POWER, PACKAGING & REGULATION

In this article, Charlotte Harvey, Consultant Mechanical Engineer, Sagentia, discusses the challenge of reconstituting lyophilised drugs, both from the perspective of the drug itself and the delivery device associated with it.

"An all-in-one reconstitution and injection device which removes responsibility from the user is the ideal."

Reconstitution devices are an ever-growing device category, due to the rise of biologics and the use of lyophilisation (freeze drying) to achieve their long term stability. With the number of lyophilised drugs on the rise, users (increasingly patients or carers in a non-clinical setting) are frequently faced with the burden of manual reconstitution. This raises usability issues around not only convenience, but also safety.

Thankfully, devices such as prefilled dual-chamber syringes are emerging to deal with this issue. However, these, and devices like them, have yet to become commonplace. An all-in-one reconstitution and injection device which removes responsibility from the user is the ideal. Here we will discuss the challenges of designing such a device.

This article will first address the challenges of reconstituting a previously lyophilised drug regardless of the delivery device in which it is to be used, before turning to the device itself – its design, primary packaging, power density and associated regulatory issues. What is not addressed here are the usability challenges that a standard injectable drug delivery device presents, such as pain management, preventing needlestick injury, the number of user steps and injection rates.

"Each lyophilised drug has different properties which will affect how easily it dissolves. Where these properties have been deliberately controlled by the formulation chemist, they are likely to have been optimised for a particular mixing methodology."

THE CHALLENGES OF MIXING

Before we turn to the design of the reconstitution device itself, we must first consider the need to mix the drug safely and effectively. The basic steps of manual reconstitution are described in Box 1. However, each lyophilised drug has different properties which will affect how easily it dissolves. Where these properties have been deliberately controlled by the formulation chemist, they are likely to have been optimised for a particular mixing methodology. The properties requiring consideration are:

- Particle size (smaller particles will present a high surface area and therefore promote dissolution)
- Drug type (larger biomolecules tend to have a higher propensity to denature in certain environments)
- Physiochemistry (e.g. drug polarity; protonated versus free base)
- Formulation additives (additives to prevent caking or aid dissolution for instance)
- Diluent pH or ionic content
- Viscosity of the resultant solution.

These properties create the boundaries which the product design must work within. It is good practice to work closely with the formulation team in order to understand the properties of the drug fully and to build a device which accommodates these characteristics.

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Optimising Dissolution

Dissolution will occur even without any mixing. However, a boundary layer may form between the constituents, consisting of a saturated solution of the powder in the diluent. In order for dissolution to complete, the drug particles must diffuse through this boundary layer, making this a slow process. When we intervene by mixing a solution, we are attempting to break up this boundary layer and prevent the diffusion limit of the drug being the limiting factor in dissolution speed. This can be done either actively or passively.

Active mixers physically move the fluid, producing turbulence to promote mixing; a magnetic stirrer bar or an ultrasonic mixer would fall into this category. Passive mixers fold the solution together as it is passed through static channels. In the case of reconstitution, we typically avoid passive mixing methods, which require two fluids as the constituents.

In the process of mixing and breaking up the boundary layer, we are also physically moving the powder and diluent until they are adjacent, causing new boundary layers to form which are then, in turn, broken up. This physical moving of the drug constituents allows dissolution to occur quickly. To maximise efficiency, the mixing method should act upon the entire volume of the liquid. When a stirrer has not been designed properly, it only moves fluid in its immediate area, rather than promoting mixing throughout. This will most often occur when the solution has a high viscosity.

Introducing Turbulence to the Mixture

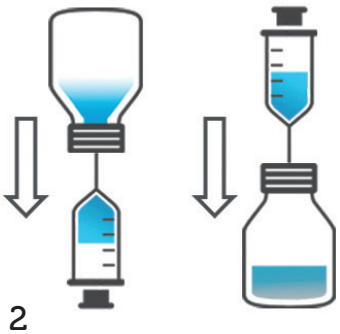
Effective mixing requires turbulent flow, making high viscosity one of the hardest drug characteristics to overcome. At a high enough viscosity, the device may be incapable of holding enough energy to take the fluid flow out of the laminar region. Even if you can provide enough energy to the solution, care must be taken that the energy input is not going to denature the drug by creating a high shear environment. For large biomolecules, this may become a significant concern, and thus mixing must be gentle. It is for this same reason that high temperatures must also be avoided.

Energetic mixing may not just risk denaturing the drug, it is also likely to cause foaming. Foaming is already a concern with manual reconstitution methods, hence users being instructed to swirl the mixture, rather than shaking it. It is also worth noting that

BOX 1: BASIC STEPS OF RECONSTITUTION

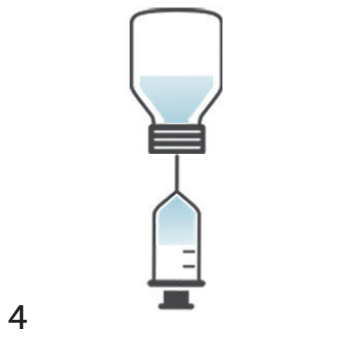
The user starts with a diluent vial, a drug and an empty injection syringe. In this instance, all diluent is to be mixed into a powder.

Diluent is moved from its vial into the powder vial via the syringe, typically using a large-gauge needle. The user should inject air into the diluent vial first to help with emptying. When emptying the vial, it should be held upside down, and moving air to the syringe should be avoided.



The vial containing both powder and diluent is swirled until the constituents are mixed. Gentle movement is used to avoid foaming. The user keeps doing this until no solid particles can be seen, possibly taking several minutes.

The reconstituted drug is withdrawn into the syringe for injection. The needle will need changing to a small gauge prior to injection.



it is much easier to mix a solution when air is present, the addition of air to the mixture further promoting turbulence. However, to avoid foaming and the formation of bubbles, we can attempt to remove the air from the mixing chamber. That may not be effective, however, as air may be released when diluent is introduced to the powder.

By minimising the volume of air, we leave ourselves with two potential mixing methods. The first is a stirrer of undetermined geometry which sits in the solution and manually moves the powder and diluent to mix. The second is ultrasonic mixing, which has the benefit of not touching the drug. As it creates turbulence through micro-cavitation, it might also blast apart any large chunks of lyophilised solid, further increasing the rate of dissolution by increasing the contact surface area.

The core mixing technology which the device is based on must work with the characteristics of the drug at hand. A balance must be struck between the speed of mixing, the energy available and the number of interactions required of the user.

CHOOSING A PRIMARY PACKAGING SOLUTION

When it comes to primary packaging, there is a choice to be made between standard vials, cartridges or syringes and something custom made. Custom solutions, either on the market already or currently in development, include bags (which are easier to fill without a large air volume) and moulded plastic containers (which allow the designer to integrate the drug container into the device's workflow better). In this section we will discuss how to make that choice.

Although custom primary packaging is becoming more prevalent, it is still far more common for commercial concerns to restrict design to the use of off-the-shelf packaging such as vials, cartridges and syringes. These concerns typically relate to the need for the requisite regulatory approval and the time and cost associated with acquiring it. Such expenditure would be particularly wasteful when designing a device for an existing drug.

The Problem with Standard Primary Packaging Solutions

Vials are the standard container for a lyophilised drug, and it is immediately evident that their size and shape is problematic. If we want our device to be capable of performing both reconstitution and injection, fully incorporating a vial will make our hand-held device too large. To get around this, the vial can be attached for reconstitution and then detached prior to injection. Alternatively, reconstitution and filling of the handheld device can be performed via a base station designed to have minimal drug contact. Either solution has the issue of adding further use steps.

Vials can also be problematic due to the large volume of air they contain. The drug will need to be drawn from the vial (probably into a syringe rather than directly into the body) whilst also avoiding removing a large portion of air. The level of concern we have here depends on the injection site (since the majority of user-performed injections are subcutaneous we will not spend much time on air injection in this discussion), but minimising air injection is always a priority. Use of a base station helps here as the orientation of the vial can be controlled, and therefore the volume of air that is removed.

Cartridges and syringes are smaller and more suitably shaped for a handheld device. It's also likely that they will be approved for use with an existing drug. However even these will hold a small amount of air under standard filling processes and this will need to be minimised if the user is going to inject from them directly – it will be difficult to control the orientation of the drug container in this instance. Additionally, accommodating our mixing methods inside these containers can be a challenge due to the shape and size available (long narrow cylinders allow for only a limited range of flow patterns). Note that a physical mixing element must be collapsible if held in the injection chamber and an ultrasonic transducer requires close coupling to the drug container to be effective. Neither solution works perfectly with these standard packaging options.

Custom Solutions

Custom primary packaging allows us to address many of the issues discussed so far. We can create a more desirable size and shape, allowing for efficient mixing within a handheld form factor, and we can minimise the presence of air inside our device, either through the filling process or by removing air after mixing. However, challenges begin to arise when we look to develop our filling process, as it is very hard to deviate from the established norm. Standard filling lines are

"Vials are the standard container for a lyophilised drug, and it is immediately evident that their size and shape is problematic."

a deeply ingrained part of an industry for which there are many barriers to change; in this instance because the change would require a significant investment of time and money.

We therefore have to make sure to include some geometrical constraints on the custom primary packaging. There are several questions that require answering if a custom primary packaging solution is to be manufactured successfully, for example:

- How close can the containers sit together?
- How large is the neck of the container?
- Will the custom packaging be able to withstand lyophilisation temperatures?
- Will elimination of the air in our container require an additional or new assembly step?

Any significant deviations from standard design are going to create requirements standard filling processes aren't used to; for instance, in a dual chamber syringe, a bung must be placed low down in the syringe barrel, whereas a standard filling process would require only a bung to seal the vial neck. It can therefore look tempting to lyophilise in a standard container and then move the powder to a new container. However, this is difficult when controlling for volume (and therefore dose).

User acceptance is likely to be lower when using standard primary packaging, so custom solutions should be sought. If commercial considerations make this impossible, consider moving away from a device which both reconstitutes and injects. Instead, have a base station which reconstitutes and fills a simplified injector. Due to the durability of the base station, we can add any additional functionality and complexity to that. If custom primary packaging is a viable option, we should aim to fit within the boundaries of standard filling processes as much as possible. If there is a need to step outside that, a filling contractor should be engaged early in the process.

POWER DENSITY

The main problem with the manual reconstitution process is the need for the user to go through a number of quite onerous steps. Therefore, so far, we have looked exclusively at fully-powered reconstitution and injection devices with the intention of improving usability.

However, given the number of steps involved in manual reconstitution, it would only require automating a few of these steps to see a significant usability improvement. We could therefore keep the mixing step as a manual process in order to reduce the power requirement of the device, thus reducing the device's power density. Given that, regardless of automation, it is a requirement for the user to be able to check that mixing has occurred effectively. It is not too burdensome for them to be fully involved in that part of the process.

If we do want to remove burden from the user via an automatic mixing procedure, it will be necessary to consider the size of the delivery device due to the power required. As mentioned previously, the properties of the drug itself will define the energy input required for effective mixing, but it could be a substantial amount. The introduction of batteries will also raise additional challenges, such as how they should be charged and disposed of. Large power requirements would most likely mean a larger device, which could become difficult to hold in the hand (once again the use of a base station can solve this problem, but this is not always a viable solution). Battery sizes can be minimised by performing non-mixing functions without electrical power, using springs for actual drug delivery for example.

REGULATORY REQUIREMENTS

Finally, there are regulatory requirements to consider, which will have a bearing on the method chosen for overcoming the technical challenges discussed prior. For instance, the user has to be able to see the quality of the mix, meaning that there must be an optical path through to the drug. Then there are requirements around patient safety, ensuring delivery of the full dose, proving that the mixing method is effective and validating any new materials put into contact with the drug. These requirements around the mixing mechanism may not be familiar to those designing more conventional drug delivery devices and will require necessary analytical testing and human factors studies before incorporation into the device development plan.

ALL-IN-ONE RECONSTITUTION & INJECTION

The reconstitution of lyophilised drugs by a non-medical professional raises a series of challenges around effective mixing and safe administration, whilst also minimising the burden on the user. The product development process must weigh up these various factors and assess the degree of development and manufacturing effort needed to produce something novel. An all-in-one reconstitution and injection device will produce the biggest improvement in patient outcomes for those using them. For this reason, it is an area of the drug industry where we are likely to see significant innovation in the coming years.

ABOUT THE COMPANY

Sagentia is a global science, product and technology development company. Our mission is to help companies maximise the value of their investments in R&D. We partner with clients in the consumer, industrial, medical and oil & gas sectors to help our clients understand the technology and market landscape, decide their future strategy, solve complex science and technology challenges and deliver commercially successful products.

Sagentia employs over 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has 16 European and North American offices, two UK-based dedicated R&D innovation centres and more than 400 employees. Other Science Group companies include OTM Consulting, Oakland Innovation, Leatherhead Food Research and TSG Consulting.

ABOUT THE AUTHOR

Charlotte Harvey is a consultant mechanical engineer at Sagentia Ltd. Her experience lies predominantly in managing medical product developments, specifically those in the surgical and injectable drug delivery fields. Recent projects have included front-end innovation in the drug delivery space, user interviewing for human factors, and several instances of developing reconstitution-based autoinjectors. Charlotte graduated from the University of Cambridge (UK) with a Masters in Mechanical Engineering.

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ADVANCED CATHETER THERAPIES

A NOVEL ENDOVASCULAR DRUG DELIVERY SYSTEM FOR PRECISION TARGETING IN MULTIPLE INDICATIONS

There remain numerous diseases for which effective treatment can only be obtained by trained medical professionals using advanced treatment delivery procedures. Here, Paul Fitzpatrick, Chief Executive Officer, Advanced Catheter Therapies, introduces the Occlusion Perfusion Catheter™, an innovative device that can target high concentrations of drug to precisely defined locations. Clinical trials of the device using long-established drugs are providing promising results, in terms of safety, tolerability and efficacy, even in very difficult to treat and even otherwise untreatable conditions.

In the world of injection devices, it is easy to focus on the novel and ever expanding field of biologics and biosimilars, and the narratives of connectivity and "at home" self-injection. However, many indications require treatments that, whilst neither novel nor unknown, are highly effective yet come with serious side effects or are highly toxic and, as such, must be administered by medical professionals. Such treatments present valuable opportunities for novel device design; there is a clear and present demand for technologies that target these indications, whilst improving upon the efficacy and mitigating the adverse effects of their treatments.

> "The treatment chamber also offers an unprecedented flexibility in drug delivery, opening up the potential for sequential drugs to be delivered, or even mixed *in vivo*, with a single device."

One such area is peripheral arterial disease (PAD). In the US alone, treatment of PAD costs an annual US$21 billion (£15.2 billion) and affects over five million people.[1] PAD requires endovascular treatment, most commonly percutaneous transluminal angioplasty, also called "balloon angioplasty". Recently, the new technology in this space is drug-coated balloons (DCBs). In regular balloon angioplasty, a narrowed artery is widened by a balloon being inflated inside it on the end of a catheter, whereas DCB technology has the balloon coated in an anti-proliferative to help prevent restenosis.

DCBs are not without problems however; toxic anti-proliferative drugs can be washed downstream and fail to penetrate quickly beyond the intima, the innermost layer of the artery. DCB trials have also struggled to produce satisfactory results in below the knee (BTK) arteries. This is of particular note, as critical limb ischemia (CLI), the most severe manifestation of PAD, is strongly associated with atherosclerotic disease of BTK vessels.[1]

Thus, the hypothesis was drawn that a novel catheter could provide the solution to DCB shortcomings by offering a device

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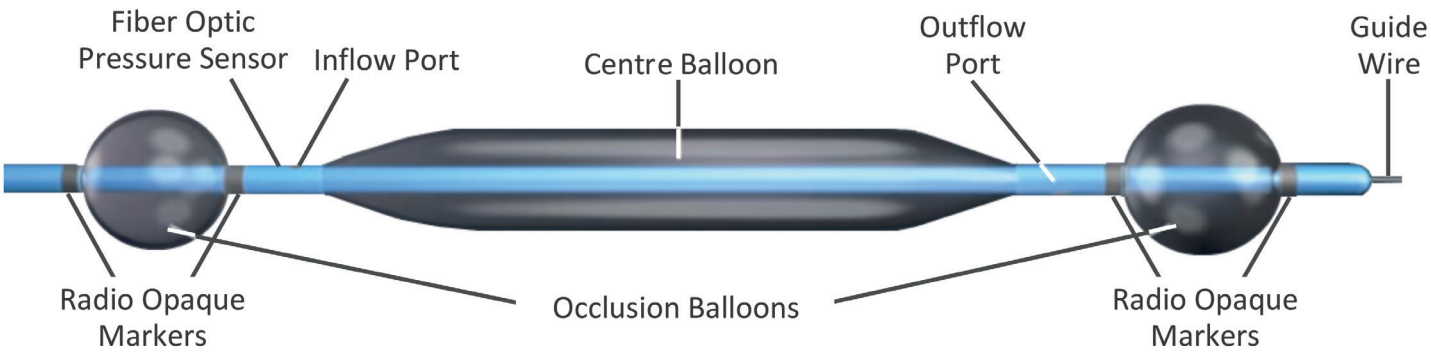

Figure 1: Schematic of the Occlusion Perfusion Catheter™.

that was able to treat multiple lesions, larger lesions and deliver drugs more effectively to the medial wall. It was upon this hypothesis that, in 2008, Advanced Catheter Therapies (ACT) was founded, and that the Occlusion Perfusion Catheter™ (OPC) was developed. Being designed as a universal device, in addition to PAD, the OPC has potential in the treatment of various therapeutic areas, including venous insufficiency, clot management, oncology, dialysis grafts and AV fistulas.

OCCLUSION PERFUSION CATHETER™

The OPC was developed to be a universal and targeted drug delivery device, able to deliver drugs locally without drug being taken up into the bloodstream and delivered systemically. As a starting point the OPC was designed to uniformly deliver, circumferentially and longitudinally within the treatment area, therapeutic agent to the medial layer. Paclitaxel was selected as the first product to be delivered via the device due to it being a well characterised anti-proliferative.

Fundamentals of the OPC

When setting out to design a universal drug delivery device, ACT settled on a set of fundamental requirements that the design had to fulfil.[1] This list guided the development of the OPC and stated that the device had to be able to:

- Deliver a drug uniformly to the medial wall, both circumferentially and longitudinally.
- Deliver a multitude of various therapeutic agents (e.g. small molecule drugs, biologics, stem cells), being a truly universal delivery device.
- Create a "Treatment Chamber" within a blood vessel, that could be filled and washed to eliminate the risk of systemic delivery.
- Monitor and control pressure and drug volume within the treatment chamber.
- Be used on multiple lesions within the same patient.
- Be used on long lesions with a single device.
- Optimise re-endothelialisation.

Operation of the OPC

The OPC is a novel catheter featuring occlusion balloons, a central balloon and inflow and outflow ports for drug delivery (Figure 1). The operative steps are:

> "Because a single device is used for the delivery of multiple agents to multiple locations in a single patient, the savings in time and materials are significant."

- **Step 1:** The catheter is inserted and moved into position so that the occlusion balloons are on either side of the lesion. The occlusion balloons are deployed, halting blood flow and creating a treatment chamber within the vessel.
- **Step 2:** Any blood remaining in the treatment chamber is washed out with saline solution, thus ensuring that blood will not interact with any drug to be delivered.
- **Step 3:** The outflow port is closed and the desired amount of drug delivered into the treatment chamber. The pressure within the chamber is controlled by inflation of the central balloon and monitored by a fibreoptic sensor. The pressure ensures the drug is delivered all the way into the medial wall (Figure 2).

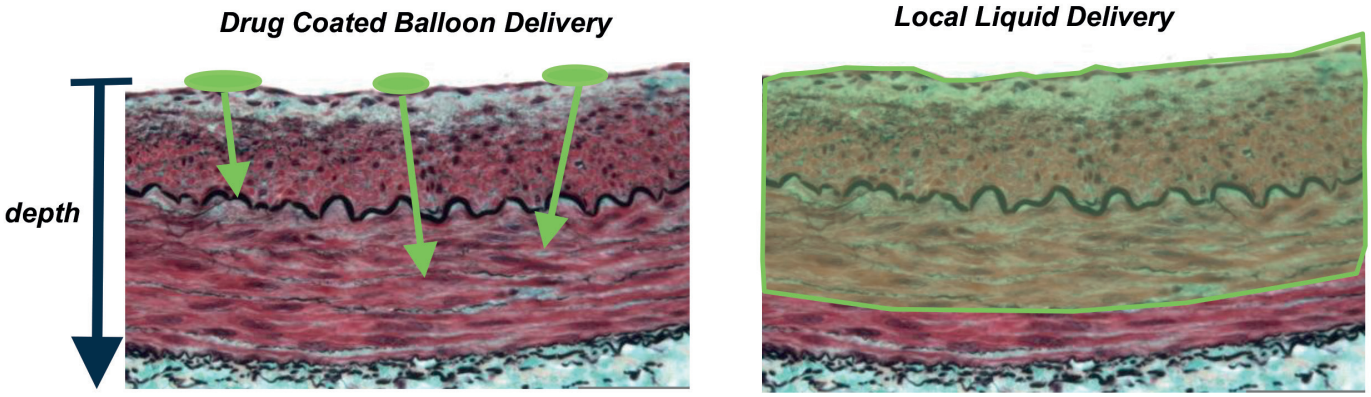

Figure 2: The OPC's local liquid delivery method results in immediate penetration of drug into the medial wall (right), compared with the time dependent diffusion from DCB technology (left).

- **Step 4:** The outflow port is reopened and saline solution is again used to wash the treatment chamber. This greatly reduces, or even eliminates, the possibility of systemic drug circulation, thus hugely reducing adverse events due to drug toxicity.
- **Step 5:** The occlusion balloons are deflated, allowing normal blood flow to resume. The OPC is then ready to be removed or redeployed to the next site within the patient.

Advantages of the OPC

There are a significant number of advantages to the OPC when compared with DCBs. The major advantage, as previously stated, is the creation of a pressure-controlled treatment chamber, which enables the drug to quickly and consistently penetrate into the medial wall, whereas for DCBs, much like stents, store drugs within the intima. DCBs are also limited by their length, requiring multiple balloons to treat long lesions, a problem solved by the OPC.

The treatment chamber also offers an unprecedented flexibility in drug delivery, opening up the potential for sequential drugs to be delivered, or even mixed *in vivo*, with a single device. This enables safer delivery as well, because the isolated nature of the treatment chamber enables the flushing with saline solution, vastly reducing systemic toxicity of drugs deployed within.

Worth mentioning also is the economic benefit of the OPC. Because a single device is used for the delivery of multiple agents to multiple locations in a single patient, the savings in time and materials are significant. With the addition of the central balloon to control pressure, the amount of drug to be delivered can also be carefully controlled, further reducing costs.

CLINICAL RESULTS

To date, two clinical studies have investigated the OPC's effectiveness, with results from one having already been reported. After promising results from *ex vivo* and preclinical studies, a study was conducted by Bunch F *et al* to assess the "feasibility, safety and initial efficacy of paclitaxel administration" using the OPC for the "prevention of restenosis in infrapopliteal *de novo* and restenotic lesions".[2]

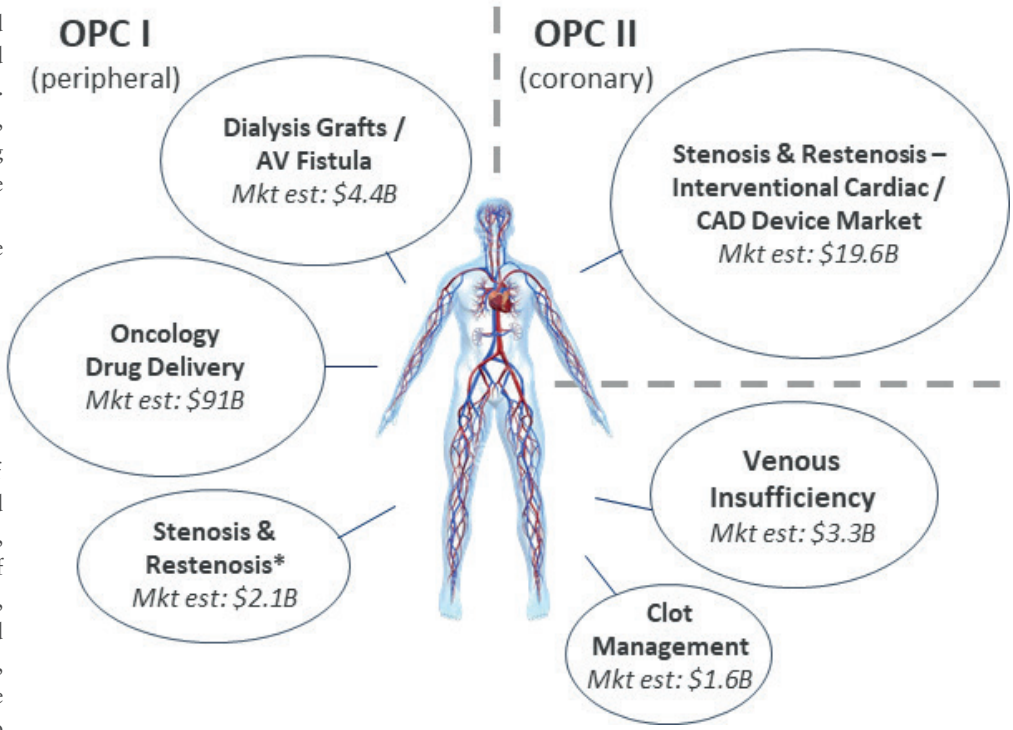

Figure 3: Potential markets for the OPC.

Buy	Build	License
Acquire ACT's OPC patent estate and licensing revenue streams	Become a co-development partner for OPC II	License the use of FDA cleared OPC I for use in new markets

Table 1: Opportunities presented by the OPC.

This first in human, multicentre study reported that, across the 10 patients tested, all tolerated the procedure well. At the six-month follow-up 70% of patients demonstrated the successful efficacy endpoint of freedom from clinically driven target lesion revascularisation (CD-TLR). 0% of patients demonstrated thrombosis, major amputation in the target limb or target limb death at either the 1-, 3- or 6-month follow-ups. The conclusion stated that the OPC showed a favourable safety and efficacy profiles and suggested that subsequent studies should be performed on a larger subject base and with direct comparison to DCBs.

> "The technology has the potential to address a much wider array of markets, including venous insufficiency ($3.3 billion), dialysis grafts/AV fistula ($4.4 billion) and oncology drug delivery ($91 billion)."

FUTURE OUTLOOK

The OPC has three separate 510k clearances, an established safety profile and US FDA approval for any drug, organ or disease. The OPC is, however, only the first in a pipeline of products in development to provide the next generation of targeted endovascular drug delivery.

There is huge market potential for this technology (Figure 3). The current OPC is designed to treat peripheral indications, such as PAD, currently focusing on stenosis and restenosis, a $2.1 billion market. Currently in development is the OPC II, looking towards being suitable for similar use for coronary indications, a $19.6 billion market. The technology has the potential to address a much wider array of markets,

> "The OPC was developed to be a universal and targeted drug delivery device, able to deliver drugs locally without drug being taken up into the bloodstream and delivered systemically. As a starting point the OPC was designed to uniformly deliver, circumferentially and longitudinally within the treatment area, therapeutic agent to the medial layer."

including venous insufficiency ($3.3 billion), dialysis grafts/AV fistula ($4.4 billion) and oncology drug delivery ($91 billion).

ACT currently holds eighteen patents across three devices, including the OPC and OPC II. The company envisages several opportunities for investors and partners in the future (Table 1), including licensing the FDA-approved OPC for use in new markets; partnering for the development of OPC II; and potentially even acquisition of ACT's OPC patent estate and revenue streams.

ABOUT THE COMPANY

Advanced Catheter Therapies, Inc (ACT) is a research and development medical device company with a portfolio of innovative catheter technologies targeting vascular disease including thrombosis, inflammation, occlusions and restenosis. ACT has initially focused its resources on the development of the 510(k) cleared and patented Occlusion Perfusion Catheter™ (OPC).

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ABOUT THE AUTHOR

Paul J Fitzpatrick brings 24 years of diverse, entrepreneurial business and healthcare experience to Advanced Catheter Therapies (ACT), with a proven track record of delivering results. His experience includes serving as Founder, Chief Executive Officer, President, Board Director, Chief Operating Officer and Executive Vice-President. Mr Fitzpatrick is a graduate of the Daniel Freeman Hospital Paramedic School (Los Angeles, CA, US), earning his board certification as a National Registered Paramedic, and holds a degree in paramedic technology from Northeastern University in Boston, where he served as an adjunct faculty member for 10 years.

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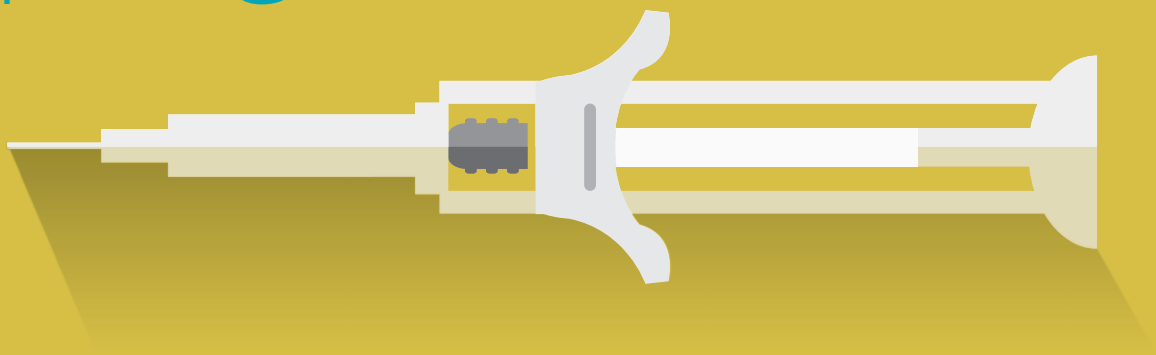

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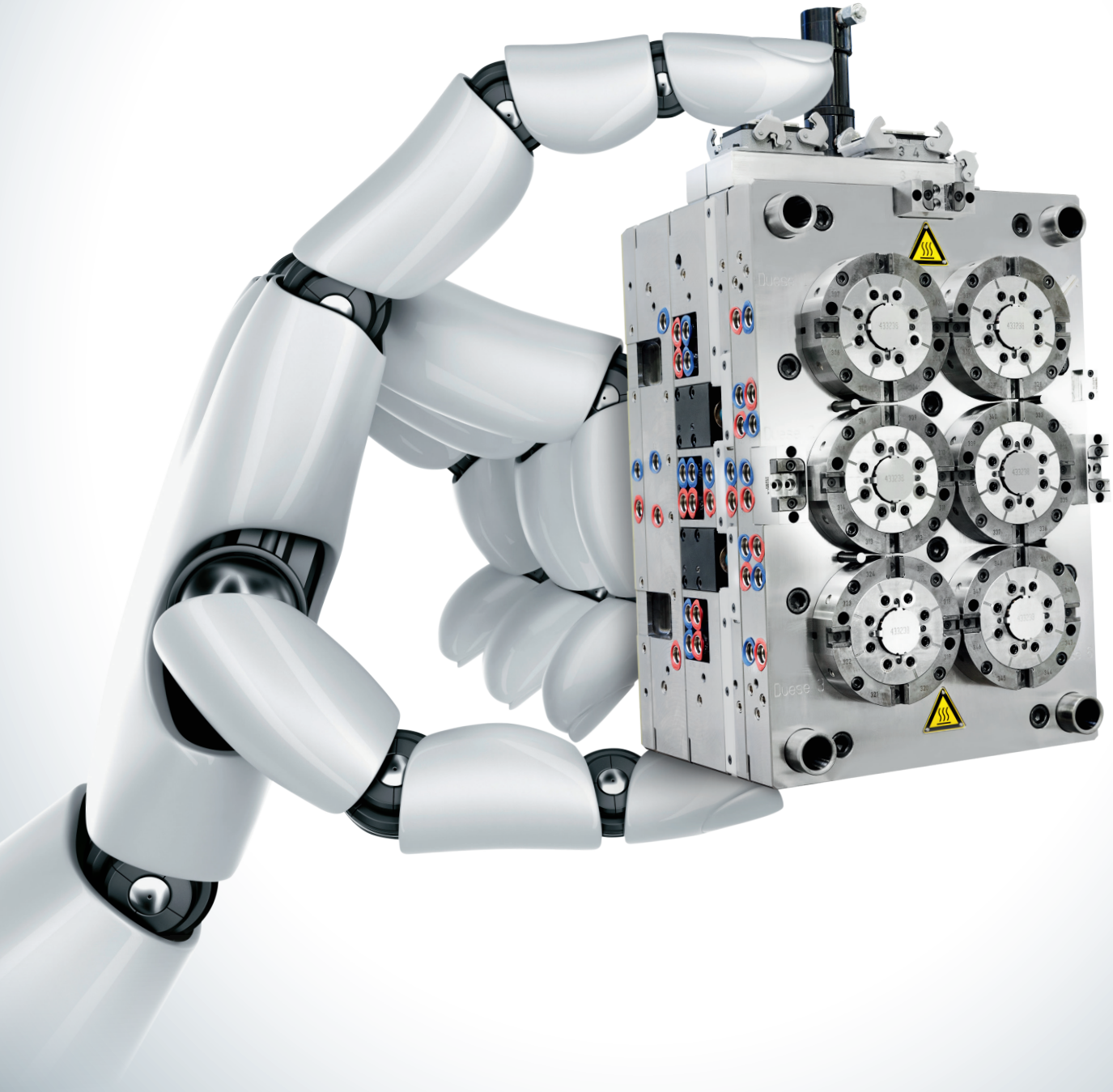

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FROM PREFILLED SYRINGES TO COMBI-FILLING

Here, Klaus Ullherr, Senior Product Manager, Bosch Packaging Technology, summarises the state of modern packaging technology in the pharmaceutical industry in the light of the biotech boom, ready-to-fill and pre-sterilised containers and the trend towards individualised healthcare.

Prefilled syringes have become a preferred format for delivering parenterals, as they make it easier to handle drugs and increase dosing accuracy. In addition, the ongoing boom in biopharmaceuticals has also promoted the growth of the prefilled syringe market. At the same time, other pre-sterilised packaging types are also on the rise, posing new challenges for pharmaceutical companies. Accordingly, machine manufacturers are working at a fever pitch to offer new, more flexible solutions – and are presenting pioneering results.

In comparison to conventional packaging, prefilled syringes not only offer greater ease of use and more precise dosing, modern prefilled syringes are also characterised by reduced product loss, which is a major advantage when it comes to expensive biopharmaceuticals. These highly individualised products, used to treat autoimmune disorders for instance, can best be administered in liquid form using syringes.

PROCESSING: A HIGH DEGREE OF AUTOMATION

As manufacturing becomes ever more automated, manual handling on the part of human operators, and subsequently the chief cause of particulate and bacterial contamination, can be reduced to a minimum (Figure 1). For some time now, the fully automated opening of sterile syringe packages has been a standard requirement for new filling lines. Moreover, isolators are becoming increasingly common, consistently separating the aseptic area from its surroundings.

> "For some time now, the fully automated opening of sterile syringe packages has been a standard requirement for new filling lines. Moreover, isolators are becoming increasingly common, consistently separating the aseptic area from its surroundings."

In-process controls (IPCs) are also an important factor in further improving the quality of the filling process. Currently, the focus is on determining the fill weight and on monitoring the presence of the stopper. In the future, there is likely to be more emphasis on additionally checking the quality of the packaging directly before filling. Is the silicone seal intact? Is the safety cap present and still in the correct position? If the answer is no, faulty syringes can be sorted out before the filling process, thus reducing product loss.

Highly automated filling machines with flexible handling units allow syringes to be precisely removed from the nest. As a result, individual syringes can be fed into an integrated inspection station. Furthermore, methods are now available for checking the thickness and distribution of the silicone layer within the syringe, thus ensuring that the stopper can glide smoothly, a particularly important factor for syringes used in autoinjectors.

> "In connection with prefilled syringes, single-use filling systems are increasingly being discussed in the pharmaceutical industry."

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Figure 1: Filling of nested vials. (© Bosch)

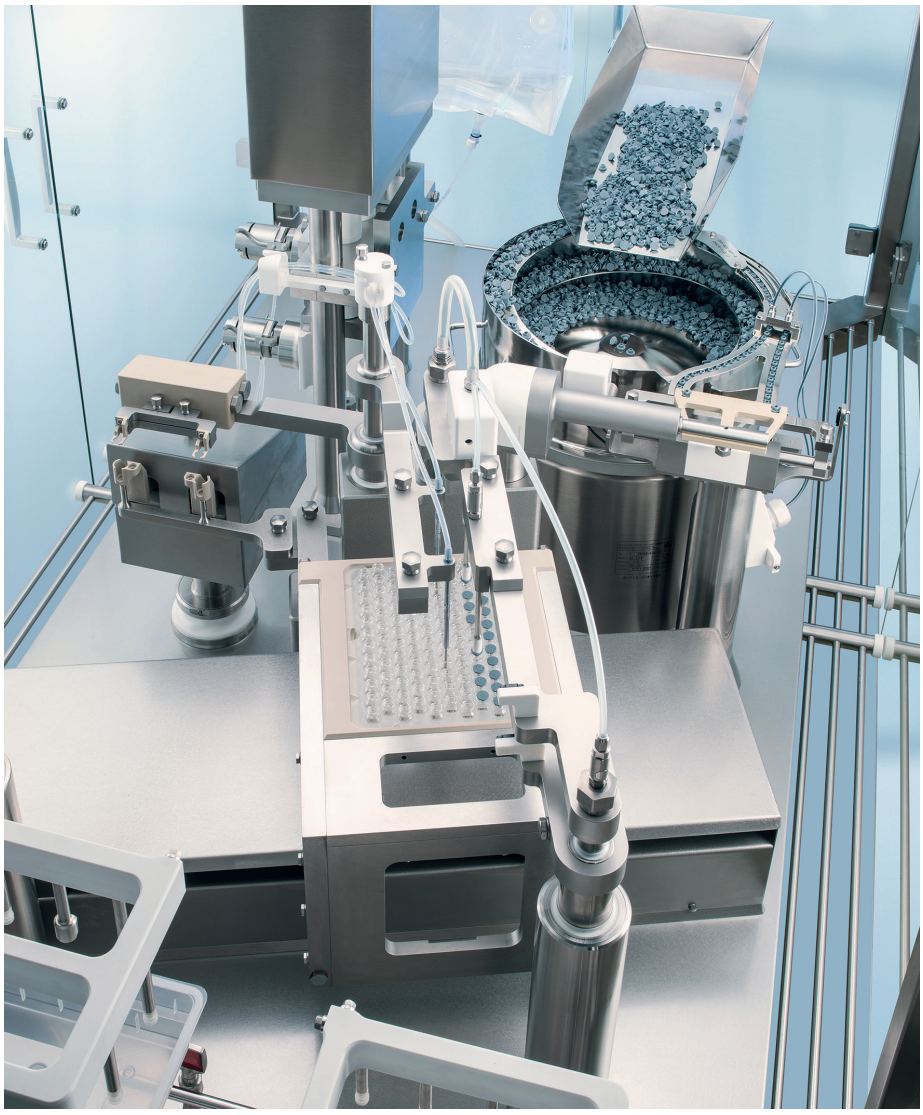

Figure 2: Complete combination filling line for nested containers. (© Bosch)

In this context, it is worth mentioning that an ever increasing number of silicone-free systems are becoming available for plastic syringes. There have also been reports of silicone-free stoppers for glass syringes, which could potentially open the door for silicone-free glass systems.

FILLING AND CLOSING: VARIOUS METHODS

In connection with prefilled syringes, single-use filling systems are increasingly being discussed in the pharmaceutical industry. This approach does away with the need to clean and validate the components that come into contact with the product, which is especially cost intensive for biotech products. In this regard, peristaltic pumps are enjoying renewed popularity, since they never touch the material to be filled. This also considerably improves machine availability, as there is no need for time-intensive cleaning in place or sterilising in place processes (CIP/SIP).

Once the filling process has been completed, a vent tube is used to close the syringe with a stopper. Due to the biotech boom, coated stoppers are becoming increasingly common, yet their coating makes them less suited for this method. Vacuum stopper insertion offers an alternative: a vacuum is created inside the syringe, sucking the stopper into place. Though this more complex approach compresses the stopper to a minor extent, it does not allow the stopper to be placed as precisely as with the vent tube insertion method. Depending on the requirements for precise stoppering and the desired residual air bubble size, the output can also be affected.

NEW PACKAGING TYPES ON THE RISE

There is no stopping the trend toward prefilled syringes. Countless new projects are based on pre-sterilised syringes – and not just for small batches, but also for high output lines. Yet other pre-sterilised packaging types are slowly but surely turning from niche products into appealing alternatives for pharmaceutical companies. Manufacturers of primary packaging made of glass – and in the meantime also plastic – are contributing to this change, for example by developing pre-sterilised, ready-to-fill vials and cartridges.

Here the greatest distinction is made between nest and tray systems: trays are

especially intended for use with classic bulk filling machines, whereas nests can normally be used with machines for syringe processing, including automated bag and tub opening, though some adjustments may be necessary, depending on the packaging geometry, material and structure (Figure 2). The broad range of resulting packing formats will confront machine manufacturers and pharmaceutical producers alike with major challenges. In this regard, initiatives akin to the ISO's standardisation work would be desirable.

STILL NO STANDARD METHOD

Another aspect that is now being intensively discussed is the infeed of pre-sterilised packaging types. Though the e-beam has long been the standard solution for decontaminating tubs in high output lines with isolators, it is generally considered too large for smaller lines. Alternatives currently being explored include:

- Tunnels or locks used in combination with plasma
- UV light
- Nitrogen dioxide
- Hydrogen peroxide.

However, none has established itself as standard yet. Aseptic transfer is possible with restricted access barrier systems (RABS) or with isolator applications, provided a suitable, fully automatic bag opener is used, combined with spray disinfection of the bag. In this regard, double bagging for added safety is becoming more common.

The more packaging types that can be filled and closed on a single machine, the more space-saving it is for users. This is possible thanks to new combination (combi-) machines for flexibly processing various types of primary packaging. By integrating both filling and capping station in a single unit, there is no need for a second machine (Figure 3). Furthermore, compatibility with various filling systems is a prerequisite for new filling and closing machines. In this regard, combi-filling stations, which can be easily reconfigured to accommodate a diverse array of filling systems without taking up more space, have quickly proven their value. They allow pharmaceutical manufacturers to adapt filling processes to their respective medications and packaging types, whilst ensuring that all filling systems are in the sterile area.

> "The more packaging types that can be filled and closed on a single machine, the more space-saving it is for users. This is possible thanks to new combination machines for flexibly processing various types of primary packaging."

HIGHER EFFICIENCY, MORE INDIVIDUALISATION

Given how costly biopharmaceutical drugs are, efficient filling methods are a priority. The key is to keep product loss to an absolute minimum, and the latest filling technologies deliver almost complete product yield. Here, above all, the focus is on the start-up and emptying process steps. A statistical or 100% IPC during production ensures that all containers leave the machine with exactly the desired amount of liquid.

In light of individualisation of products being the current industry trend, more customer specific, flexible solutions are also taking on a new importance. Clinical studies in particular require the highest possible flexibility in a very compact space, which can be achieved

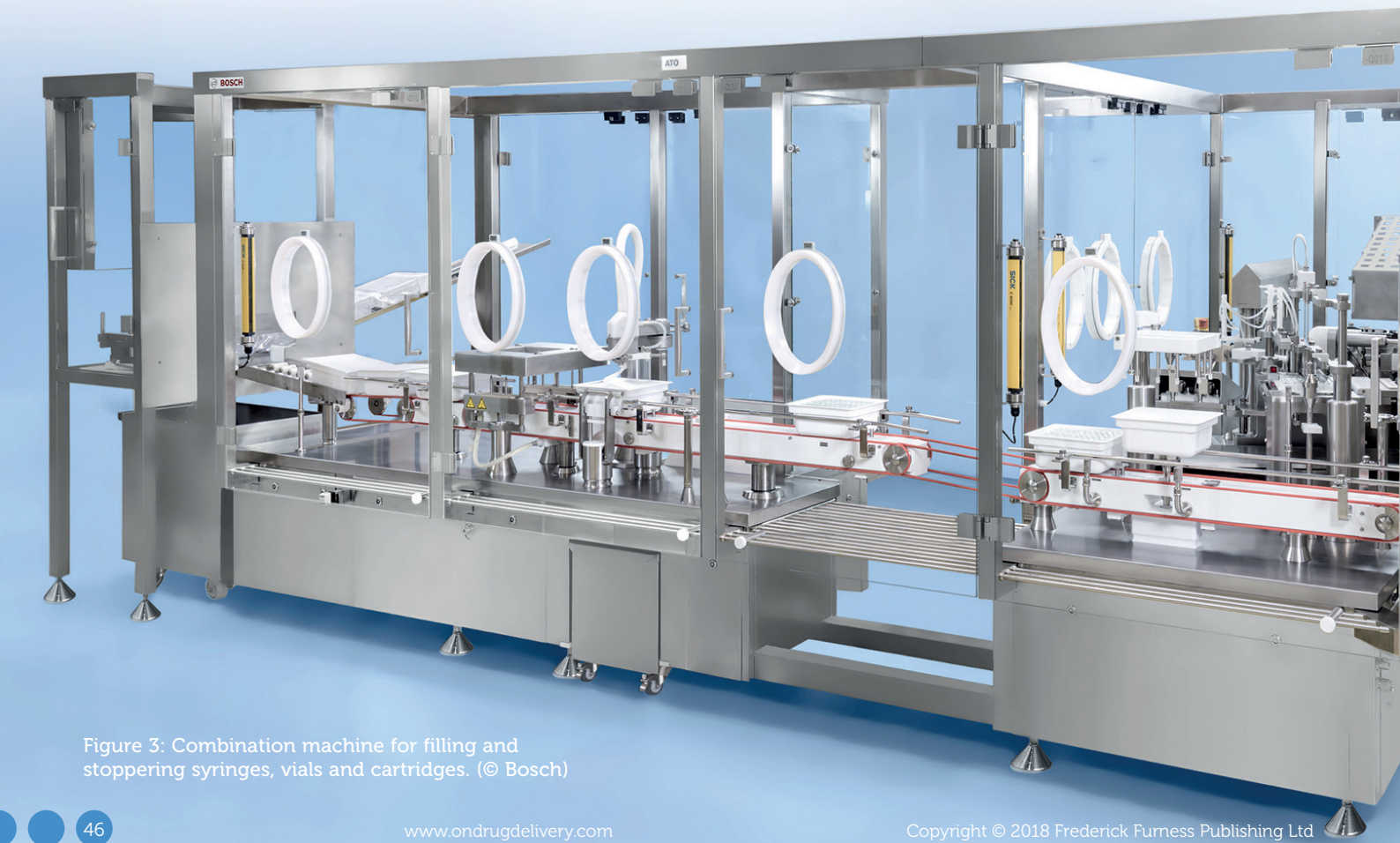

Figure 3: Combination machine for filling and stoppering syringes, vials and cartridges. (© Bosch)

"In light of individualisation of products being the current industry trend, more customer specific, flexible solutions are also taking on a new importance. Clinical studies in particular require the highest possible flexibility in a very compact space..."

by combining manual, partly and fully automated processes, together with different packaging types. In this case, the infeed can be either manual or semi-automated so as to accommodate the new variety of packaging types, especially with regard to the outer packaging, and in turn the filling would be fully automated. To ensure that the individual work steps can be adapted to future types of packaging, the use of robots is advisable, be it for transporting packages from one station to the next or even for filling (Figure 4). Adding a reserve station at some point in the future is also worth considering.

Figure 4: Fully automated robotic filling of syringes. (© Bosch/AbbVie)

COMPLETE LINE CONCEPTS

What pharmaceutical producers expect from their systems or lines can vary considerably, depending on their respective therapeutic area, region or company size. Yet they all share a focus on ensuring the best possible protection for the product and their machine operators. Accordingly, new filling and closing machines are, as a rule, characterised by a high degree of automation and equipped with either RABS or isolators. When they are used with upstream automatic tub and bag openers, and in combination with downstream process steps like inspection, plunger-rod insertion and labelling, the result is a complete filling and closing line – and in the near future, not just for prefilled syringes, but increasingly for other pre-sterilised containers too.

ABOUT THE COMPANY

Bosch Packaging Technology – product division Pharma is one of the leading providers of process technology and packaging solutions for the pharmaceutical industry. The company's portfolio includes single units, complete lines and integrated systems for the manufacturing and processing of liquid and solid pharmaceuticals. It also includes process technology, primary packaging and inspection technology for different application fields and packaging types. Secondary packaging with qualification and validation, software solutions for "track and trace" and technical customer service are also available. The following product brands are part of the Bosch portfolio for the pharmaceutical industry: Hüttlin, Klenzaids, Manesty, Moeller & Devicon, Pharmatec, SBM Schoeller-Bleckmann Medizintechnik, Sigpack and Valicare.

ABOUT THE AUTHOR

Klaus Ullherr holds a degree in electrical engineering. After university he worked for several years as a project manager in the electrical industry before joining Bosch Packaging Technology in March 2000. During his first two years there, he was project manager responsible for handling complex customer orders. Since 2002 he has been product manager for the business field's syringes and cartridges with global product responsibility. Mr Ullherr's main functions are market analysis, initiating new product developments, business development and resident expert for syringe processing. He is a member of the PDA Interest Group "Prefilled Syringes" and works as an expert in the DIN/ISO group for primary packaging. He is also a speaker at many conferences covering trends and solutions for fill/finish equipment, especially for prefilled syringes.

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CRITICAL CONSIDERATIONS IN CHOOSING HIGH VISCOSITY/HIGH VOLUME DRUG DELIVERY DEVICES

Innumerable questions inevitably arise over the course of any drug/device development programme. There are, however, some particular considerations that are common across the spectrum of biologics development. Here, Bill Welch, Chief Technical Officer, Phillips-Medisize, discusses these considerations, highlighting the advantage conferred by accounting for them early in the product lifecycle.

With the ongoing increase in biologics development, early involvement between drug manufacturers, device designers and device manufacturers is critical to the development of an effective and efficient drug/device lifecycle strategy. Many biologics are highly concentrated, so a prescribed dose may be very viscous, or require large volumes of the medication to be injected slowly over time. This can make it difficult to deliver a consistent dose, potentially impacting patient adherence to a given therapy, and so it naturally follows that device development considerations should begin as early as possible.

These particularities of biologics have led to a rise in the popularity of wearable self-injection systems. Instead of scheduling a doctor's appointment for certain treatments, a wearable device allows patients to self-administer large volume injectable medications. Some estimates predict that, by 2020, biologics will make up more than half of the world's top 100 selling drugs. To keep pace, device designers must needs overcome the myriad challenges associated with delivering these drugs.

Chief amongst the issues associated with biologics are those of high viscosity and high volume. For proteins, issues of viscosity, solubility and protein aggregation become major obstacles, especially with the smaller-gauge needles that patients prefer. Biologics cannot be taken orally, so the question of how to deliver them via an injection, in a fashion satisfactory to the end-user, cannot be circumvented. Whilst these challenges are not unique to biologics, these drugs demand special attention from device developers.

DEVICE DESIGN CONSIDERATIONS

From a delivery device perspective, higher viscosity drugs require more force to push fluid through the narrow orifices used in delivery, for example a cannula. This force,

> "Upon first consideration, the simplest solution would be to increase the needle diameter, thereby reducing plunger force to accommodate a more viscous formulation. However, a larger needle would increase pain at the site of injection, decreasing patient acceptance and adherence."

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or "syringeability" as it often called, is dependent upon many more factors than formulation viscosity alone, including desired flow rate, needle length and needle diameter. Any small change in the needle diameter will result in a large change in the plunger force.

"The conundrum for device designers is obvious, how best to balance these two opposed design problems and create the most positive user experience possible?"

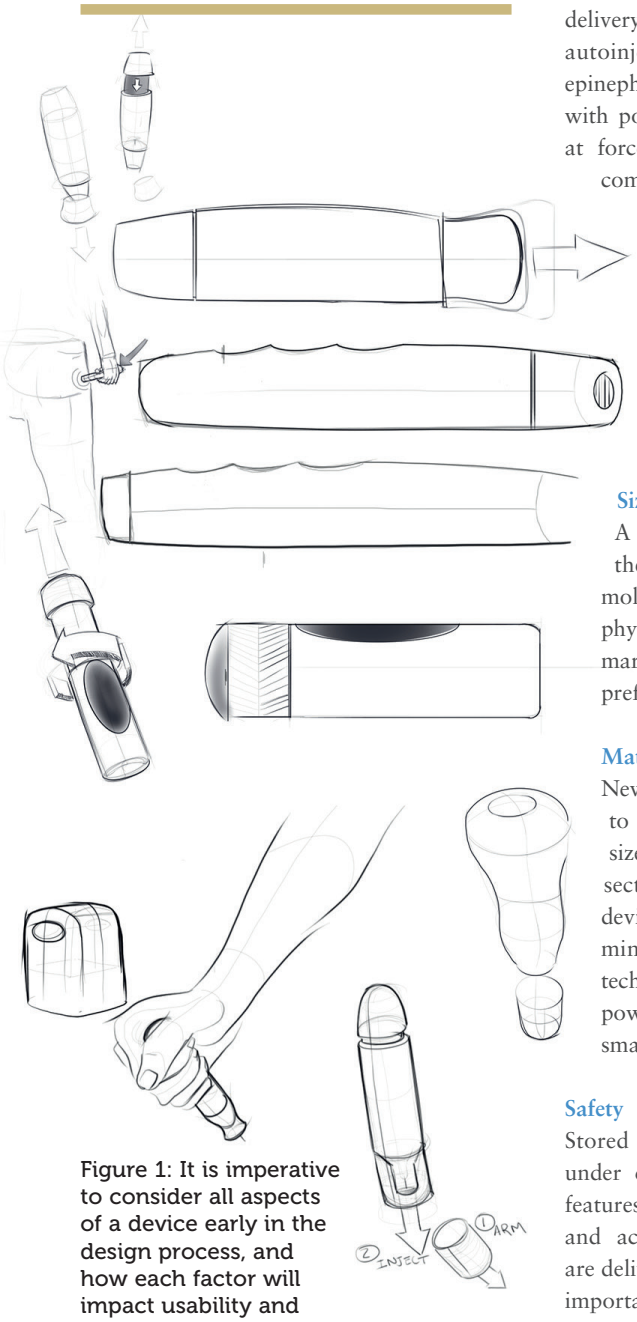

Figure 1: It is imperative to consider all aspects of a device early in the design process, and how each factor will impact usability and patient adherence.

Upon first consideration, the simplest solution would be to increase the needle diameter, thereby reducing plunger force to accommodate a more viscous formulation. However, a larger needle would increase pain at the site of injection, decreasing patient acceptance and adherence. But then again, maintaining a smaller needle will lead to higher than "normal" plunger force, leading to user fatigue and poor user experience. So, the conundrum for device designers is obvious, how best to balance these two opposed design problems and create the most positive user experience possible?

AUTOINJECTORS

One solution is the use of an assisted delivery device, a common example being autoinjectors such as those used for epinephrine delivery. These can be fitted with power sources that drive the plunger at forces higher than could be provided comfortably by the user. This approach enables device designers to maintain a smaller gauge needle and place the burden on the power source to provide the high force needed for delivery. However, this approach comes with its own set of concerns and considerations (Figure 1). These include:

Size

A power source capable of providing the force required to push large molecules through a small needle is often physically large. This goes contrary to market trends, which suggest that users prefer smaller devices.

Material

New high-strength materials can be used to help alleviate the aforementioned size issue by deploying smaller wall sections and structural features in devices and container closures, thereby miniaturising them. New material technologies can also be used to derive power sources, usually springs, that are smaller and yet provide the same forces.

Safety

Stored energy devices, such as springs under compression, require robust safety features to prevent injury, device failures and accidental actuation. Where devices are delivering viscous drugs, this is crucially important. An accidental drop, material fatigue, failure of the glass container closure or excessive vibrations can lead to catastrophes that could injure users or prevent lifesaving drugs from being administered.

The autoinjector approach focuses on maintaining a smaller needle diameter by accepting a higher plunger force. This approach centres on different ways of executing a high force power source. Another approach could be reducing plunger force, whilst still maintaining a smaller gauge needle, by simply lowering any of the variables in the numerator of the Hagen-Poiseuille equation, assuming pressure at the needle is constant:

$$F = \frac{(128Q\mu LA)}{(\pi D^4)}$$

Where:

- F is the plunger force
- L is the length of the needle
- μ is the viscosity
- Q is the flow rate
- A is the area of the plunger
- D is the internal diameter of the needle.

One possible change would be to reduce the diameter of the plunger and thus the plunger area. However, this has size implications, as the syringe or device would need to become longer to accommodate the same drug volume, which raises further problems. Alternatively, the flow rate could be reduced, lowering the force but increasing delivery time. Likewise, decreasing viscosity can be achieved through dilution but the increased volume also increases delivery time. Therefore, these solutions require a different delivery approach that cannot be achieved through direct injection methods.

"Unlike prefilled syringes or autoinjectors devices, where the user maintains constant interaction throughout the injection, users of body worn devices cannot be expected to remain vigilance over the course of the procedure, which may take several minutes or even hours."

WEARABLES

IV delivery is the extreme case. IV solutions have a much reduced viscosity over syringe based formulations, as well as a significantly reduced flow rate. However, this method greatly prolongs the delivery time. Whilst patients may accept this form of delivery for otherwise unavailable therapies, quicker and more convenient delivery methods are always preferred and are vastly more suitable for non-clinical settings. In response to these limitations, body-worn infusion pump devices may be an alternative worth investigation and investment.

These are already common in diabetes treatment, in which users wear an insulin pump connected to their body via a cannula. However, for delivering high volume drugs, a different perspective is required: the device needs to be treated as a prolonged injection device rather than a continual-use pump (Figure 2). Ergo, such wearable injectors carry their own new set of challenges:

Size

The size challenge in body worn devices lies in the necessity to slow down the delivery speed. While the delivered force required to push the drug through a needle may be smaller, it needs to take place over a period of several minutes to a few hours. Any additional components that may be required to modulate the delivery rate will require more space, causing an undesirable creeping increase device size.

User Interface

Unlike prefilled syringes or autoinjectors, where the user maintains constant interaction throughout the injection, users of body worn devices cannot be expected to remain vigilance over the course of the procedure, which may take several minutes or even hours. Therefore, the ability of the device to provide error alerts, indicate progress and confirm delivery becomes critical, freeing the user to perform other activities whilst the wearable injector does its work.

> "Connected devices are becoming more prevalent in the healthcare sector, as tech companies turn their attention to drug delivery devices and device designers take more note of the benefits connectivity has brought to other industries."

Figure 2: An example wearable injection device.

Body Fixation Method

The first challenge with wearable devices is where they should be placed on the body (Figure 3). There are numerous questions that must be considered before a conclusion can be drawn:

- How sensitive is the tissue?
- Can an adhesive be used on this part of the body?
- Is the adhesive aggressive enough to hold the device in place over the required time period?
- Will it cause allergic reactions?
- Could or should a band of some description be used instead of an adhesive?
- Will the device need to survive wet conditions or withstand physical activity?
- How will the patient feel about wearing a device, is it obvious or obnoxious?
- Will the skin surface need to be shaved before application?
- Does the patient feel "tethered" by their device?

Another consideration is looking at alternate injection platforms departing completely from the conventional needle based designs. Microneedles and needle-free technologies are potential alternatives that could be explored for delivering high viscosity and/or high volume drugs.

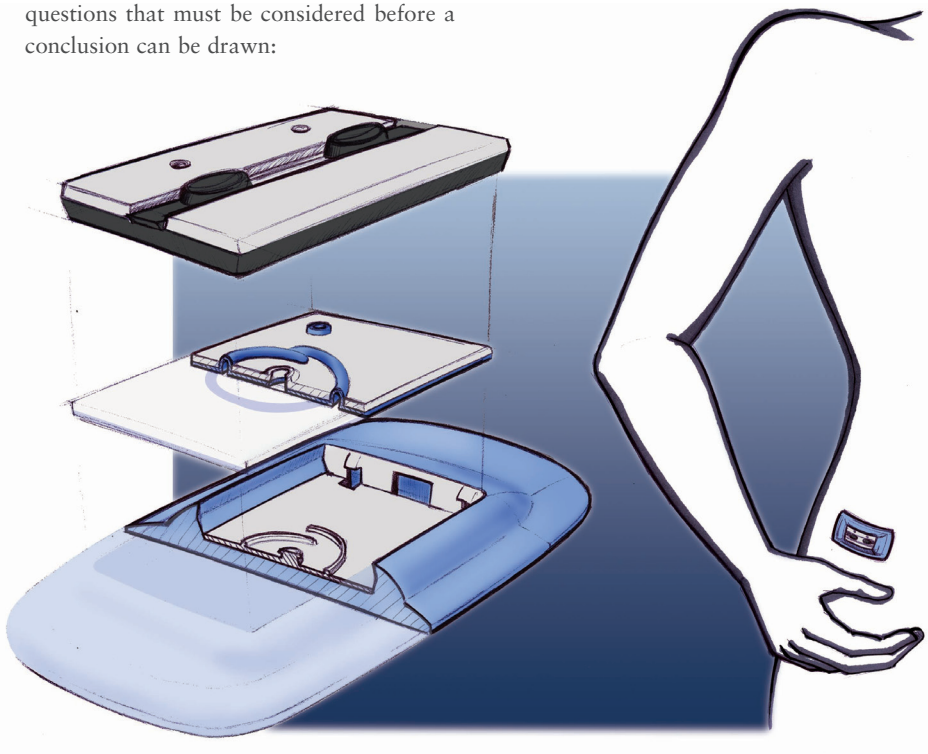

Figure 3: Where a wearable device is to be worn is a crucial factor to consider, alongside the components of the device itself.

Human Factors Considerations

As evidenced by the US FDA's increased attention to human factors considerations in their appraisal of drug delivery devices, a thorough investigation of a user's interaction is as important as the actual performance of the device. A device that is difficult for a patient to understand or use intuitively, even if it performs sublimely under perfect conditions, can detract from compliance. As such, device developers will often conduct design and manufacturing process failure mode and effects analyses (FMEAs) early in the product lifecycle. Discovering a significant potential use error, once the development or manufacturing phase has begun, can be costly.

CONSIDERING CONNECTIVITY

Connected devices are becoming more prevalent in the healthcare sector, as tech companies turn their attention to drug delivery devices and device designers take more note of the benefits connectivity has brought to other industries. These benefits include monitoring patient compliance, tracking user activity and location to customise patient care, and managing refills. But these benefits need to be weighed against the implications of their deployment.

- What are the regulatory implications of including these technologies?
- Can third party apps be permitted and, if so, will necessary software updates be managed?
- How will the distribution of apps be managed for drug delivery devices?
- How will the user data, and the entities that hold and manage it, be regulated?
- What are the infrastructure implications?
- Who will manage user data?
- Will user data need to be anonymised?
- Which connectivity technologies should be used?
- How should device recycling or disposal be managed, is conventional sharps disposal compatible with electronic devices?
- Is hacking a threat and, if so, what is the best way to protect against it?

CONCULSION

Manufacturers of devices will continue to repeat the mantra of "early engagement" with device designers and developers. This stems from the simple premise that it is easier, cheaper and quicker to make the inevitable change to a design at the beginning of the development cycle than it is toward the end. Manufacturing issues discovered after a design has been locked can cause severe delays or even derail the entire programme. This thought process applies to the drug developer and device designers alike, as earlier considerations regarding device strategy can avoid crippling challenges down the road.

Of course, it is worth restating, here at the conclusion, that the most critical and central consideration for device designers must always be the wellbeing of the patient.

ABOUT THE COMPANY

Phillips-Medisize is a leading global outsource provider of design and manufacturing services to the drug delivery, consumable diagnostics and medical device, and speciality commercial markets. 85% of the company's revenue comes from drug delivery, medical device, primary pharmaceutical packaging and diagnostic products such as: disposable insulin pens, glucose meters, speciality inhalation drug delivery devices, single use surgical devices and consumable diagnostic components.

ABOUT THE AUTHOR

Bill Welch has more than 25 years of contract design, development and manufacturing experience, primarily serving customers in the drug delivery, health technology and diagnostics markets. In his current capacity as Chief Technical Officer at Phillips-Medisize, he leads a global, over-500 person development, engineering, tooling, programme management and validation organisation. He has been with Phillips-Medisize since 2002.

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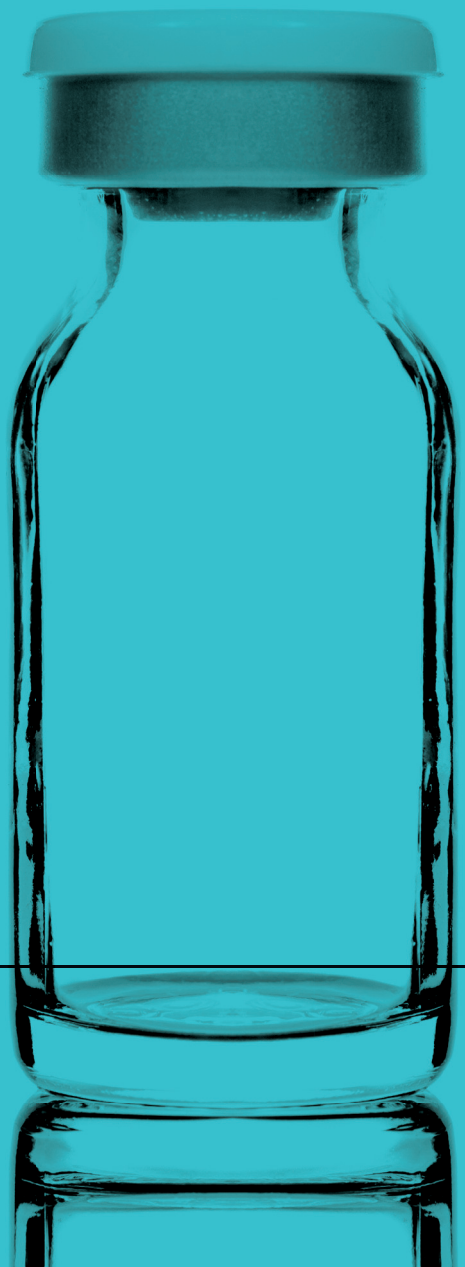

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5 THINGS TO CONSIDER
WHEN MANUFACTURING CONNECTED DRUG DELIVERY DEVICES

The estimated number of connected drug delivery devices continues to increase and the impact of this trend could be significant, explains Phillips-Medisize

While digital connectivity or connected health can improve the coordination and delivery of patient care, original equipment managers need to keep these five things in mind when creating connected drug delivery devices:

1. **Development strategy and design consideration**
2. **Situation analysis and patient compliance**
3. **Connectivity ecosystem**
4. **Wireless subsystem**
5. **Security of device and information**

As the Internet of Things continues to become an integral part of people's lives, the opportunity to use it within drug delivery device applications remains promising. The manufacturers and device designers must identify, investigate and overcome these challenges so that the implementation of wireless and other related smart technologies can be achieved. When done successfully, connected systems enable the patient and caregivers to have a 360° view of both the patient and the disease – not only to manage adherence, but to improve results by understanding the effect of the regimen.

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SUNDEEP KANKANALA, BD

Sundeep Kankanala, PhD, is Vice-President of R&D for BD Medical – Pharmaceutical Systems (PS). His responsibilities include leading product and technology development across the PS project portfolio. Prior to this, he was the Director of Smart Device and Data Sciences focus area at BD Technologies and Innovation and a member of the Infusion Therapy business.

Prior to joining BD, Dr Kankanala was a Subject Matter Expert in Smart Materials and Advanced Safety Systems at Ford Motor Company. His fifteen years at Ford spanned a range of assignments, from leading research in biomechanics and smart materials to technology development and launch of advanced occupant safety systems in cars and trucks. He holds a PhD in Aerospace Engineering from the University of Michigan for his theoretical and experimental work in magneto-elasticity. He also earned an MBA from MIT's Sloan School of Management.

In this interview, Dr Kankanala discusses the challenges faced by today's biopharmaceutical industry, in particular those posed by the need for large volumes and the issues caused by the use of silicone in prefilled syringes. He goes on to detail BD's latest technology, BD XSi™, which builds upon BD Neopak™, and how it presents answers to these problems.

Q What would you say is the greatest challenge in the biopharmaceutical market today?

A The overriding challenge facing biopharmaceutical companies today is the increasing pressure around time to market. Factors influencing this include longer approval processes, more stringent guidelines, downward price pressure and high failure rates seen throughout development.

While this is true of all drug research, it is even more challenging for biosimilars and innovative biologics, due to problems encountered when developing suitable parenteral formulations and combination products. These biosimilar and innovative therapeutics are at the cutting edge of science; the fact that they are complex and potentially unstable molecules makes them very expensive to develop and manufacture, and therefore demands another paradigm shift.

"The most recent development is the BD Neopak™ XSi™, an extension to the BD Neopak™ platform which allows companies to adopt a proactive, rather than reactive, approach to their combination product development."

Q Given that, how has BD contributed to biopharma in the past, and how is it rising to the challenge now?

A Over the past three decades, BD has worked collaboratively with biopharmaceutical manufacturers to put solutions in place at the outset, to avoid disruption to manufacturing and to ensure regulatory readiness. This approach has been highly successful, and has earned BD a reputation for developing innovative technologies which help companies achieve ambitious time-to-market goals.

BD's long collaboration with biopharmaceutical companies has allowed us to anticipate emerging needs, improve components and find solutions to complex delivery requirements. One such requirement is to reduce dosing frequency to improve patient experience and compliance. Some companies try to achieve this by increasing drug concentrations. As this is often not possible or sufficient to the level required for optimum dose delivery, larger injection volumes of 2 mL or more are required.

The growing trend towards higher drug concentrations and larger injection volumes has presented new delivery challenges, including increased viscosity. Larger volumes of very valuable drugs also introduce a critical economic component as the cost of wastage increases. We responded by developing the BD Neopak™ glass PFS platform. This innovation was made possible by a near total redesign of our existing PFS, 80% of its features being either new or improved. Based on a quality-by-design approach, BD Neopak™ features single-digit ppm product performance attributes, aiming at Six Sigma level quality.

BD Neopak™ is available in both 1 mL and 2.25 mL formats, the latter of which has helped break the "1 mL barrier" for subcutaneous injections which had existed in the heads of many stakeholders; it has been actively adopted for the development of innovative therapies with larger volumes.

By reducing cosmetic defects and improving breakage resistance, we have also enabled our BD Neopak™ customers to significantly reduce their manufacturing costs by decreasing scrap and rates of rejection. Not insignificant numbers of PFS are scrapped by companies when they fail to meet the required standards. When filled with very expensive biological or biosimilar drugs, such scrappage costs can far exceed the purchase cost of the syringe. BD Neopak™ has been shown to significantly reduce scrap and rejection rates by up to 90%.

"It should be noted that the same regulatory standards apply to all containers bellow 100 mL, as they are defined per syringe rather than per mL, making it even more challenging to comply with those standards for larger volumes."

The most recent development is the BD Neopak™ XSi™, an extension to the BD Neopak™ platform which allows companies to adopt a proactive, rather than reactive, approach to their combination product development. BD XSi™ features an innovative immobilised silicone coating that addresses potential silicone-related concerns while being fully compatible with existing practices and infrastructure. Our biopharmaceutical partners can now adopt a platform approach and transfer from BD Neopak™ to BD XSi™ if improved silicone functionality is required, enabling concerns to be addressed without major disruptions to, or investment in, the development and manufacturing process.

Q Could you elaborate on the concerns silicone poses to biopharmaceutical development, and what BD offers to mitigate them?

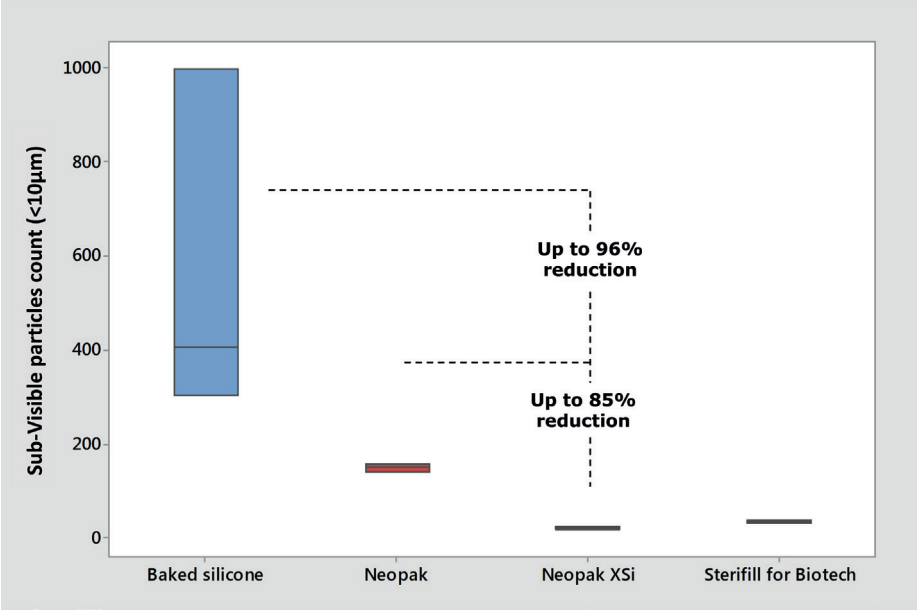

Figure 1: BD Neopak™ XSi™ displays significantly reduced particles >10 µm compared with alternatives.

A A critical factor in syringe gliding performance is the integrity of the silicone coating that lines the glass barrel. This requires a robust lubrication layer, especially in high-dose formulations where the surfactants used can "wash away" the silicone coating. Degradation of the silicone layer can become a significant barrier to development if it reduces gliding efficiency and the capacity to deliver a full dose, risking complaints and product recall.

On the other hand, migrating silicone can generate sub-visible particles (SbVPs) which, in the worst-case scenario, leads to non-compliance with USP 788 standards and registration failure. US and EU licensing regulations specify permissible numbers of SbVPs with a diameter over 10 µm and over 25 µm, although the US FDA has begun asking for data on smaller particles in the 2-10 µm range. This may become even stricter, as it is now possible to look for particles smaller than 0.5 µm in diameter.

It should be noted that the same regulatory standards apply to all containers below 100 mL, as they are defined per syringe rather than per mL, making it even more challenging to comply with those standards for larger volumes. Companies who foresee these potential challenges early in drug development, and adopt a successful risk mitigation strategy, avoid the risk of delays and registration failure.

Overcoming the problems associated with silicone requires a more stable silicone layer which can protect against drug interactions, minimise SbVP levels, retain gliding performance, improve patient experience, and reduce complaints and recall risks.

BD XSi™ incorporates a more inert, immobilised crosslinked silicone and this significantly reduces the number of SbVPs.

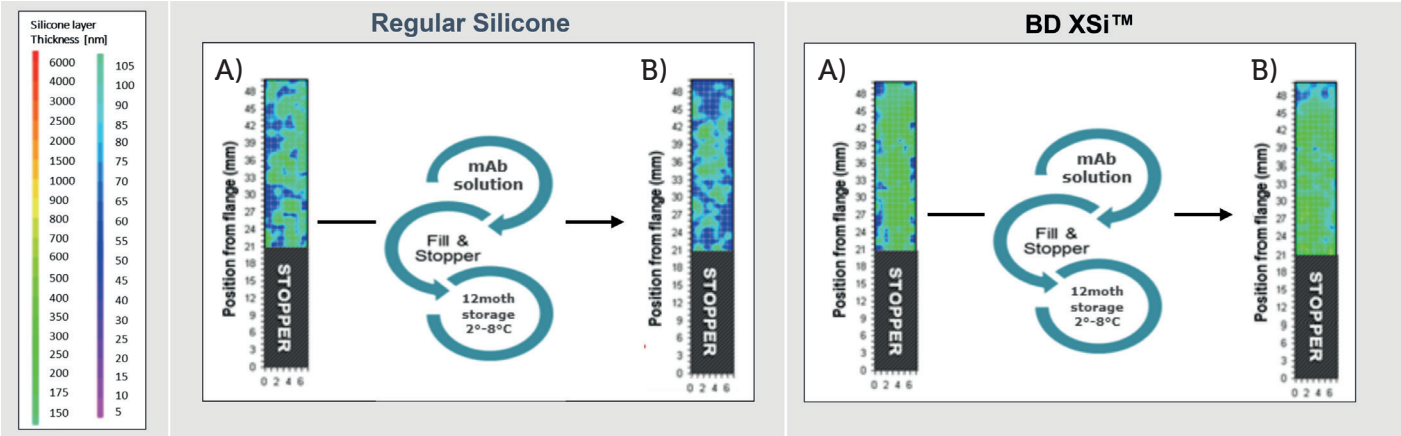

Figure 2: BD Neopak™ XSi™ maintains coating integrity and gliding performance compared with regular silicone, both at baseline (A) and at 12 months (B), measured by reflectometry.

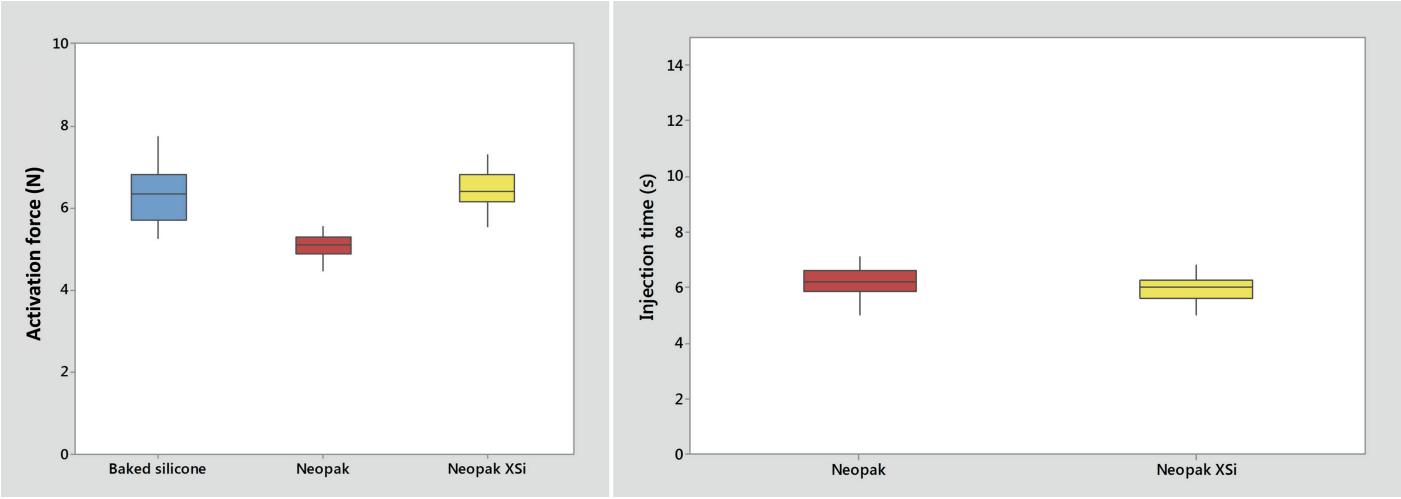

Figure 3: BD Neopak™ XSi™ maintains state-of-the-art gliding performance.

This notably outperforms other coatings, such as baked and sprayed silicone, and achieves true particle reduction across the 2-25 µm diameter range, not just shifting counts from one size to another.

This breakthrough technology uses the gold-standard DC360 silicone, and so does not introduce any new chemistry.† It builds on the best in class BD Neopak™ syringe and is fully compatible with existing development and manufacturing practices and secondary device standards.

BD XSi™ is a revolutionary offering to biopharmaceutical companies, as it allows them to initiate development with BD Neopak™ and then later opt for BD XSi™ if a particular molecule in their pipeline requires its additional features. As both products belong to the same manufacturing platform, this poses minimal risk to development timelines.

In a 2017 study, BD XSi™ was shown to significantly reduce particles of less than 10 µm compared with BD Neopak™ and BD's baked silicone solutions by up to 85% and 96%, respectively (Figure 1). The particle production with BD XSi™ was comparable to that of a non-siliconised polymer syringe, for example BD Sterifill™ for Biotech.

"BD XSi™ is a revolutionary offering to biopharmaceutical companies, as it allows them to initiate development with BD Neopak™ and then later opt for BD XSi™ if a particular molecule in their pipeline requires its additional features."

"This breakthrough technology uses the gold-standard DC360 silicone, and so does not introduce any new chemistry."

Furthermore, the BD XSi™ layer has been shown to generate a very low percentage of SbVPs compared with other silicone coatings even after 48 hours of agitation, which may predict long-term stability. This is supported by previous study from Depaz *et al*, which showed that the required thickness and homogeneity of the lubricant coating was maintained over 12 months with BD XSi™. In comparison, the conventional silicone layer became thinner and disintegrated, making full dose delivery from an autoinjector less likely (Figure 2).

The stability of the BD XSi™ layer is key to maintaining coating integrity and gliding performance. BD XSi™ achieves a similar level of filled gliding force to conventional siliconised syringes, including BD Neopak™, which is particularly important for autoinjectors (Figure 3).

Q **Finally, can you succinctly explain the benefits of the BD XSi™ technology?**

A BD XSi™ is a significant step forward for the development of innovative, PFS-based biologicals, bringing multiple benefits to biotechnology manufacturers and patients with chronic diseases. Manufacturers now have a stable, robust product for advanced biological formulations, with reduced risk of development delays, registration failures, field complaints or product recalls. All these factors contribute to reduced total ownership costs and time to market, helping to maximise the number of patients who can benefit from innovative therapies.

This determination to deliver new technologies led to a paradigm shift, aimed at minimising delays in approval and decreasing time to market, and earning BD the trust of the pharmaceutical industry in the process. A benchmark study conducted by a leading pharmaceutical company evaluated four manufacturers against set criteria, and led to BD being selected as the partner of choice because of superior process capability, innovation potential and strategic fit.

†BD XSi™ does not introduce new chemical substances and only modifies the distribution of chemical functions which already exist in PDMS silicone.

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ON drugDELIVERY

2018/19 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
March 2018	Skin Drug Delivery: Dermal, Transdermal Microneedles	Feb 8th 2018
April 2018	Pulmonary & Nasal Drug Delivery	Mar 8th 2018
May 2018	Injectable Drug Delivery: Devices Focus	Apr 5th 2018
June 2018	Connecting Drug Delivery	May 3rd 2018
July 2018	Novel Oral Delivery Systems	Jun 7th 2018
August 2018	Industrialising Drug Delivery Systems	Jul 5th 2018
September 2018	Wearable Injectors	Aug 2nd 2018
October 2018	Prefilled Syringes & Injection Devices	Sep 6th 2018
November 2018	Pulmonary & Nasal Drug Delivery	Oct 4th 2018
December 2018	Connecting Drug Delivery	Nov 1st 2018
January 2019	Ophthalmic Drug Delivery	Dec 6th 2018
February 2019	Prefilled Syringes & Injection Devices	Jan 3rd 2019

THE DIFFERENCE OF ONE DRUG DELIVERED

BY TACKLING SILICONE-RELATED CONCERNS.

At BD, we're committed to improving delivery of injectable drugs—for every patient, every time. It's why we partner closely with leading pharmaceutical companies to support their successful development and commercialization of combination products. Our partners have made clear that in some cases silicone, used as standard lubricant in syringes, has been a source of concerns in relation to drug quality and flawless delivery–concerns that could delay drug development timelines, impact drug availability and even lead to recalls of combination products. With BD Neopak™ XSi™, BD has developed an innovative lubricant technology to help alleviate silicone-related concerns while building on gold standards to be most compatible with processes and infrastructures. Discover the difference of better technology. **Discover the new BD.**

Minimizes sub-visible particle generation with BD Neopak™ XSi™[1]

Learn more about our prefilled syringes at **bd.com/NeopakXSi**

BD

[1]BD Neopak™ XSi™ competitive benchmark [internal study]. Le Pont-de-Claix, France: Becton, Dickinson and Company; 2017.

Ompi
Stevanato Group

ALBA: AN OPTIMISED PLATFORM FOR HIGHLY SENSITIVE BIOLOGICS AND THE IDEAL SYRINGE SOLUTION FOR OPHTHALMIC DRUGS

Here, Alessio Bonati, EZ-Fill Product Development & CTS Manager, Ompi, discusses the problematic interactions between drugs and their primary containers. Mr Bonati goes on to introduce the Alba platform, Ompi's range of primary glass containers designed to address these issues and unify drug-container interactions over a product's lifecycle. The platform is particulary well suited to ophthalmic drugs.

The sensitivity of drugs to one or more elements of their primary packaging has always been a potential problem for the pharmaceutical industry. Biologics in particular are highly sensitive, leading to a higher risk of incompatibility between them and their containers (i.e. stability test failures). This potential incompatibility, and the consequent instability of formulations, may have multiple causes; it may be linked to the presence of silicone oil droplets, to an interaction between the drug and the surface of the primary container (leading to the protein aggregation phenomenon), or instead to the particles generated by the rubber in the closure system, such as plungers, stoppers, etc.

> "Ompi decided three years ago to set up a project that could solve the problems associated with the interaction between drugs and their primary packaging."

Another well-known phenomenon representing a potential source of instability is delamination, especially in vials. This occurs because of the interaction between highly aggressive drugs and the internal glass surface of the container, appearing as visible flakes (lamellae).

In 2014, Ompi started the Alba project some market analysis suggested that anything from 5% to 15% of drug formulations had a high degree of sensitivity to one or more of the components of a primary container. On account of the increase of biological drugs, this figure is now in the region of 20-30%. Ompi decided three years ago to set up a project that could solve the problems associated with the interaction between drugs and their primary packaging.

The result has been the EZ-fill® Alba product range, a sterile glass container platform including vials, cartridges and syringes, with equivalent chemical and mechanical characteristics. The platform represents the ultimate primary packaging for biologics and for very sensitive and demanding drugs in general. All the Alba products have an internal layer, based on the standard silicone oil, Dow Corning 360 1000 cst, which is crosslinked with the surface of the glass.

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For syringes and cartridges, the Alba treatment replaces the standard siliconisation normally used to create a lubricant layer (silicone oil and baked-on silicone). This ensures that the number of particles present is normally one order of magnitude lower than standard oil siliconised syringes, simultaneously ensuring high performance in terms of glide and break-loose forces.

In addition, the Alba layer creates a barrier between the drug and the glass, thus reducing the amount of inorganic extractables significantly, compared with a standard bulk container, or even with the glass container before it was formed. The level of specific inorganic extractables (SiO_2, AlO_3, B_2O_3) is also a good indicator of the container's propensity to delaminate. The low concentration of inorganic extractables and the negligible surface corrosion indicate the low delamination propensity of Alba containers.

SOLUTION FOR BIOLOGICS AND OPHTHALMIC

The main technical improvement of the Alba layer is the strength of the chemical bond it forms with the glass surface of the container. This is considerably stronger than the one normally found with standard silicone oil or baked-on silicone. This characteristic is the main reason why there is an extremely low level of particles, together with a very good, stable and functional performance in terms of glide and break-loose forces.

The high performance of the Alba syringe was demonstrated by a comparison study with a syringe with standard silicone oil treatment, using a 1 mL long staked needle format. The syringes were filled with 1.3 mL of filtered (0.22 µm) distilled water and autoclaved for 1 hour at 121°C, which is definitely much more stressful than the standard method described in the US Pharmacopeia. The liquid was analysed by an MFI ProteinSimple 5200 series instrument.

As shown in Figure 1, the number of particles released from Alba syringes is normally one order of magnitude lower than from standard siliconised oil syringes.

The strong interaction of the Alba treatment with the glass surface limits the well-known effect of silicone migration that normally happens during the storage of filled containers. This characteristic leads to increased stability of the functional performances (glide and break-loose forces) of Alba containers.

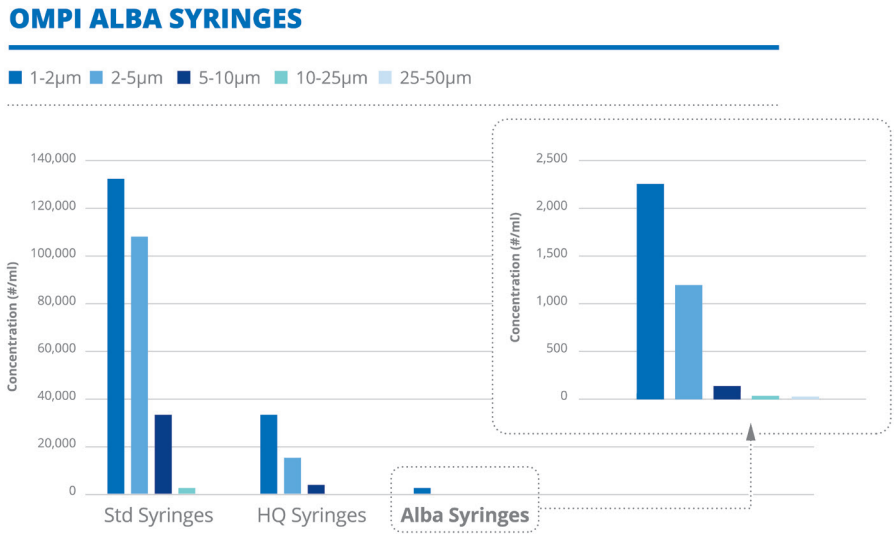

Figure 1: Alba syringe particle release performance in comparison with standard and high quality syringes.

> "The number of particles present is normally one order of magnitude lower than standard oil siliconised syringes."

With vials, for which the lubricant aspects are not relevant, the main added value of the Alba treatment is the barrier effect, preventing the occurrence of delamination after interactions with solutions of aggressive drugs and limiting the migration of inorganic extractables from the glass to the solution.

To demonstrate the barrier effect of the Alba treatment, a comparison study with a bulk vial was performed using a 2R ISO standard format. The vials were filled with 3.6 mL of distilled water and autoclaved for 1 hour at 121°C. The extracted solution was analysed using an ICP-OES iCAP 7400 Thermo instrument.

Figure 2 shows the comparison between bulk vials, Alba syringes and Alba vials, demonstrating the lower inorganic oxides extraction from the Alba vials and the compatibility with Alba syringes.

FROM CONCEPTION TO INJECTION

The Alba platform has also been designed to support new drug development "from conception to injection", with the aim of de-risking any switch from one container

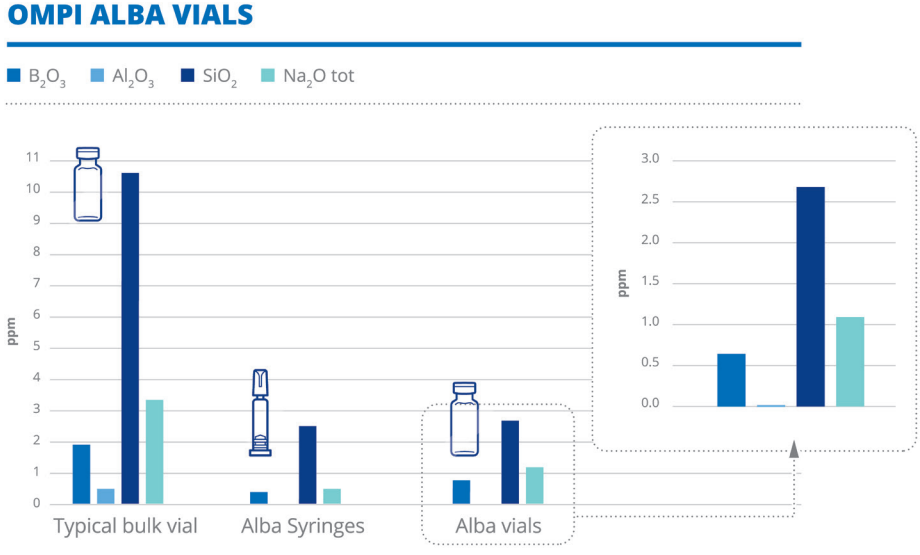

Figure 2: Alba vials inorganic extractables release performance in comparison with bulk vials and Alba syringes.

> "The key benefit of the Alba platform is that all the containers, from vials to syringes and cartridges, show the drug the same contact surface."

format to another. The final form of a drug is usually selected during clinical Phase II.

In fact, when the development process switches from the early phase container (normally a vial) to the final one (syringes or cartridges in many cases) the drug comes into contact with new materials (i.e. silicone oil and tungsten), not present in the relatively simple early phase container, that may compromise drug stability.

Even in the best case scenario – that is, if no problems occur – this switch of container will require a new stability study. In the worst case scenario, the drug would have to be reformulated, increasing both the time-to-market and the development costs.

This situation has been assessed by Ompi, conducting 30 interviews with pharmaceutical industry experts from different companies in 2014. The survey showed that there were different views about the recurrence of delays associated with failed stability tests in prefilled syringes due to drug instability. Nevertheless, all interviewed experts recognised that if a problem occurs at that stage it has a significant impact on the drug development process, leading to additional costs and delays in the product launch.

The key benefit of the Alba platform is that all the containers, from vials to syringes and cartridges, show the drug the same contact surface, thus removing the uncertainties associated with new packaging materials when moving from Phase II to Phase III, thereby de-risking the whole drug development process.

The same concept and the same benefits can also be applied to marketed drugs, when the pharmaceutical company decides to change the packaging, putting the drug in a different container format (e.g. from vial to syringe, or from syringe to wearable device cartridge). In this case, the Alba platform ensures that the switch can be made, drastically reducing the need for new characterisation and testing.

Because a relevant particle release contribution is normally generated by interaction between the rubber components and the drug, Ompi collaborated closely with rubber manufacturers during the Alba platform development, so as to screen the best off-the-shelf components that align with its key benefits. This screening was focused on different aspects: the best performance in terms of low particle generation, lower inorganic and organic extractables, glide performance and the availability of the formulation for all the container formats included in the Alba platform (i.e. vial stoppers, syringe plungers and cartridge plungers). In this way, the value proposition related to the reduced variability of materials in contact with the drug applies to the rubber components as well as the glass barrel.

CONCLUSION

Alba represents a turning point in the development of parenteral primary packaging and is the best-in-class solution for biologics and ophthalmic drugs. The drastic reduction of silicone oil particles and the extremely low propensity to delaminate address some of the key requirements of protein-based drugs and help them to stay compliant with the latest guidelines coming from regulatory bodies.

Finally, the very limited variability of materials in contact with the drug throughout its lifecycle makes the Alba platform a perfect solution to de-risking the development process, saving on costs and securing a fast introduction to the market.

ABOUT THE COMPANY

As part of the Pharmaceutical Systems division of Stevanato Group, Ompi offers the widest range of glass primary packaging from the traditional, such as vials and ampoules, to the high-value, such as syringes and cartridges for autoinjectors and pen injectors. Vials, cartridges and syringes are available, sterile and ready-to-fill (Ompi EZ-fill®).

Ompi boasts a global footprint with high-quality production plants in Europe (Piombino Dese and Latina in Italy, Bratislava in Slovakia), Mexico (Monterrey), China (Zhangjiagang, near Shanghai) and a brand new plant in Sete Lagoas (Brazil).

ABOUT THE AUTHOR

Alessio Bonati holds a Master's degree in Electronic Engineering from the University of Ferrara and an MBA degree from Bologna Business School. Over the last 11 years, Mr Bonati has worked for international companies in several different businesses, but always with roles related to portfolio management and business development. He is currently EZ-Fill® Product Development & Customer Technical Support Manager for Ompi, the pharmaceutical glass primary packaging company, responsible of new product developments for all the business lines related to Ompi's portfolio, from vials to cartridges and syringes, all in a "ready to use" format.

Stevanato Group

PHARMACEUTICAL SYSTEMS

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Using the same container lining throughout development improves life-cycle management and avoids validation failures. Alba platform maintains the advantages of siliconized containers, while guaranteeing ultra low particles quality.

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IMPROVING PATIENT EXPERIENCE WITH PREFILLED SYRINGES AND NEW ONBOARDING TECHNIQUES

In this article, Paul Sullivan, Associate Director of Business Development, Noble, outlines how the growing trend towards patient self-injection, outside of the clinical setting, places an ever greater emphasis on quality training and onboarding. Mr Sullivan specifically explains how such training can help overcome the issue of patient needle fear or anxiety.

The rapid growth of innovative biologic therapies, currently 20% of the pharma market and the fastest growing part of the industry,[1] has fostered the need for innovative drug delivery systems. This, combined with a strong trend towards patient self-administration using prefilled syringes (PFS), has led to the growth of the PFS market, projected to reach global sales of $7.9 billion by 2024.[2]

> "Every year, more patients are introduced to injection devices for home treatment. With self-injection comes a variety of emotional and environmental factors, potentially causing inconsistencies in treatment."

For some patients diagnosed with chronic medical conditions, self-administration using drug delivery devices is often a necessary component of a successful treatment programme. Every year, more patients are introduced to injection devices for home treatment. With self-injection comes a variety of emotional and environmental factors, potentially causing inconsistencies in treatment. Recent studies have shown that many patients are struggling to follow all of the required steps outlined in instructions for use (IFU) documents.[3]

THE VALUE OF PROPER ONBOARDING

As the preference remains to self-administer therapy, pharmaceutical manufacturers, physicians, patient advocates, payers and other industry stakeholders have come to realise the importance of training programmes designed to help patients properly self-administer treatments in order to promote positive patient outcomes and effective disease management. Many studies suggest that without proper training during the onboarding process, defined as the first 30 to 90 days of treatment (Figure 1), patients are more likely to drop off from therapy or incorrectly use drug delivery devices, such as PFS and other forms of self-administration.[4]

A focus on the human factors at work here is crucial. Classical conditioning studies have shown that experience and familiarity reinforce patient behaviour. In contrast, uncertainty leads to a lack of adherence. All patients are aware of the long-term benefits of pharmacotherapy, however, although specific medications are effective in combating disease, their full benefits are often not realised because a substantial subset of patients do not take their medications as prescribed.

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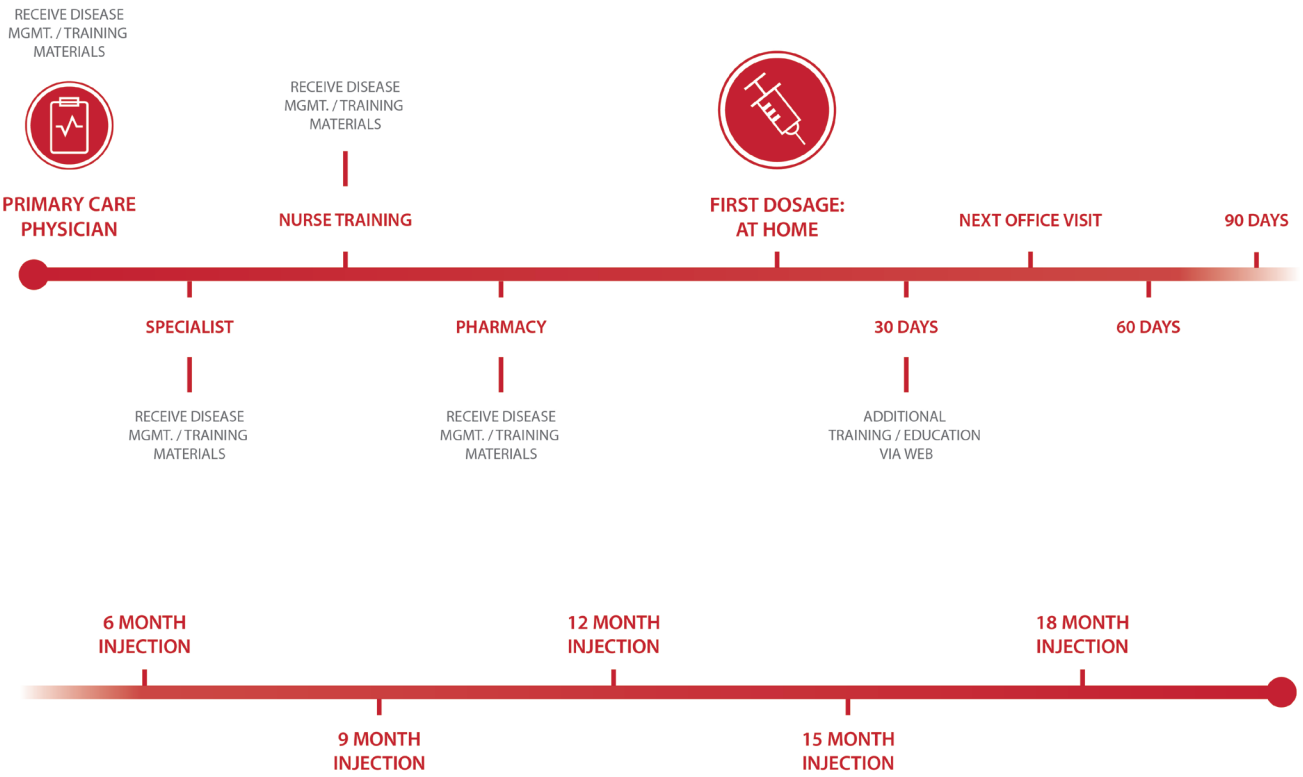

Figure 1: Timeline showing onboading including initial and subsequent injections at different dosing frequencies.

> "One specific form in which poor adherence can manifest itself is needle/injection anxiety, also known as belonephobia. Many people fear needle-sticks to some extent, but when this fear becomes persistent, excessive and unreasonable, the fear becomes a phobia."

Factors contributing to poor medication adherence are myriad,[5] including but not limited to:

- Patient related:
  - Suboptimal health literacy
  - Lack of involvement in the treatment decision making process.
- Physician related:
  - Prescription of complex drug regimens
  - Communication barriers
  - Ineffective communication of information about adverse effects
  - Provision of care by multiple physicians.
- Healthcare system related:
  - Office visit time limitations
  - Limited access to care
  - Lack of health information technology.

NEEDLE/INJECTION ANXIETY

One specific form in which poor adherence can manifest itself is needle/injection anxiety, also known as belonephobia. Many people fear needlestick injury to some extent, but when this fear becomes persistent, excessive and unreasonable, the fear becomes a phobia. The problem arising from such phobia is exponentially exacerbated in patients who are called upon to perform self-injection using PFS devices.

Patients with needle anxiety require reassurance about the prevalence of needle fear and clarification about methods available to counter their reactions. Healthcare practitioners can communicate empathy and respect for the patient's feelings, and institute a number of potentially useful strategies to reduce the level of fear they are experiencing. Steps that have been proposed include recognition and relaxation techniques such as cognitive behavioural therapy; adoption of control and preparation strategies such as having a support person present during injection; and graded exposure.[6] The utilisation of innovative onboarding programmes can clearly serve as an integral component to successful patient compliance.

The benefits of innovation in PFS devices can be appreciated by assessing research undertaken to gauge the relationship between anxiety, injections and device training. According to a study published by Elsevier Science Ireland, injection anxiety could result in decreased compliance, leading to 45% of patients skipping or avoiding injections due to anxiety or fear.[7] Based on a literature review and R&D activities to develop the most effective PFS trainers (including a needle insertion force profile analysis, using cadavers and 18, 25 and 30 gauge PFS, performed at a Florida hospital), a study conducted by Noble further explored the relationship between anxiety, injections and PFS training devices that simulate real device characteristics.[8]

The aim of the study was to investigate whether needle-naïve participants using a PFS training device demonstrated decreased anxiety compared with users who did not utilise a training device. A total of 45 respondents were randomly assigned to one of three groups: participants receiving no training; participants receiving 'traditional' training (i.e. in-office training and IFU); and participants receiving traditional training plus a PFS training device. In addition, the participants were surveyed at three points in time: before, during and after the mock injection.

The study produced several notable findings. Most significantly, coupling traditional training methods with PFS

training devices utilising needle simulation technology was found to reduce anxiety over traditional training in isolation or no training at all. Feedback from the study reported that:

- 73% of users reported that only having IFU and no other training materials would increase their anxiety.
- 64% of users reported having a training device to practice with at home would help decrease anxiety.
- 89% of users reported it is very important to have the most realistic training possible.
- 87% of users reported it is important to have a needle tip that closely simulates a real needle.
- 89% of users reported a better understanding of a real injection when having a simulated syringe during training.

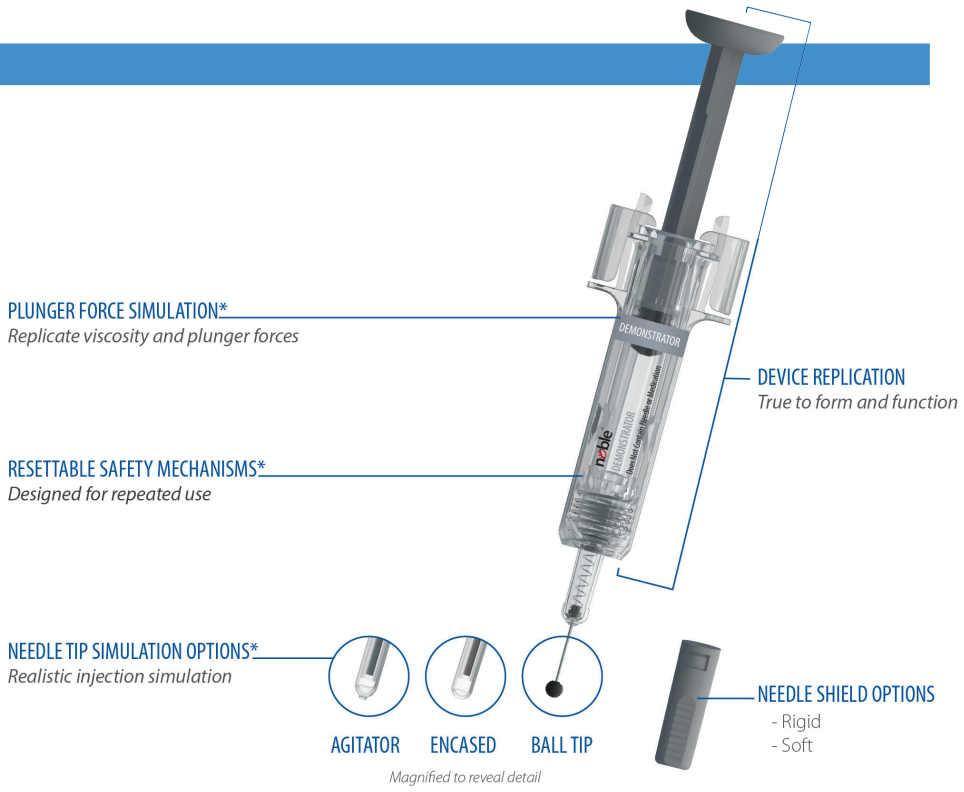

Figure 2: Noble offers a variety of innovative features designed to simulate BD UltraSafe™ with the goal of familiarising and preparing patients to self-inject

Advances in PFS training technology are clearly important with regard to how they simultaneously enhance the patient experience and reduce patient anxiety. In a Noble user study, designed to evaluate the effectiveness of training, participants completed a multi-step injection process, during which errors were observed and tabulated.[9] A post-injection interview and survey were conducted to evaluate the effects of training methods on confidence, anxiety and injection outcomes. Across all groups tested, independent of education, age, gender and salary, confidence increased and anxiety decreased in tandem with the extent of training use, while errors decreased with the use of error-correcting devices such as those provided by Noble's proprietary technology.

SOLVING SELF-ADMINISTRATION CHALLENGES WITH EFFECTIVE TECHNOLOGY AND TRAINING

But how, specifically, can technology be integrated most effectively? Noble continues to push the boundaries of the answer, developing novel PFS trainers and onboarding platforms, in collaboration with device design companies, to help patients with both initial device training and the overall onboarding process (Figure 2). The goal of these initiatives is to counteract self-injection training decay to improve adherence and, ultimately, the therapeutic outcomes.

Some of the proprietary PFS training device enhancements at Noble include tailored plunger resistance and breakout forces, accurately simulating actual PFS resistances and drug viscosity, and needle insertion technologies, simulating needle sensation and force. These features habituate patients early on to the feel of the injection, enhancing its familiarity. Noble is collaborating with pharmaceutical teams to improve these outcomes through "true to form and function" platforms, including safety and standard PFS trainers as well as "Smart Injection Pads" (wirelessly connected error-correcting injection training pads used for instructing, tracking, monitoring and collecting data to assist in improving adherence).[10]

These error-correcting features are complemented by plunger force/viscosity simulation, needle force and feel simulation, aimed to provide users with realistic simulation. Multisensory features, designed to provide patients with the most realistic simulation possible, include:

- Agitator needle simulation tips, designed to replicate the feel and forces involved for manual insertion.
- Resettable safety systems, allowing users to train multiple times prior to an actual injection.
- Device replication, designed to simulate all aspects of the patient experience, including:
  - design form
  - colour adjustments
  - window size
  - tactile feedback
  - cap removal force
  - actuation force.

The sophistication, attention to detail and level of functionality of these trainers offers several advantages over traditional saline solution injection demonstration procedures. Due to there being no actual injection involved, there is no risk for misuse during the training regimen. Also, it is more cost-effective to utilise a reusable device such as a trainer, rather than expend an actual syringe that must be discarded following the demonstration.

Research has also determined a link between device training and patient compliance. Based on a literature review and other activities, a study conducted by Noble sought to further explore the

"Across all groups tested, independent of education, age, gender and salary, confidence increased and anxiety decreased in tandem with the extent of training use, while errors decreased with the use of error-correcting devices such as those provided by Noble's proprietary technology."

relationship between device training and patient compliance.[11] The objective was to investigate if compliance differs between patients who trained with a needleless training device versus those who did not.

The research consisted of a 31 question online survey to patients who regularly self-administer a prescription injection medication. Patients were asked detailed questions related to the training and onboarding of their injectable prescription drug. Amongst the findings it was discovered that:

- 61% of patients do not completely read the IFU.
- 56% of patients have never used a trainer.
- 90% of patients rated the value of a trainer "7" or higher on a scale of 1 to 10.
- 74% of patients reported that, in hindsight, they should have used a training device.
- As respondent age increased, the perceived value of device training increased.
- Patients who are recommended to use a trainer by their healtchcare provider and use it as recommended are more compliant.
- Patients who use a trainer were found to be more compliant overall and less likely to discontinue treatment.

In light of all of these insights, and the continued growth of the PFS market, ensuring compliance will continue to be a priority. The future is likely to bring additional benefits to pharmaceutical companies and healthcare providers utilising innovative, realistic onboarding training methods and smart devices with PFS to help ensure optimal patient care.

ABOUT THE COMPANY

Noble® works closely with the world's leading pharmaceutical and biotechnology companies to develop autoinjector, prefilled syringe and respiratory device training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes. Cross-disciplinary designers and engineers provide fully customised solutions from the first concept sketch through production, in both regulated and non-regulated environments.

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ABOUT THE AUTHOR

Paul Sullivan is Associate Director of Business Development at Noble, a product development company with a focus in designing and manufacturing drug delivery training and patient onboarding solutions. Prior to Noble, Mr Sullivan worked at Informed Medical Communications, as Director of Business Development and Client Service and before that, as a pharmaceutical sales representative with Procter & Gamble. He holds a Kinesiology degree with Honours from the University of Western Ontario, Canada.

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safer, easier and faster drug delivery

SUPERCAPSYRINGE® PASSES THE TEST

In this article, Hans Peter Manser, Chief Operating Officer and Business Director, Weibel CDS, alongside Lisa Lippuner and Sarah Raible, both BSc Nursing at FHS St Gallen, University of Applied Sciences, Switzerland, discuss the findings of a study conducted to test the qualities of Weibel's SuperCapSyringe®.

Weibel CDS, the developer and producer of the SuperCapSyringe® (Figure 1), claims that the product reduces the risk of contamination, handling errors and needlestick injuries. The Health Department of FHS St Gallen, University of Applied Sciences, Switzerland conducted a series of tests to verify these claims. This work was carried out by Lisa Lippuner and Sarah Raible, under the leadership of Prof Heidi Zeller, PhD.

"Following Weibel's mission to support safer, easier and faster preparation and administration of drugs, all functions and parts needed for a specific drug application are integrated into one product."

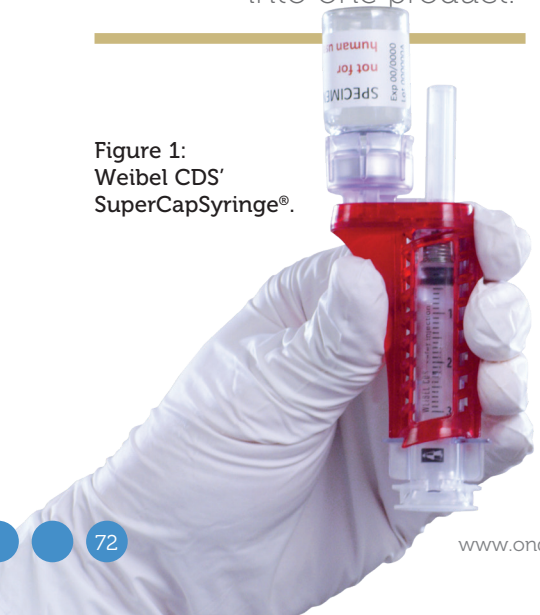

Figure 1: Weibel CDS' SuperCapSyringe®.

"The SuperCapSyringe® product family works as an add-on to a standard vial, upgrading it effectively into a prefilled syringe."

BACKGROUND

The SuperCapSyringe® product family works as an add-on to a standard vial, upgrading it effectively into a prefilled syringe. Based on a modular design, the syringe is fully adaptable to a client's application needs. It is supplied in different sizes and with staked needles including a passive safety device.

Following Weibel's mission to support safer, easier and faster preparation and administration of drugs, all functions and parts needed for a specific drug application are integrated into one product. The user only opens one package and the drug is handled entirely within a closed system in order to reduce the risk of contamination, handling errors and needlestick injuries, as well as being a quicker and easier process (Figure 2).

With SuperCapSyringe®, the drug is contained in its original vial, which is attached to the vial adaptor. The drug is then drawn into the SuperCapSyringe® for injection. After withdrawal of the syringe a passive safety system slides over the needle providing the highest safety levels against needlestick injuries.

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Under the title "*Standard versus SuperCapSyringe® – Comparison between the standard, open preparation of parenteral injections versus the SuperCapSyringe®*", Lisa Lippuner and Sarah Raible conducted a study to ascertain the truth of Weibel's claims. The criteria to be tested were:

- Contamination
- Dosing Accuracy
- Timing.

The goal was to identify which method offered the greatest patient safety for the lowest cost and time required.

THE TEST

Method

Within an evaluation study the participants were instructed to carry out the preparation and injection process to verify the stated claims. Each participant was asked to carry out 50 preparations and injections using the standard, open method (Figure 3) as well as with the SuperCapSyringe® (Figure 4). In order to verify dosing accuracy, the authors defined a prescription to be followed by the participants. Prior to each preparation, a fluorescent media was applied to the hands of the proband allowing the identification of possible contamination.

Figure 2: The SuperCapSyringe® is entirely contained in a single package.

Video sequencing enabled exact timing of each preparation, allowing for a calculation of the cost per preparation and injection. This cost was added to the material and general cost to generate a total cost perspective.

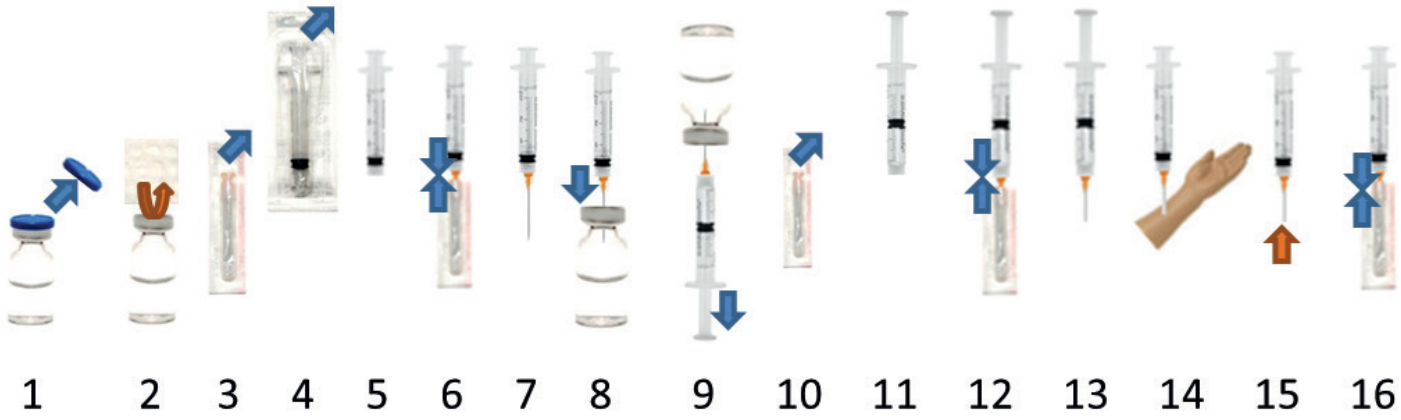

Figure 3: The standard, open preparation and administration of liquid drugs requires as many as 16 individual steps.

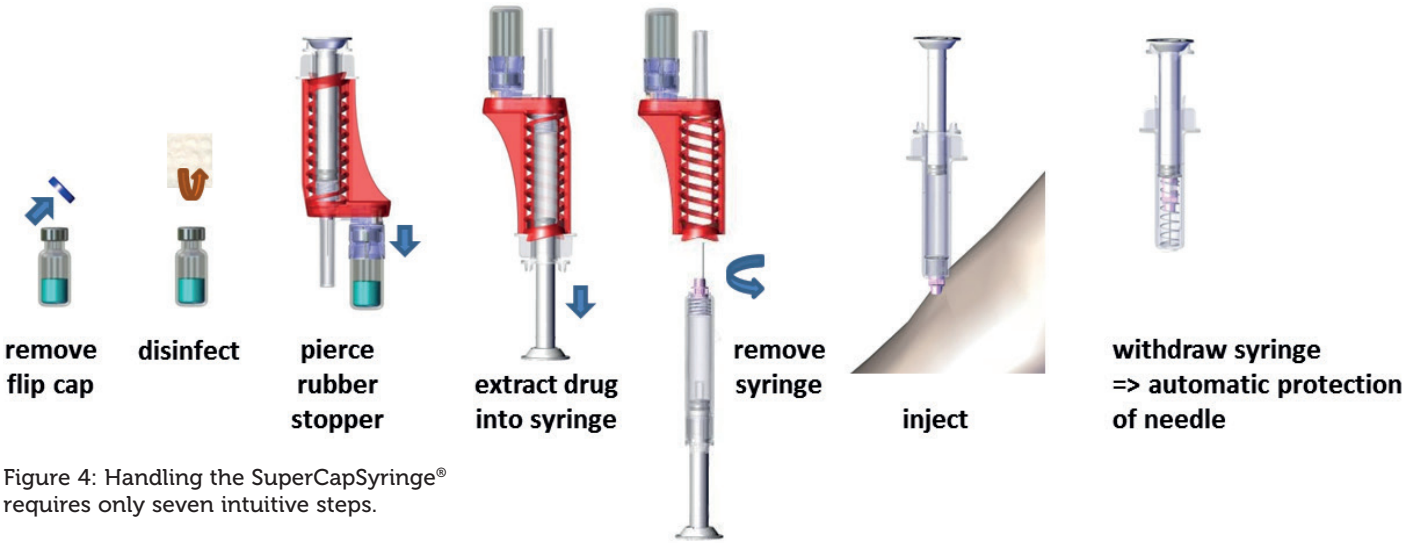

Figure 4: Handling the SuperCapSyringe® requires only seven intuitive steps.

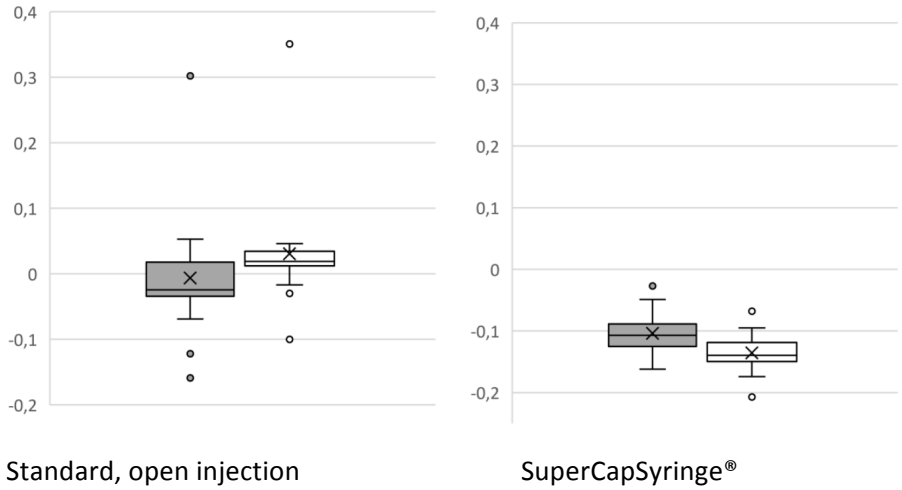

Figure 5: A comparison of dosing accuracy between the standard, open injection method and SuperCapSyringe®.

Contamination

Healthcare personnel are subjected to physical and mental stress, as well as time pressure. Due to this lack of time, the risk of poor adherence to proper hygienic guidance increases.[1] Manipulation during the preparation of injectable drugs can influence sterility and cause contamination. Often contamination is caused by contacting the syringe luer cone, as well as the cannula hub, coming into contact with either hands or surfaces.[2]

The test was set up to identify contamination on the plunger rod, the luer cone and the cannula. Especially on the luer cone and cannula the result was extraordinary as for the standard, open injection contamination occurred in between 9% to 40% of cases, whereas there was no contamination observed throughout the entire test for participants using the SuperCapSyringe®.

Dosing Accuracy

Using a prescription of 1 mL the Standard Deviation for the dosing accuracy was at 0.091 for the standard, open injection and at 0.032 for the SuperCapSyringe®. As can be seen in results displayed in Figure 5, the homogeneity of an administration of 1 mL is clearly better using the SuperCapSyringe®.

Economic Aspects

The average time required for the preparation was 62 seconds for the standard, open injection, and 34.5 seconds for the SuperCapSyringe®, a reduction of almost half. With the learning curve considered, this value dropped to less than 30 seconds for the SuperCapSyringe®, whereas for the standard, open injection the study observed no noticeable change over time.

The WHO estimates that 16 billion injections are administered worldwide every year. Considering that number of injections, the potential for saving time is immense. A total cost of ownership (TCO) calculation resulted in a total saving of 42% for the SuperCapSyringe®. This calculation included a comparison of device cost as well as the saving in labour cost.

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ABOUT THE AUTHORS

Hans Peter Manser, Chief Operating Officer and Business Director at Weibel CDS, holds a diploma in Business Administration and Applied Technical Management. After perennial stays in the UK, Australia, US, France and Germany, he assumed sales management and executive functions in the communications industry with global responsibilities. Mr Manser transitioned to the pharmaceutical packaging business in 2001 and subsequently joined Weibel CDS in May 2011 as Business Director responsible for setting up and management of all administrative and commercial aspects of the company.

Lisa Lippuner, BSc in Nursing, Health Department of FHS St Gallen, University of Applied Sciences, Switzerland, has had internships in paediatrics at Münsterlingen Cantonal Hospital, medical at Grabs Hospital, rehabilitation at the Zihlschlacht Rehabilitation Clinic and urology (surgery) at the Grisons Cantonal Hospital.

Sarah Raible, BSc in Nursing, Health Department of FHS St Gallen, University of Applied Sciences, Switzerland, is a medical practice assistant, having performed internships in orthopaedics, medical, acute psychiatry and geropsychiatry at the Cantonal Hospitals in Thurgau and Münsterlingen.

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Nemera

AUTOINJECTOR DESIGN ADJUSTMENT TO CONTROL NEEDLE INSERTION AND INJECTION SPEED

Pascal Dugand, Technology Product Manager, Nemera, relates a study conducted by Nemera to determine a way to optimise the transition from needle insertion to syringe emptying for parenteral devices. This piece was originally presented as a poster at PDA Vienna 2017.

INTRODUCTION

Subcutaneous is a common route of administration for parenteral drug delivery. Injection is performed by patients or healthcare professionals using syringes or other delivery devices, such as autoinjectors. Due to the increasing number of marketed and in development biologics, more treatments require subcutaneous injection of a larger dose, greater than 1 mL.

It is observed that larger doses of viscous formulations lead to higher viscous back forces. Usage of higher energy levels to deliver viscous formulations could result in higher shocks on the syringe, especially at the end of syringe insertion and start of syringe emptying.

Controlling needle insertion speed can reduce these shocks. Lowering this shock will allow a smooth transition to syringe emptying.

OBJECTIVE

Nemera conducted a study with the objectives to:

- Estimate needle insertion speed and energy level transmitted to the syringe by calculation.
- Propose a practical way to optimise injection devices allowing smooth transition between needle insertion and syringe emptying, especially for viscous, large dose formulations and thin needles.

METHOD

Firstly, the theoretical calculation approach was based on a 2.25 mL syringe. Insertion speed, and energy transmitted to the syringe were calculated.

In the case of stiff spring usage, it is possible to lower the speed and energy by:

- Specific cam profile for needle insertion
- Using a counter spring back force.

In a second step, tests were performed to verify the theoretical calculation approach (Figure 1).

THEORETICAL APPROACH

First part of calculation is aiming to predict needle speed during the insertion phase. After this phase, the plunger pusher is colliding with the plunger rod and injection begins. Calculations are based on the models shown in Figures 2-4 and the equations:

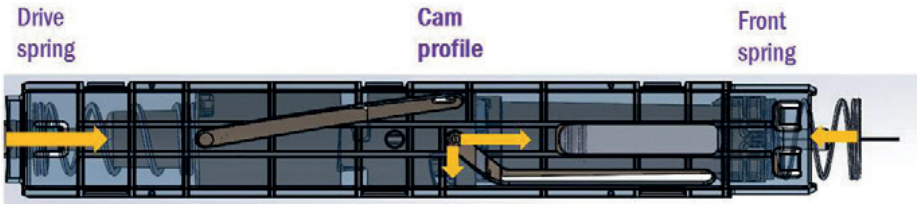

Figure 1: Injection sequences for injection force measurements.

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$$\begin{cases} m.\frac{\partial^2\lambda}{\partial t^2} = -z.k + F_z \text{ Translation on } \vec{z} \text{ axis } Eq_1 \\ J.\frac{\partial^2\theta}{\partial t^2} = R.F_\theta \quad \text{Rotation on } \vec{z} \text{ axis: } \quad Eq_2 \end{cases}$$

With:

- J, inertia of parts in rotation,
- R, radius of the cam shaft
- m, mass of translating part
- k, stiffness of the equivalent spring
- λ, distance from equilibria position λ=(L0– z).

Friction was not taken into account.

With the equation of the cam:

$$\begin{cases} \theta(z) = f(z(t)) \; Eq_3 \\ F_\theta = F_z.\frac{\partial z}{R.\partial\theta} \quad Eq_4 \end{cases}$$

By combining the three previous equations:

$$m.\frac{\partial^2\lambda}{\partial t^2} = -\lambda.k + J.\frac{\partial^2\theta}{\partial t^2}.\frac{\partial\theta}{\partial z} \; Eq_1{+}Eq_2{+}Eq_4 \Rightarrow Eq_5$$

The final differential equation is:

$$m.\ddot{z} = J.(f'(z).\ddot{z} + f''(z).\dot{z}^2).f'(z) - \lambda.k$$
$$Eq_5{+}\,Eq_3 \Rightarrow Eq_6$$

Solving this differential equation by numerical calculation provides solutions for the axial position and axial speed at each step of needle insertion stroke. Figure 5 shows that the device with a cam shaft shows a 23% theoretical reduction of needle insertion speed.

PRACTICAL APPROACH

Physical tests were then carried out and the results compared with the theoretical approach.

Test sample properties:

- 2.25 mL
- 27G ½" TW
- Filled with water
- 30N drive spring.

Needle insertion speed was measured with a camera:

- Without cam: up to 3.5 m/s
- With cam: 0.9 m/s.

Compared with the theoretical calculation, the needle insertion speed decreased due to friction in prototype parts, not considered in the mathematical model.

Without a cam, jetting is observed at the start of injection. This jetting can be explained by the high impact energy transmitted by the plunger rod to the plunger stopper at start of injection, once the needle is inserted.

With a cam, jetting is not observed at the start of injection. This can be explained by the lower impact energy transmitted by

Figure 2: Real model.

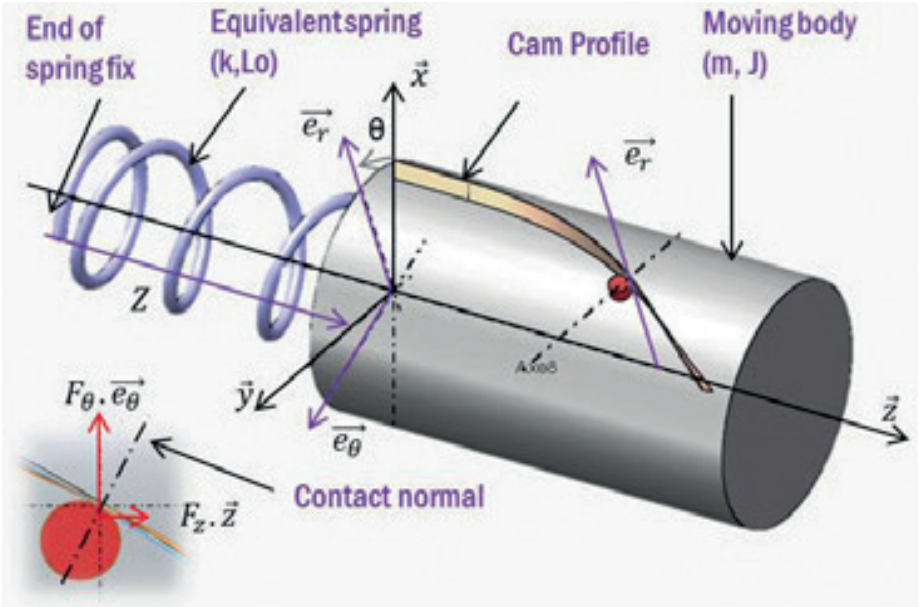

Figure 3: Mathematical model.

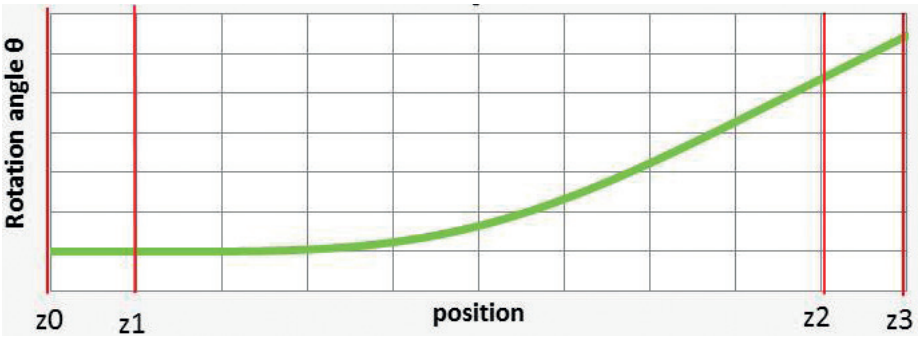

Figure 4: Rotation angle by syringe position.

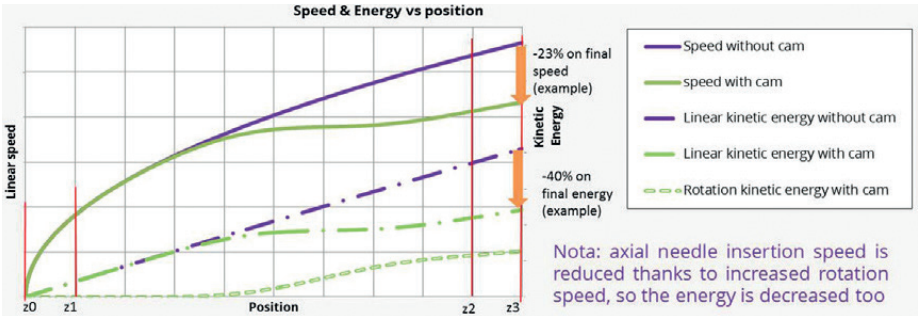

Figure 5: Needle insertion speed and energy, with and without a cam.

the plunger rod to the plunger stopper at the start of injection.

CONCLUSION

- Needle insertion speed profile can be tailored to minimise the shock on a syringe, which can consequently reduce initial peak injection flow.
- New generations of autoinjectors have to deliver larger volumes, often of highly viscous formulations. Controlling needle insertion speed is a way to have a smoother transition to injection.

ABOUT THE COMPANY

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

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

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

ABOUT THE AUTHOR

Pascal Dugand graduated as a Polymer Engineer from EAHP (Strasbourg, France). He holds a Master's in Polymer mechanics and joined Plastic Omnium in 1990 where he started in Development and Innovation. In 2004, the medical division of Plastic Omnium was acquired by Rexam, and more recently the four drug delivery devices plants, including the Innovation Centre became Nemera. Today, Mr Dugand is an experienced medical device developer engineer specialised in the development of parenteral drug delivery devices. He worked on the development of Nemera's own IP products, including the Safe'n'Sound® safety device and Safelia® autoinjector, as well as working on several customer injectable product developments.

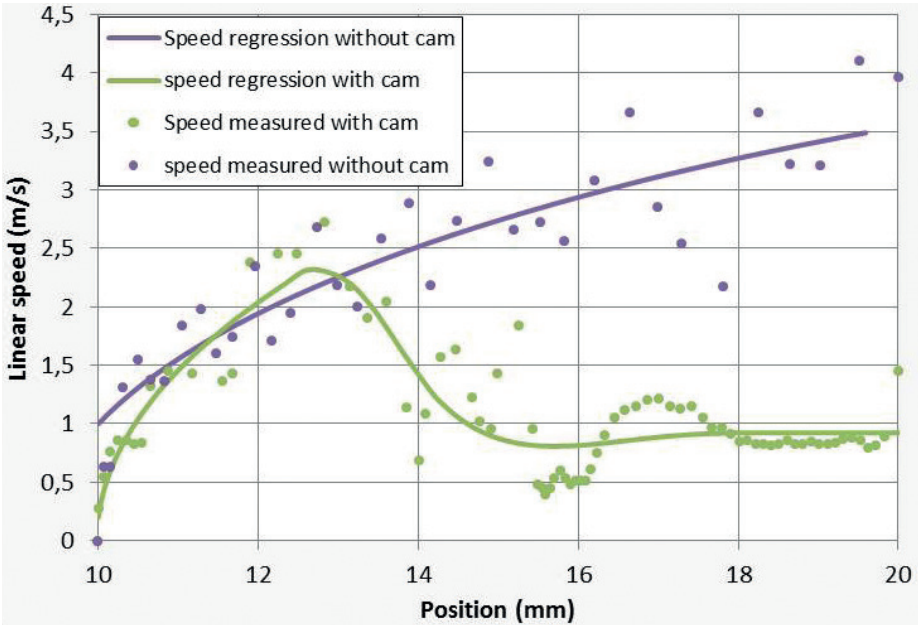

Figure 6: Measured needle insertion with and without a cam.

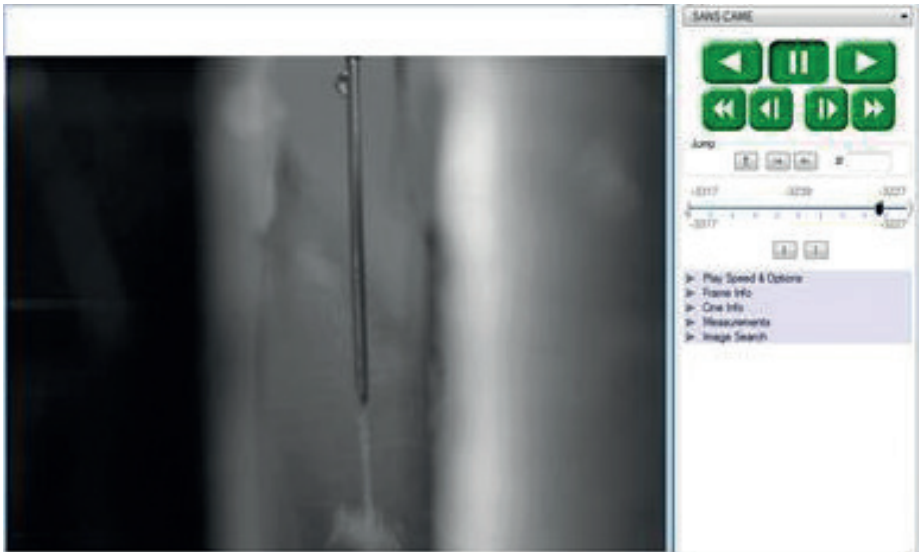

Figure 7: Start of injection just after needle insertion without a cam.

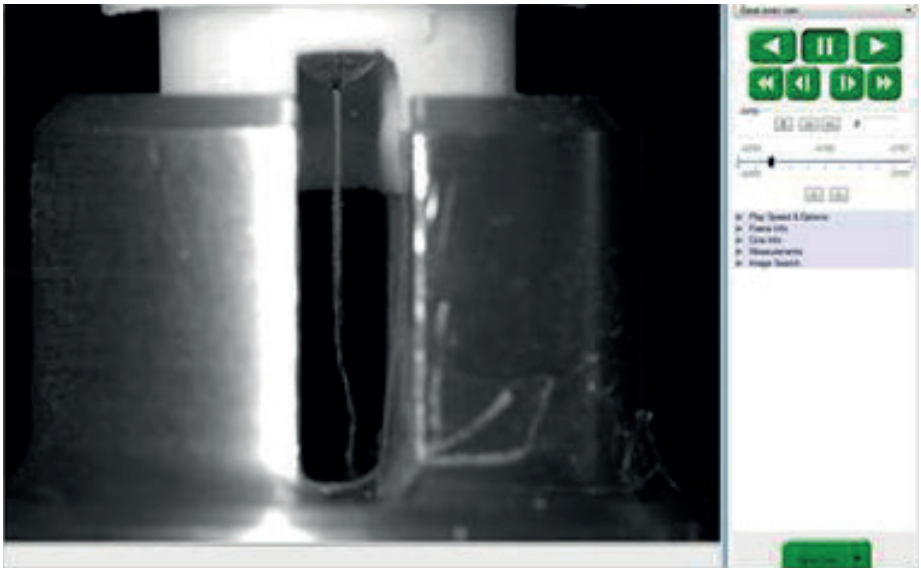

Figure 8: Start of injection just after needle insertion with a cam.

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DIVIDELLA
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DIGITISATION & INDUSTRY 4.0 IN PHARMA PRODUCTION

Christoph Hammer, Chief Executive Officer, Dividella, gives an overview of the Industry 4.0 concept, and its pharmaceutical application Pharma 4.0. Furthermore, Mr Hammer provides examples of what Pharma 4.0 can offer, discussing solutions shown at Interpak 2017, Düsseldorf.

OVERVIEW

The current trend towards digitisation, including the use of big data and interconnectivity, offers potent advantages for the pharma industry, particularly when it comes to embracing Industry 4.0 design philosophies. To fully realise the potential of emergent "smart" technologies, however, a modular approach must be adopted at every level, from design concepts to engineering, construction and processes. Modularity is essential to fully exploit the connectivity and data sharing capabilities of these technologies, an inherent aspect of the Industry 4.0 concept and its Pharma 4.0 derivative.

> "By taking a modular approach when adopting digitised pharma, production one is able to achieve greater interconnectivity, interoperability, data sharing and information transparency."

MODULARITY AND DIGITISATION

In essence, by taking a modular approach when adopting digitised pharma production, one is able to achieve greater interconnectivity, interoperability, data sharing and information transparency. In turn, this allows for a much higher level of technical support and enables a more decentralised decision making process.

Dividella, as a member of Medipak Systems Group, is part of a modular ecosystem of related skills and competences. Dividella's process and machinery expertise is combined with the specialities brought by Rondo, Werum IT Solutions, Fargo Automation, Mediseal and Seidenader, using the latest information and communications technologies. Together these companies are making a concerted move towards an Industry 4.0 future, thus enabling them to provide a wider range of innovative solutions on materials and packaging, together with easier upgrade and expansion paths.

INDUSTRY 4.0

Industry 4.0 is the fourth revolution in production, following on from mechanisation, mass production and computerised automation. It describes the adoption of data exchange and artificial intelligence (AI) in manufacturing technologies, leveraging "cloud" data storage, cognitive and cyber-physical computing and the Internet of Things (IoT).

Industry 4.0 extols the implementation of smart factories, structured around modular production lines. Such factories would employ cyber-physical systems (those formed of integrated computing, networking and physical components) to monitor physical processes, utilise virtual models to maximise productivity, and operate on decentralised decision making models. Cyber-physical systems can intercommunicate in real time over the IoT, enabling users to offer and share internal and cross-organisational services across the whole production chain.

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In order to harness the advantages of the Industry 4.0 concept, industrial solutions must obey four basic principles:

1. **Interoperability**: The capability of machines and processes to directly interact with one another.
2. **Information transparency**: The ability of information systems to create virtual models by combining digital plant systems with real time sensor data to create data that can be readily analysed and acted upon.
3. **Technical assistance**: The ability to automatically aggregate and visualise information to solve urgent problems, and also create cyber-physical systems that can take on problematic tasks.
4. **Decentralised decisions**: The usage of cyber-physical systems that are able to make decisions and perform tasks autonomously, only delegating to humans in exceptional circumstance.

PHARMA 4.0

"Pharma 4.0" refers to the application of Industry 4.0 concepts to the pharmaceutical industry, encompassing everything from outflowing goods to the feedback of real time patient data. Pharma 4.0 is, in part, driven by an overall trend in the pharmaceutical and healthcare industry towards more individualised, patient-specific therapies that is creating a growing need for quality data and diverse formats. This new dynamic comes with ever more pressure to make smarter use of data to avoid production bottlenecks.

This trend towards personalised therapies requires a shift away from traditional mass production processes, which tend to be inflexible in design, to manufacturing individually tailored products. This transformation depends on changing the perception of data and content in three main areas:

- **Moving away from paper**: Many so-called "state of the art" execution systems still rely on paper based processing for GDP (Good Documentation Practice) record keeping. Pharma 4.0 means handling GDP compliant documentation in new electronic formats.
- **Merging data**: GDP relevant records will increasingly be defined by application, making the differentiation between GDP and non-GDP less relevant, requiring greater security for non-GDP areas.
- **Global collaboration**: Freeing content and data from company silos will allow them to be securely shared among virtual teams that can be quickly changed and reconfigured.

INTERPAK 2017

Dividella presented several Pharma 4.0 solutions at Interpak 2017 in Düsseldorf.

Smart Device Control

A Dividella NeoTOP x TopLoad packaging machine for combination products (Figure 1), controlled and monitored remotely via a smart device. With the aid of the device, multiple production units can be scheduled, coordinated and controlled in parallel. The solution, based on HTML 5, is compatible with all systems and mobile terminals.

Condition Monitoring & Predictive Analytics

Dividella also presented a prototype solution for remotely monitoring the status of the NeoTOP x using data captured in real time. The solution then applies algorithms to generate forecasts which predicts critical changes, thus allowing for corrective interventions to be scheduled before any actual failures occur.

Figure 1: Dividella NeoTOP x – a highly flexible TopLoad packaging machine for processing small to medium lot sizes, equipped with a collaborative robot for the greatest possible filling flexibility.

"Pharma 4.0 is, in part, driven by overall trend in the pharmaceutical and healthcare industry towards more individualised, patient-specific therapies that is creating an ever greater need for quality data and diverse formats."

Figure 2: Rondo uses NFC chips integrated in the pack to improve patient communication. The NFC chip transmits its information as soon as a 'read' terminal is within range.

Figure 3: Werum's new Plug & Produce solution allows for fast and easy integration of machines and automation systems into a pharmaceutical production environment.

Smart Packaging

Product personalisation and product security can be taken to new levels by enabling smart communication between the packaging and the patient, as well as by enhancing communication with the machines in the production process. In addition to the actual product, consumers can request additional services via the package, which also communicates with the packaging machine to control settings for individual, personalised products. These solutions use NFC chip technology developed by Rondo (Figure 2).

Plug & Produce

Vertical integration (creation of a standardised interface between production machines and control systems) is fundamental in implementing Pharma 4.0 solutions. Plug & Produce, developed by Werum, is like connecting USB devices, making it possible to 'plug and play' systems or packaging machines within the overall networked system (Figure 3).

Enterprise Manufacturing Intelligence

Enterprise Manufacturing Intelligence (EMI) can improve product quality (process stability) and productivity (process efficiency) by supervising production almost in real time. Processes can be continuously verified, and subsequently the production data can be applied to support decision making. The customer can make better informed decisions on process stability and process efficiency, to enhance both quality and productivity.

ABOUT THE COMPANY

Swiss-based parenteral packaging specialist Dividella has built up an impressive reputation across the global pharmaceutical industry for the quality and effectiveness of its TopLoad cartoning machines. This success has been established on a holistic approach that recognises that machine and pack design go hand in hand.

Dividella's production units at Grabs in Switzerland exclusively design and manufacture machines for packaging pharmaceutical products, with total focus on the specific requirements of parenteral pack products, i.e. liquid pharmaceuticals that are packaged in syringes, flasks, vials, autoinjectors and the like. These are highly sensitive products that demand thoroughly developed solutions.

MEETING THE INCREASING REQUIREMENTS FOR HUMAN FACTORS CONSIDERATIONS

Human factors engineering (HFE) is now an essential requirement for all new drug delivery combination product approvals to ensure devices are safe and effective for users. This can represent a significant challenge for pharmaceutical companies, which need to make sure that any changes required happen as early as possible in the development process to avoid costly mistakes later on. Karen Guerrero, PhD, Medical Affairs Safety Platform Manager at BD Medical – Pharmaceutical Systems, outlines how they can help to streamline HFE for pharmaceutical manufacturers.

In the past, drug delivery devices were considered primary or secondary packaging, with little effort given to understanding how people interacted with the technology, or the resulting impact of user interface design. Today, it is recognised that drug delivery device presentation can have a significant impact on convenience, ease of use and acceptance by patients who self-inject. Devices represent a critical part of the user experience, and must be proven safe and effective to use prior to receiving regulatory approval.

Assessing the safety and efficacy of device use is the focus of human factors engineering (HFE), and is a required component of the regulatory approval process. HFE is defined as "the application of knowledge about human behaviour, abilities, limitations, and other characteristics of medical device users to the design of medical devices, including mechanical and software-driven user interfaces, systems, tasks, user documentation, and user training to enhance and demonstrate safe and effective use."[1]

Today's regulators demand more stringent requirements to ensure medical devices are safe and effective for the intended users, uses and use environments (Figure 1). HFE is now a prerequisite for all new medical device and drug device combination product approvals.

With the combination product market expected to reach US$177.7 billion (£128.8 billion) by 2024,[2] and more combination products targeted for home use by patients and lay caregivers, pharmaceutical manufacturers will need to make significant investments in HFE to secure approval for their new drug-device combinations. Moreover, with the inevitable increase in market penetration by biosimilars,[3] the usability, acceptability and favourability of a manufacturer's delivery device could either increasingly serve as a differentiator in crowded therapeutic spaces or comparative human factors studies could also be required to give evidence of the similarity between the Reference Listed Drug (RLD) and the drug delivery device.

> "The ability to obtain trustworthy data much earlier in the development process provides pharmaceutical companies with leverage that enables them to focus on other critical areas that require their resources and attention..."

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"A clear, intuitive and accurate IFU is a critical component of successful device use, and can be a core component of device training for users in specific situations."

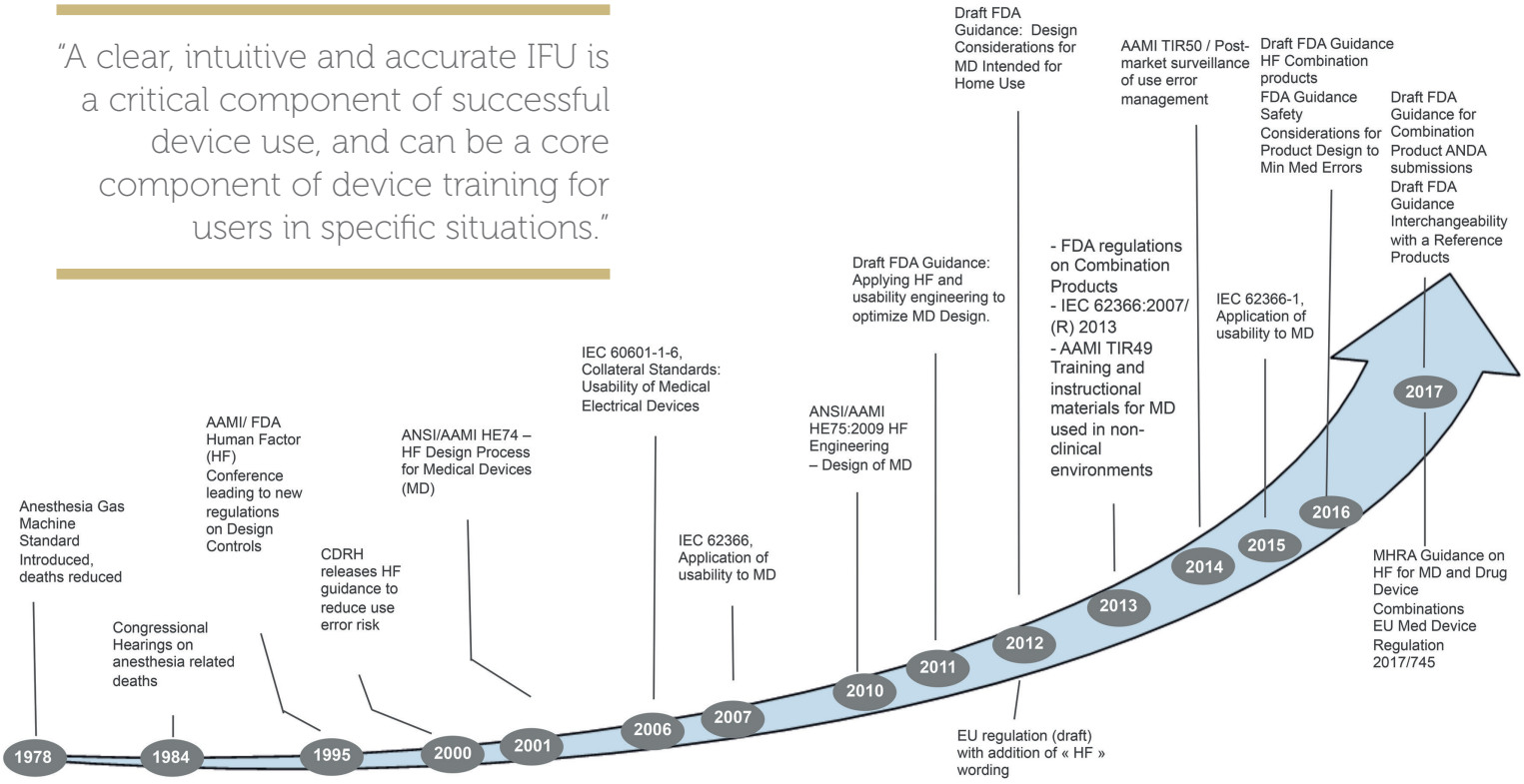

Figure 1: Requirements to ensure medical devices are safe and effective.

MITIGATING THE BURDEN ON PHARMACEUTICAL COMPANIES

For pharmaceutical companies, the complexity of bringing various components from different manufacturers together to create a combination product can result in disconnects and inefficiencies in generating the required usability data. Pharmaceutical development focuses on formulation first, resulting in device considerations often happening later in the development process.

From an HFE standpoint, the later in the development process that correctable use errors are identified, the costlier it is to fix them and the greater the potential impact on market launch.

As a trusted leader in the medical device industry, BD is rightfully focusing on the end user and placing emphasis on building and sharing HFE capabilities. BD has taken the initiative to build HFE capabilities and conduct comprehensive HFE testing on its devices and components, and then may provide the HFE data (when available) and regulatory guidance to their pharmaceutical customers.

The ability to obtain trustworthy data much earlier in the development process provides pharmaceutical companies with leverage that enables them to focus on other critical areas that require their resources and attention, and move towards launch sooner. This benefit is especially valuable to small pharmaceutical companies that lack resources or expertise, but can also benefit larger companies by freeing resources for other activities.

OPTIMISING DESIGN FROM CONCEPTION TO VALIDATION

BD's knowledge and experience of its products place it in a unique position to optimise combination product development at every stage. For recent products and those under development, this is accomplished through an applied, iterative, patient-centred design approach, where early studies with patients inform requirement definition and device design, which are later verified by patients through experimental investigation (Figure 2, next page). Moreover, BD's existing rigorous product testing, instructions for use (IFU) development, and design validation can streamline HFE for pharmaceutical manufacturers and improve time to market.

Design Conception

In the design conception stage, BD conducts formative studies with users to ensure the device design is robust enough to move to validation. This requires a deep understanding of the intended user populations, including the physical, cognitive and disease-related limitations of those particular patients, and potential sources of error. It also involves ensuring the study participants are representative of end users and the product can be used safely and effectively by the targeted end users. This means that during the recruitment phase for the usability studies, BD ensures that a broad population of both experienced and naive users are surveyed across multiple countries to ensure proper representation.

In addition to the formative usability testing, BD also utilises a combination of human factors and market research to improve insights into barriers to adherence, which informs the delivery device design. The collaboration of commercial, medical and design teams early in the device development process is key to developing a product well-accepted by the intended end-user populations.

Throughout this process, BD engages industrial designers to refine device design so that it reflects patient feedback and improves usability. BD has evolved its approach to device design not only to work for the target patient populations, but to provide an aesthetic appeal that may increase confidence and reduce anxiety in patients who self-inject.

An example of the benefits of this upfront testing is the favourable usability results

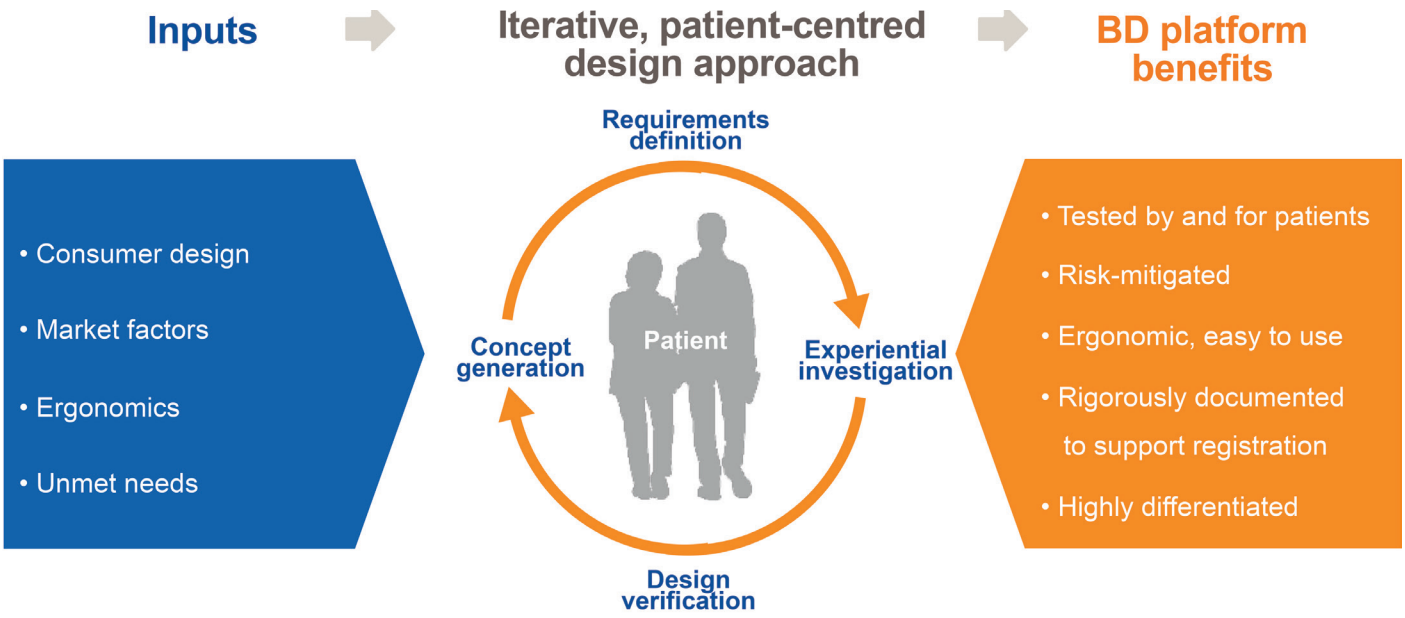

Figure 2: Using an iterative, patient-centred design approach to inform device design.

that were obtained using the BD UltraSafe Passive™ Needle Guard and secukinumab with patients who have moderate to severe psoriasis. This study found that the syringe equipped with the safety device was effective, with an acceptable safety profile and high usability.[5] BD's rigorous testing increased the confidence of a positive outcome.

BD can provide guidance to pharmaceutical manufacturers on how to design and conduct formative studies with its product and the intended users. This allows manufacturers to identify critical tasks very early on, avoiding potential design issues, and having to iterate to move to the next stage of development with the most favourable design possible.

Risk Management

The risk management aspect of BD's HFE offering includes the development of IFUs to support and enhance the safe and effective use of combination products. A clear, comprehensible and accurate IFU is a critical component of successful device use, and can be a core component of device training for users in specific situations. If the IFU is inadequate, it may result in user errors or difficulty performing tasks, and ultimately require additional testing to ensure safety risks are mitigated before approval.

As a result, entering design validation with a robust IFU is key to enabling development to proceed efficiently. BD strongly recommends that pharmaceutical customers should take into consideration the IFU developed for the device for their final combination product labelling.

> "Increasing regulatory requirements, both in the US and globally, when it comes to drug device combination products have created added complexity for pharmaceutical manufacturers to navigate."

Design Validation

During design validation, BD conducts a final summative validation study to confirm that the target users can safely and effectively use the final device design. BD has vast expertise in this area with strong capabilities in performing these simulated use studies for human factors testing. The intended users are tested for their ability to complete the series of critical tasks with and without training and use of the product's IFU. The output of this study supplies usability and acceptability data to help meet the health agencies' (US FDA/MHRA[4]) HFE requirements and support pharma company combination product filings.

As an additional service, BD can provide insights from its validation testing, along with data from previous formative studies, to help pharmaceutical manufacturers develop the appropriate protocol for their specific product filing to reflect different intended use populations, viscosities and volumes. These could include the study design and methodology, protocol, intended use, endpoints, and target user population and recruitment.

Market Launch

BD can provide commercial, medical and regulatory resources to support pharmaceutical companies' launch strategies. BD has a strong history of commercial success with combination product launches, with a recent example published in the *British Journal of Dermatology*.[5]

Within this specific publication, one of the objectives of the authors was to demonstrate efficacy, safety and usability of a prefilled syringe (PFS) with a safety device for self-administration by patients with moderate-to-severe plaque psoriasis. The study concluded that the PFS usability was high with 100% of subjects successfully self-administering treatment with high acceptability.

Overall, this positively illustrates how a combination product design can offer patients the clinical benefits of a drug, with increased convenience.

LEVERAGING INTEGRATED SYSTEMS

In addition to HFE services, the integrated nature of BD device components, including primary containers, secondary delivery systems (e.g. autoinjector or wearable injector) and add-on needlestick safety

guards, facilitate streamlined usability testing and easy-to-use product design. Because BD makes and tests these components individually and together from a technical and HFE standpoint, these data can inform pharmaceutical company test protocols and reduce the risk of unforeseen issues throughout the process.

For pharmaceutical manufacturers, this could mean reduced delays by avoiding re-testing of individual components and minimising device failures associated with a non-integrated system (e.g. injection depth variability, syringe breakage, incomplete injection). It also means increased confidence that the combination product will ultimately operate in a user-friendly manner when brought to market.

NAVIGATING REGULATORY REQUIREMENTS

Increasing regulatory requirements, both in the US and globally, when it comes to drug device combination products have created added complexity for pharmaceutical manufacturers to navigate. This is particularly disruptive for smaller manufacturers that may be resource-constrained to focus solely on the drug product itself, or for others just entering the combination product space.

BD offers HFE and regulatory affairs services to guide customers throughout the process, including providing documents and guidance to support their filing and ensuring they meet regulatory agency requirements. BD's Regulatory Affairs team has extensive experience with legislative and regulatory bodies at the local, regional and international levels, and can advise customers accordingly.

Figure 3: Elements that facilitate speedy time to market.

BD's ability to provide data on device testing, inputs to HFE protocol development, regulatory strategy or even conduct testing for the pharmaceutical company with their drug product in the BD device, can help reduce regulatory hang-ups and speed time to market (Figure 3).

In addition, BD can provide valuable insights to manufacturers seeking to "lifecycle manage" a product from one container or delivery device to another, such as from a PFS to an autoinjector. BD's ability to offer customised containers and devices enables support for evolving portfolios.

CONCLUSION

The evolving landscape of combination products and human factors engineering requirements from regulatory agencies has increased the burden on pharmaceutical companies that have historically been primarily focused on drug efficacy.

Device manufacturers should no longer be considered suppliers of components but instead as partners in the combination product development process. As a result, it is important for device manufacturers to provide support to pharmaceutical companies with their design validation requirements, especially as it relates to usability and ease of use of the delivery device.

An effective collaboration across device teams ultimately contributes to successful product development and patient acceptance. Furthermore, selecting a delivery device that has been developed by a leading medical device provider instills confidence that the device has been designed to meet end-user requirements, perform consistently within a clinical trial and also meet regulatory authority combination product regulations.

ABOUT THE COMPANY

BD is a global medical technology company advancing the world of health by improving medical discovery, diagnostics and the delivery of care. BD leads in patient and healthcare worker safety and the technologies that enable medical research and clinical laboratories. The company provides innovative solutions that help advance medical research and genomics, enhance the diagnosis of infectious disease and cancer, improve medication management, promote infection prevention, equip surgical and interventional procedures, optimise respiratory care and support the management of diabetes. The company partners with organisations around the world to address some of the most challenging global health issues. BD has more than 45,000 associates across 50 countries, who work in close collaboration with customers and partners to help enhance outcomes, lower healthcare delivery costs, increase efficiencies, improve healthcare safety and expand access to health.

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ABOUT THE AUTHOR

Karen Guerrero is Medical Affairs Safety Platform Manager for BD Medical – Pharmaceutical Systems. She contributes to product design, from concept phase (medical input) until product launch (clinical and human factors impacts assessment for BD drug delivery devices), in the context of BD-sponsored and BD customer-sponsored projects. She holds a PhD in Physiology and Pharmacology and has been working for several years in the medical devices research field.

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