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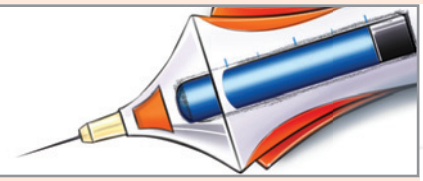

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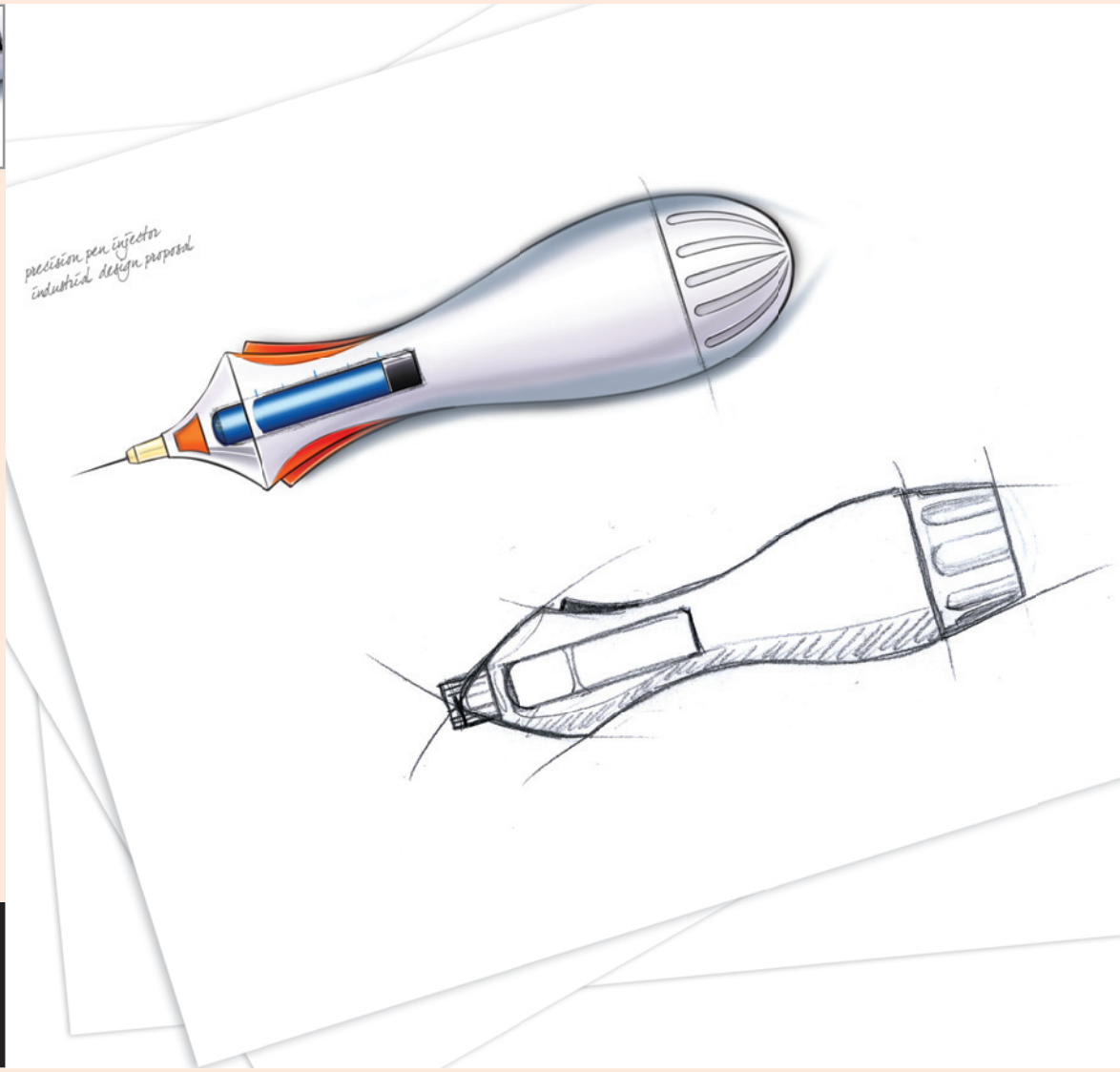

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"Prefilled Syringes: the Human Factor"

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Front cover image, "Examples of Device Design 2D Sketches", courtesy of SHL Group, whose article appears in this issue on Page 39. Reproduced with kind permission.

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3P'S ASEPTIC FILL2WEIGHT™ POWDER DISPENSER: AN ENABLING TECHNOLOGY FOR PARENTERAL RECONSTITUTION DEVICES

The trend within the pharmaceutical industry towards large-molecule biologic drug substances is well documented. Due to the fragile nature of these compounds, they often need either cold-chain logistics or reconstitution prior to administration. Innovation in reconstitution devices and in formulations has been stifled by the inability of conventional powder handling systems to dispense small and precise amounts of reconstitution powders aseptically. This paper, from Tom Bailey, Managing Director, and Dave Seaward, Projects Director, both of 3P Innovation, describes how the company's innovative gravimetric Fill2Weight™ system overcomes these technical challenges to enable advances in both formulations and parenteral device design.

BACKGROUND – THE RISE OF BIOLOGICALS

Traditional small-molecule pharmaceutical blockbusters are increasingly subject to generic price competition as they drop off the "patent cliff". Large pharmaceutical companies are banking on replacing their lost revenue streams with large-molecule biological blockbusters. These are developed through biological processes using living cells and organisms.

The birth of the biologicals industry can be charted back to 1976 when biochemistry professor, Robert Swanson, met with venture capitalist, Herbert Boyer, in California to rough-out a business plan for what became

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Genentech. It was only six years later, in 1982, when Eli Lilly launched Humulin®, the world's first recombinant DNA drug product, using Genentech's technology.

Lists of the top selling pharmaceuticals now include a significant and increasing number of biologicals. For example, Abbott was recently able to spin out AbbVie on the back of Humira® which is currently the third-largest pharmaceutical product by sales.[6] There are currently over 900 biological compounds under development by US research companies, which target 100 disease groups: many of these have blockbuster potential.[4,6] It is not surprising, therefore, that revenues for biologicals are predicted to exceed US$220 billion (£136 billion) by 2019.[7]

Whereas solid oral dose delivery (tablets, capsules etc) is the first choice for the majority of small molecules, it is not suitable for most biological compounds which do not survive the gastrointestinal tract and first-pass metabolism. In order to achieve sufficient bioavailability, injection is the only practical route available. Parenteral drug delivery is far more costly and complex than solid oral delivery systems, and less convenient for the patient. It also presents a unique set of technical challenges which has led to the rise in popularity of formulations that rely upon the reconstitution of freeze-dried powders.

THE RISE OF RECONSTITUTION DEVICES

Patient and practitioner convenience has led to a proliferation of prefilled syringes and auto-injectors for liquid formulations. Despite the best efforts of formulators, biologicals are often not shelf stable as liquids at room temperature. The pharmaceutical developer typically has two methods of delivering an adequate shelf-life: cold-chain logistics or reconstitution devices. In cold-chain applications, the drug is manufactured, distributed and stored at low temperature. For example, Humira®, mentioned earlier, must be kept between 2-8ºC and protected from light to deliver an 18-month shelf-life. Maintaining a 6ºC storage window for 18 months from factory to administration is challenging with associated high and sometimes prohibitive costs. The alternative solution is reconstitution of a powder with a liquid diluent just prior to use.

Reconstitution devices rely upon storage and distribution of the drug substance as a powder which is shelf-stable at room temperature. Prior to administration, the powder is reconstituted with a liquid to form an injectable solution or suspension. This overcomes the costs associated with the cold chain but introduces a different set of technical challenges. Ideally the diluent and

powder would be transported together in pre-measured amounts but for obvious reasons need to be kept apart during the supply chain. They also need to be brought together and mixed in a reliable and convenient manner by the administrator of the medicament. Ensuring correct mixing can be a challenge as many biological compounds dissolve very slowly and poorly.

POWDER-DRYING TECHNOLOGIES

A common technique to improve the solubility of a powder is to produce it from a liquid via freeze-drying. Freeze-drying or lyophilisation has become the standard method for producing reconstitution powders. A solution containing the active pharmaceutical ingredient (API) and any excipients is first produced and dispensed, using standard pumping systems, into a primary pack. Water is then removed by sublimation in a vacuum: any residual water is removed by raising the temperature very slowly. The resultant material is a solid cake with an amorphous or crystalline structure and the open structure promotes ease of dissolving.

There are two main lyophilisation technologies available depending upon whether the primary package is a vial or a dual-chamber cartridge/syringe. Vial systems are less complex to produce than dual-chamber systems and are therefore easier to develop but the final administration is more complex and more reliant on the expertise of the administrator. In a dual chamber system (such as Vetter's Lyo-ject® syringe) the drug substance is lyophilised on top of a first rubber bung inside the glass cartridge. The first bung acts as a barrier between the lyophilised powder and the diluent which is added after the lyophilisation step. The system is completed by a second bung and a plunger. The first bung and a bypass in the glass act as a valve. The valve allows the diluent into contact with the powder once pressure is applied to the plunger (hydraulic pressure moves the lyophilised cake and first bung forward to expose the bypass valve). The diluent then passes over the cake of powder. Once fully dissolved a needle can be attached and the injection administered.

Both systems rely upon a very slow lyophilisation process (typically 2-5 hours) which must also be carried out in an aseptic environment. In-vial or in-cartridge lyophilisation requires complex and precise control of both low temperatures and low pressures. Vials sit on shelves and are heated using a process governed by conduction from the shelf through the glass vial, whereas dual-chamber systems rely upon convection and radiation due to the very poor conduction path through both glass and the first rubber bung.

In the last four years more than one-third of all parenterals approved by the US FDA were for lyophilised substances[5] and this remains the technology of choice for most reconstitution parenteral applications. There is however significant research into the use of both bulk lyophilisation within trays and spray-dried formulations: this is driven by both process and formulation flexibility and overall cost. It is claimed that bulk tray-dried lyophilised materials save around 30% of the costs compared to vial systems.[1]

An alternative powder formation technology which is also enjoying increased interest for parenteral applications is spray drying. In a spray dryer a continuous feed of liquid is atomised and rapidly dried into particles via a drying gas. The spray droplets have extensive surface area such that the drying can be achieved very rapidly and at relatively low temperatures. Hence, spray drying has the ability to formulate very sensitive biological drugs which would be damaged by lyophilisation. This has led to the recent development of aseptic spray drying technology. It offers lower drying costs and (as a continuous process) the ability to produce larger batches without the scale-up headaches normally associated with freeze drying. Unlike the amorphous cake pro-

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duced by bulk lyophilisation, which requires further processing to form a powder, spray drying produces discrete particles.

If bulk lyophilisation and spray drying offer pharmaceutical formulators such significant advantages for reconstitution devices, then why has there been such a limited uptake?

THE CHALLENGE: ASEPTIC DISPENSING OF POWDERS

Both spray dried and bulk lyophilised biological powders tend to have very poor flow properties, are sticky (adhesive and cohesive), are moisture sensitive and are also sensitive to shear. This means that they are very difficult, if not impossible, to dispense using traditional means. Ingham recognised that the poor flow characteristic of these powders was acting as a commercial barrier to adoption.[2,3]

Reconstitution powders typically have true densities around 1.4-1.6 g/cm^3, with the bulk density of 0.4-0.8 g/cm^3. This means 50-75% of the volume of the material to be dispensed is air. This air acts to lubricate the system. Changes in the amount of air entrained within a powder will therefore alter both the powder's density and its flow properties. Powders are usually non-uniform materials and uniquely have "dynamic" physical properties as they constantly aerate or settle and cake: they can behave like solids, or like liquids (and occasionally like gases). Lyophilised powders are usually very cohesive and tend to agglomerate. This does not suit standard volumetric filling technologies. One of the common methods of improving the dose-to-dose weight repeatability is to compress the powder into a fixed volume prior to dispensing, which removes inconsistent voids of air: powder compression can however damage biologicals and will reduce the propensity to dissolve.

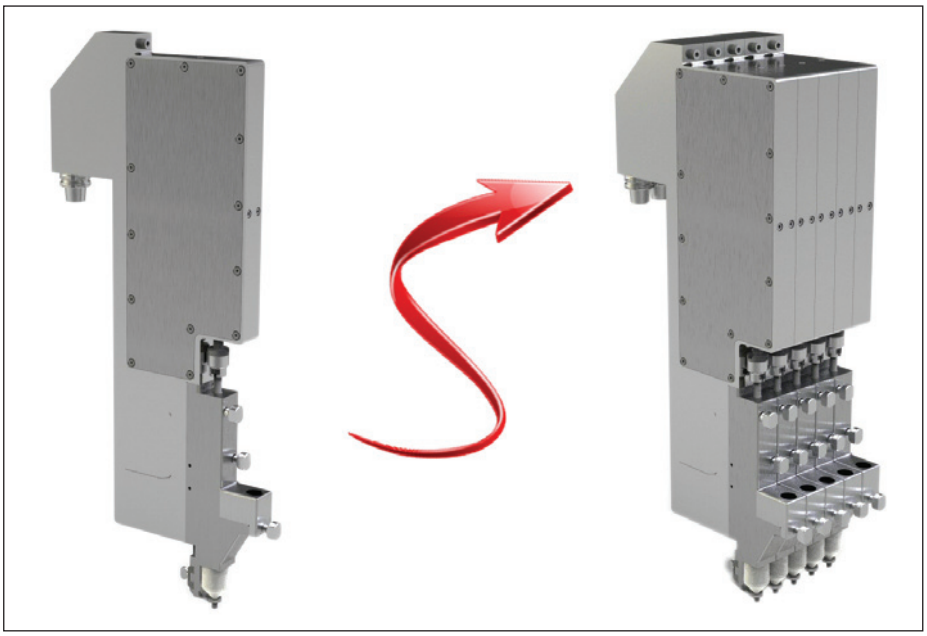

Figure 1: A single Fill2Weight™ Head (left) used for clinical supply can be multi-tracked (right) for commercial applications to provide a scalable solution.

Furthermore many reconstitution formulations, being hydroscopic, require processing in low humidity, which then creates sensitivity to static electrical charges. It is often not appreciated that forces due to static electricity are often orders of magnitude higher than gravity, such that particles of powder can move in an uncontrolled manner around the dispensing area. As a result, powder can adhere and coat areas of either the primary container or the machinery. Uncontrolled particulate matter in an aseptic isolator is obviously not ideal or acceptable.

As a result of the above technical challenges, traditional powder dispensing technologies such as augers and dosators do not function with reconstitution powders. The equipment is prone to mechanical seizure, and the dispensed weight is impossible to control to the tolerances required by the pharmaceutical industry. In addition they tend to shear the powder, which can damage the biological compound. Some low-volume, high value-added applications rely upon operators: powder is dispensed manually, through glove ports, into primary containers using spatulas and analytical balances. This is very slow, labour-intensive and normally uneconomic. There are also some laboratory automatic systems which rely upon slow dispensing of powder over an analytical balance, until the correct weight is achieved. These laboratory systems remain slow for commercial applications (30 seconds to several minutes per dispense) and are unsuitable for operation in an aseptic isolator.

Aseptic equipment has to meet a number of additional technical requirements. The powder dispensing equipment must be able to survive any aggressive decontamination cycle, such as hydrogen peroxide vapour (HPV). Any parts which contact the powder must be made from a limited number of pharmaceutical-grade materials suitable for both autoclaving and direct contact. Most aseptic isolators rely upon unidirectional airflows to maintain sterility. The design of the equipment must therefore ensure that the airflow does not become turbulent: a narrow powder filling machine footprint is ideal.

It is not surprising that Ingham recognised that the technical challenges associated with dispensing reconstitution powders was acting as a commercial barrier to adoption.

AN ENABLING TECHNOLOGY?

It is worthy of note that most liquid-dispensed medicinal products are regulated by volume and therefore dispensed by volume, whereas most powder-based products are regulated by weight and yet dispensed by volume. It is stranger still

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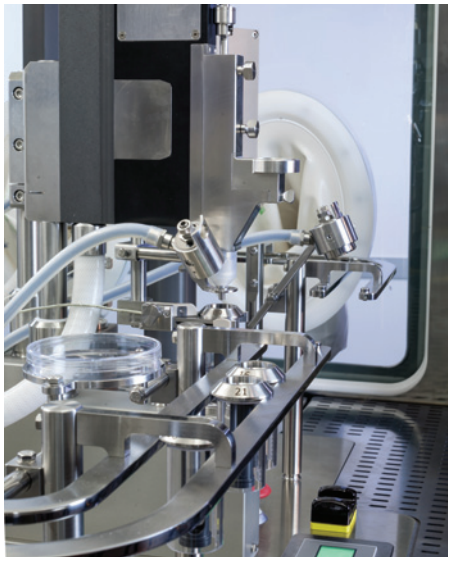

Figure 2: Fill2Weight™ Powder Dispensing Systems inside an aseptic isolator.

when one considers that powders, by their very nature, have "dynamic" physical properties such that density varies with time.

This dichotomy is a result of the inability to dispense powders by weight at required commercial rates when compared with volumetric dispensing methods: commercial pressures for high outputs and tradition has led to the vast majority of powder dispensing systems using volumetric methods with a statistical process control (SPC) check of actual weights.

Would it not be more logical to dispense a weight of powder by weight? This is known as gravimetric dispensing. The concept is simple: a powder flow control device (a valve) is opened and closed in response to a weighing system. Such systems have been available for many years but until recently the inherent slow response of weighing systems meant they were relegated for use only in laboratory settings. The increased speed in microprocessors has enabled a new generation of sub-milligram, accurate, stable and fast weighing systems to be produced. In turn, this enables high speed gravimetric filling of powders. Originally developed for inhaled applications, 3P's Fill2Weight™ system is the most advanced gravimetric system available.

Fill2Weight™ uses the latest high-speed weighing technology combined with a powder-flow control valve designed to dispense very cohesive to very free-flowing powders without any change parts. The valve minimises powder shear which is ideally suited to biological powders. The computer control necessary to link the valve and weighing technologies also enables self-tuning. It "learns" optimum settings for given powders and automatically compensates for the "dynamic" changes in a powder's physical properties.

By design both the powder dispensing and the weighing system have a narrow form factor which ensures systems can be stacked in a very small space for commercial applications. It is therefore possible to use a single head for preclinical and clinical trials and to scale the same process for commercial applications (see Figure 1). The traditional project delays associated with scale-up are therefore eliminated. The narrow form factor is ideal for use in unidirectional airflow in an aseptic isolator (see Figure 2). It will be appreciated that the system provides end-users with 100% weight verification of dispensed weight.

3P has a team of engineers with more than 100 combined man-years of powder dispensing experience drawn from a wide range of industries. This experience has been put to good use in the flexible design of Fill2Weight™: it can fill the widest range of powders from very free-flowing to highly cohesive and from 1 mg to 20,000 mg without change parts. The system has a wide variety of software-configurable features which may or may not be required for a given application. Target weight and product change is managed via software, such that its control algorithms continually optimise internal settings: these also compensate for changes in powder physical properties between batches and within a batch. Every dose is weighed and internal control parameters recorded such that a very detailed batch record can be produced: the system delivers true Quality by Design (QbD) and enables parametric or real time release. By setting reject levels, 100% of production can be guaranteed to be within predetermined weight tolerances.

The powder dispensing valve or "nozzle" with an integrated hopper conveniently clips on and off the drive module. The integrated nozzle and hopper can therefore be easily removed for cleaning, and it can be autoclaved. Alternatively the low cost silicone moulded hopper can be considered a disposable item to eliminate cleaning costs. For cohesive and adhesive powders the silicone hopper has the distinct advantage that powder does not adhere to it (a common problem in many powder dispensing systems).

At the base of the silicone hopper is an orifice which can be closed by the tip of a close fitting pin. The pin is driven vertically up and down to open and close the orifice to allow more or less powder to flow. It is important to deliver repeatable and consistent powder flow since this relates to the variability of dispensed weight. In order to provide precision and speed at the low end of the system's range (1-10mg) the relative position of the nozzle orifice to the tip of the pin is controlled to micron precision via a high-performance servo system.

The system as described so far will perform well with very free flowing powders, however cohesive powders will tend to bridge over the small orifices required to control the required low flow rates (the system can control below one milligram per second). Additional features have therefore been integrated into the flexible design to deal with normally troublesome, highly cohesive powders.

Firstly the pin is designed to spin clockwise and/or anticlockwise with its angular position and velocity controlled precisely. This ensures that powder doesn't adhere to the pin and prevents bridging (which tends to occur with stationary pins). Secondly a set of fine spinning stirrers are used to mobilise the powder within the hopper and are designed to disrupt any bridges at the most critical area which is at the tip of the nozzle. Thirdly, the system is provided with a sonic vibration source which is used to excite the powder particles within the hopper such they will flow consistency without bridging. With some powders switching the vibration on and off with the pin permanently open is sufficient to control the powder flow. Typical accuracies for a range of formulations normally considered impossible to dispense with conventional equipment are shown in Figure 3.

The system does not need to compact the powder to improve dispensing accuracy. Indeed the stirrers and vibration source can aerosolise the powder to provide zero compaction which improves subsequent reconstitution times. The system integrates with de-ionisers to reduce the impact of static electricity both on the primary container and within the powder. For reconstitution devices it is also important to keep the stoppering area of any primary container clean: an elongated shield at the

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FillWeight	Lyophilised Placebo Formulations	Repeatability (RSD%)
150mg	Mannitol and Immunoglobulin G (IgG) – Formulation 1	0.60%
150mg	Mannitol and Immunoglobulin G (IgG) – Formulation 2	0.78%
150mg	Mannitol and Immunoglobulin G (IgG) – Formulation 3	0.90%
150mg	Mannitol and Lactate Dehydrogenase (LDH) - Formulation 1	1.30%
150mg	Mannitol and Lactate Dehydrogenase (LDH) - Formulation 2	1.30%
150mg	None freeze Dried Mannitol	0.76%
150mg	None freeze Dried Sucrose	1.40%
10mg	Mannitol and Immunoglobulin G (IgG) – Formulation 2	1.30%
10mg	Mannitol and Lactate Dehydrogenase (LDH) - Formulation 1	0.70%
10mg	None freeze Dried Mannitol	2.20%
10mg	None freeze Dried Sucrose	1.30%

Figure 3: Table showing typical dispense weight accuracy from Fill2Weight™ measured as a relative standard deviation for a range of lyophilised formulations.

exit of the powder dispensing valve ensures that powder is filled from the bottom of the container which ensures powder does not contaminate the stoppering region.

3P has an advanced powder dispensing system suitable for use in an aseptic environment. The narrow form factor is ideally suited to applications requiring unidirectional airflow. It can operate in harsh decontamination environments such as HPV sterilisation or autoclaving. Together with anti-static measures it can dispense powders at low relative humidity.

FILL2WEIGHT™ A TRUE ENABLING TECHNOLOGY

With Fill2Weight™ formulators of biological compounds have fewer constraints and can now consider using either bulk lyophilised or spray-dried formulations, which were previously commercially unviable. The cost of goods will consequently reduce. In addition injection device designers can now consider previously nonviable options. Fill2Weight™ is available to enable major advances is formulations and devices within the biological delivery sector (see Figure 4).

CONCLUSION

This article has described the trend in the parenterals market towards dual-chamber reconstitution devices. This is driven by the rise of biological compounds. Their poor powder-flow characteristics have, however, limited commercialisation to a limited number of technologies. This limit has been overcome by 3P's novel gravimetric powder dispensing system, Fill2Weight™.

Fill2Weight™ dispenses both bulk lyophilised and spray dried formulations quickly, precisely and aseptically into vials, cartridges and syringes. It is a scalable technology suitable for early phase clinical supply through to commercial manufacture. The weight can be dialled-in via the control system and 100% of all weights are recorded. Both formulation scientists and device design teams have greater freedom to innovate thanks to this enabling technology.

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Figure 4: Novel configurations of reconstitution devices enabled by Fill2Weight™.

ABOUT 3P INNOVATION

3P innovation Limited is a successful pharmaceutical automation and consultancy company based in the UK. 3P is focused on the supply of bespoke machinery and production solutions to an array of industry sectors. 3P's services include product design for manufacture, proof of concept rig development, test & inspection equipment, and custom production equipment. 3P also has a range of scalable powder dispensing systems, of which Fill2Weight™ is just one example. 3P takes a holistic view of all technical challenges, looking for opportunities to enhance the product, enable efficient process and thereby support commercially viable production. This combined expertise includes many decades of industrial design and process engineering within the pharmaceutical, medical device and fast moving consumer goods industries.

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A DIFFERENTIATED, CUSTOMISABLE PORTFOLIO TO LEAD A NEW ERA OF INDUSTRY GROWTH

In this article, Alan Shortall, Chief Executive Officer, Unilife, describes the company's portfolio of injectable delivery devices in the context of a number of specific current pharmaceutical industry trends.

A series of trends are converging to redefine the injectable drug delivery industry. Device manufacturers who are able to provide pharmaceutical companies with a broad, flexible and differentiated portfolio of prefilled syringes and injectable drug delivery systems that can address market needs will lead the industry into this new era of growth.

Pharmaceutical companies utilising prefilled syringes for their injectable drugs and vaccines have traditionally been restricted to sourcing glass barrels, elastomers and associated materials from device manufacturers specialising in the production of commoditised products at high unit-volumes under a one-size-fits-all model. This traditional approach to the production and supply of prefilled syringes has created many challenges for pharmaceutical companies, including:

1. **Differentiation:** When conventional devices sourced from different manufacturers all share the same functionality and visual look, the pharmaceutical company has minimal scope to differentiate their injectable product from brand-name, generic or biosimilar competition
2. **Customisation:** Where device manufactures are unable or unwilling to customise a product to address specific formulation, marketing or user requirements, a pharmaceutical company is hindered from providing its customers with patient-centric product that can optimise preference and therapy compliance rates
3. **Materials:** When a device manufacturer is seeking only to market their own proprietary products or materials for use with a prefilled product; the ability of a pharmaceutical company to select their preferred material, lubricant or coating is constrained
4. **Platform Integration:** Where there is fragmentation between suppliers of prefilled syringes, auto-injectors and ancillary safety products, pharmaceutical customers must bear ultimate responsibility for the integration of these devices, which may not be designed

"AS REPORTED BY ERNST AND YOUNG IN THEIR PROGRESSIONS 2012 REPORT: "HEALTHCARE EVERYWHERE", MORE THAN 50% OF ALL HEALTHCARE WITHIN A DECADE WILL NO LONGER BE ADMINISTERED IN HOSPITALS AND DOCTORS OFFICERS BUT IN THE "THIRD PLACE", OR IN ESSENCE WHEREVER THE PATIENT IS DURING THEIR NORMAL DAILY LIFE"

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upfront for optimal compatibility; and

5. **Safety:** When pharmaceutical companies are required to comply with needlestick prevention laws, they must purchase and attach ancillary safety products onto a standard prefilled syringe, creating extra steps in manufacturing and adding up to 70% in shipping, transport and storage volumes. The bulkier size of prefilled syringes with ancillary safety products and need for additional non-intuitive steps for use may also contribute to a sub-optimal rate of non-adherence to prescribed injection techniques.

Because of these and other unmet market needs and emerging market trends, this traditional model is fast becoming obsolete. In its place, pharmaceutical companies are quickly embracing a new paradigm for injectable drug delivery that encourages close, long-term collaborations between drug and device manufacturers. With such long-term partnerships seeking to enable and enhance the delivery of an injectable therapy, these collaborations may originate early in the clinical development process and then extend through the regulatory approval and lifecycle management of the combination product.

There are many factors behind this redefinition of the market for injectable drug delivery systems.

REGULATORY EMPHASIS ON HUMAN FACTORS

The US FDA and other regulatory agencies are placing increased emphasis on human factors during their review of drug applications, with user studies required to show that products are safe, simple and reliable for administration to the target patient population. Human factor studies can seek to confirm patient acceptability across factors such as initiation force, glide force, activation force for a safety mechanism, finger-flange design, ease-of-use, and convenience of disposal. The data generated by these user studies can add significant value to the regulatory approval and commercial success of the combination product. In particular, drugs which are supplied pre-packaged and pre-assembled ready for injection and require minimal steps of use are likely to generate strong rates of user preference and be encouraged for prescription.

SHIFT TO PATIENT SELF-INJECTION

As reported by Ernst and Young in their Progressions 2012 report: "Healthcare Everywhere", more than 50% of all healthcare within a decade will no longer be administered in hospitals and doctors officers but in the "third place", or in essence wherever the patient is during their normal daily life. Pharmaceutical companies are responding to this trend towards patient self-administration with the provision of biologics and other injectable therapies in devices that are customised to address the specific needs of the target patient population. From prefilled syringes with extended finger flanges, soft rubberised grips and extended thumb pads on the plunger to support user dexterity challenges, to auto-injectors that are ultra-portable and convenient for disposal, drug delivery systems are becoming more ergonomic and tailored to the needs and lifestyle of the target patient.

"WHEN DEVICE MANUFACTURERS HAVE AN INTEGRATED PORTFOLIO OF PRODUCTS AND ARE OPEN TO BUILDING CLOSE COLLABORATIONS WITH THE PHARMACEUTICAL CUSTOMER, THE RISK OF PRODUCTION PROBLEMS OR DOWNSTREAM USER ISSUES CAN BE MINIMISED"

PLATFORM APPROACH TO DEVICE COMPATIBILITY

To accommodate the needs of an entire patient population fully, from mild to severe cases, some pharmaceutical companies are seeking to market an injectable therapy in multiple device configurations including a standard prefilled syringe as well as a disposable or reusable auto-injector. For such therapies, there is a growing preference amongst pharmaceutical companies to ensure that the prefilled syringe and auto-injector will be fully compatible and not create challenges during assembly, packaging or use. When device manufacturers have an integrated portfolio of products and are open to building close collaborations with the pharmaceutical customer, the risk of production problems or downstream user issues can be minimised.

OPEN ARCHITECTURE SUPPLY CHAIN MODEL

With biologics now comprising a large and growing proportion of a pharmaceutical company's clinical pipeline, the flexibility to select a preferred material or elastomer coating is becoming increasingly important. This is giving rise to an open architecture model amongst some device manufacturers, where they will work with each pharmaceutical company to select components and materials from a range of established and verified suppliers.

OPTIMISING LIFECYCLE MANAGEMENT

The continuous enhancement of an injectable therapy throughout its commercial lifecycle is becoming a standard method of building market share and fighting off competition from current or prospective drug rivals. Traditionally, a pharmaceutical company would launch its therapy lyophilised in a vial, then transition a few years later into a liquid-stable format with a standard prefilled syringe, and then perhaps later add an auto-injector. Today, however, the initial launch of an injectable therapy in a prefilled format is considered to be the absolute bare minimum required to compete. Many pharmaceutical companies are seeking first-launch of their injectable therapies in, for example, a prefilled syringe with needlestick prevention features, or an auto-injector or, in the case of drug reconstitution, a dual-chamber system.

MAKING SAFETY A COMPETITIVE ADVANTAGE

Needlestick prevention represents a particular area of need for pharmaceutical companies, healthcare workers and their patients. Europe and other international healthcare markets are now following the US toward the mandatory use of devices with needlestick prevention features. These laws require the frontline staff of healthcare facilities to play a role in the evaluation, selection, and use of devices including prefilled drugs that can eliminate or minimise the risk of occupational exposure to the lowest possible extent. For pharmaceutical companies that must comply with these needlestick prevention laws, the selection of a prefilled syringe that optimises levels of protection to healthcare workers can represent a significant competitive edge.

Traditionally, pharmaceutical companies have had two options for needlestick compliance. In the case of drugs and vaccines targeted for intramuscular injection, they can

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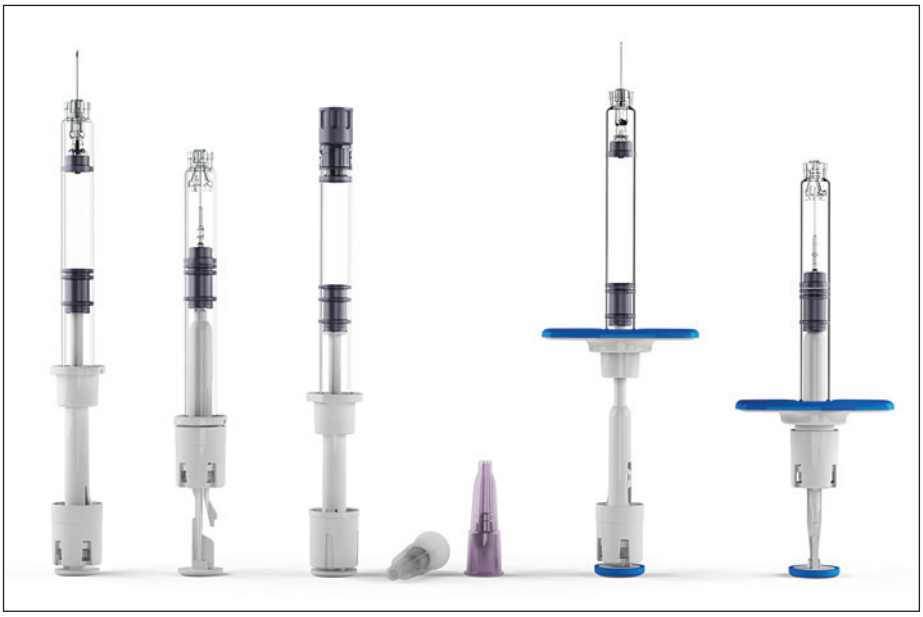

Figure 1: The Unilife® ready-to-fill syringe portfolio.

Figure 2: Unifill Assure, for the intuitive self-injection of biologics by patients with reduced dexterity.

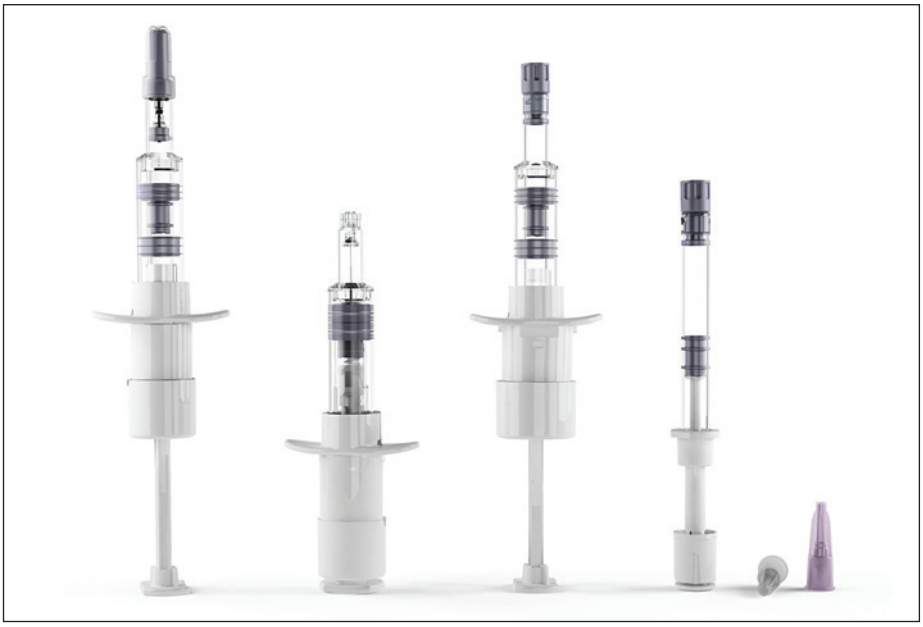

Figure 3: EZMix dual chamber reconstitution syringes.

utilise a prefilled syringe in a needleless format. Such devices require healthcare workers to attach a safety mechanism, such as a needle guard onto the prefilled syringe, immediately before injection. However, data suggests that such manual safety products are frequently not activated by the healthcare worker, or associated with needlestick injuries either during use or after disposal.

A more common approach has been to attach an ancillary safety product onto the prefilled syringe after it has been filled with the drug and prior to packaging. The process of attaching an ancillary safety product can require the purchase, installation, and operation of additional assembly systems within the pharmaceutical cleanroom. Any problems associated with the breakdown of these assembly systems or the subsequent breakage of the prefilled syringe can impact the financial efficiency of the entire fill-finish process. The bulky size of these ancillary safety products compared with a standard prefilled syringe also increases packaging, transport, and storage volumes by up to 60-70%.

The US Occupational Safety and Health Administration (OSHA), the FDA, and many healthcare associations cite a preference amongst healthcare workers for the selection and use of devices with automatic (passive) and integrated safety features that can minimise the risk of harm and best comply with routine injection procedures. Pharmaceutical companies that select such prefilled devices with automatic, integrated safety features will be in a strong position to leverage these protective and functionality benefits to build user preference rates and optimise market share.

LEVERAGING DEVICES TO BEAT THE COMPETITION

Devices that are differentiated and provide true benefits to the user can be leveraged by pharmaceutical companies to optimise the commercial value of their injectable therapies. In particular, devices which are visually elegant during all stages of use, devoid of unsightly springs or mechanisms and compact in size for convenient handling and disposal can generate powerful brand differentiation for a drug product. When these devices can then be further customised to address the specific needs of a therapy and create the safest, simplest possible injection experience for the target user population, the pharmaceutical company will be ideally positioned to build or protect market share by driving patient, payer and prescriber preference towards their product.

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UNILIFE'S INNOVATIVE, DIFFERENTIATED AND CUSTOMISABLE PORTFOLIO

Unilife, a US-based global leader for injectable drug delivery systems is collaborating with many pharmaceutical and biotechnology companies to enable and enhance their injectable therapies. The mission of Unilife is to serve customers fully under long-term partnerships so they can leverage the company's high-quality, differentiated products to improve patient care, maximise revenues and out-perform the competition.

Six proprietary product platforms have been developed by Unilife for the safe, intuitive delivery and convenient disposal of injectable drugs and vaccines. These platforms, which include prefilled syringes, dual-chamber syringes, auto-injectors, wearable injectors, ocular delivery systems and novel devices, represent arguably the most extensive array of differentiated injectable devices in the industry (see Boxed Text).

Unilife's platform-based approach to product design means that all base technologies are fully established, with the company able to rapidly customise each product to address specific customer, drug and patient requirements.

SINGLE CHAMBER PREFILLED SYRINGES

Unilife has developed a full platform of ready-to-fill syringes under its Unifill® brand for use with all prefilled biologics, drugs and vaccines (see Figure 1). Unifill syringes are designed with USP-compliant materials in the primary drug container, and can be integrated with standard packaging and filling processes. They are designed for intuitive use and compact, convenient disposal by healthcare workers or patients. Human factor studies continue to highlight strong rates of acceptability and preference amongst a range of target user groups.

A common preference cited in these user studies is the audible click and tactile feel that is registered upon full dose delivery and the automatic activation of an integrated needle retraction mechanism. The user can control the speed of needle retraction directly from the body into the barrel to prevent exposure to a non-sterile needle. Automatic re-use prevention further eliminates the risk of device reuse or needle re-exposure.

Unifill syringes are highly customisable to address specific customer, drug and patient requirements with a selection of product configurations including the:

- **Unifill Syringe:** Featuring a staked (fixed) retracting needle and designed for use with liquid stable drugs.
- **Unifill Select:** Allows the user to attach retracting needles of various sizes at the point of delivery. Designed for use with either a liquid-stable drug or vaccine, or a diluent to reconstitute and deliver a lyophilised drug supplied in a vial.
- **Unifill Assure:** Featuring an extended, easy-to-grip finger flange and a widened thumb press for the intuitive self-injection of biologics by patients with reduced dexterity (shown in 2).

Figure 4: LISA™, an electromechanical reusable auto-injector.

DUAL-CHAMBER RECONSTITUTION SYSTEMS

Unilife has developed the EZMix platform of dual-chamber syringes (Figure 3) to serve as a safe, simple and efficient system for the reconstitution and delivery of liquid or dry drug combination therapies. An innovative and proprietary reconstitution technology allows healthcare workers or patients to mix together a combination of liquid or lyophilised drugs intuitively with minimal steps. The process of reconstitution is ventless and orientation-free to maintain sterility and minimise the risk of drug wastage. EZMix syringes utilise the Unifill platform of fully integrated and automatic safety features to virtually eliminate the risk of needlestick injuries, prevent device reuse and encourage convenient, safer disposal. Product configurations include the EZMix syringe with a staked retracting needle, and the EZMix Select with attachable retracting needles.

HANDHELD INJECTORS

Unilife has developed a broad platform of auto-injectors that are designed for exclusive use with the Unifill syringe. This proprietary range of auto-injectors are compact in size, intuitive to use and can be customised to address specific customer, drug or patient needs. Unilife considers itself not only to be the first company to offer both disposable and smart reusable auto-injectors, but also the only company with devices that feature true end-of-dose indicators.

RITA™ is a disposable auto-injector designed to inject the prefilled dose from a single Unifill syringe. RITA is more compact in size than many other marketed auto-injectors for improved patient portability, intuitive handling and convenient disposal. In addition to there being no visible springs or mechanisms, the needle is hidden from view until the completion of the injection when it can be viewed in its retracted state through a window on the side of the barrel. The true end-of-dose indicators (audible click and tactile feel) associated with the Unifill syringe can also help to minimise potential drug wastage and optimise therapy compliance.

"OSHA, THE FDA, AND MANY HEALTHCARE ASSOCIATIONS CITE A PREFERENCE AMONGST HEALTHCARE WORKERS FOR THE SELECTION AND USE OF DEVICES WITH AUTOMATIC (PASSIVE) AND INTEGRATED SAFETY FEATURES"

LISA™ (see Figure 4) is an electromechanical reusable auto-injector that completely automates the removal of the needle shield and the speed of needle insertion and retraction. In addition to enabling a user to select the speed and depth of dose delivery to help minimise pain and discomfort during an injection, the device features a single activation button, LED indicators and a push-on skin sensor. To Unilife's knowledge, LISA is the first and only known reusable auto-injector that protects the patient from the risk of needlestick injury when removing a used syringe from the device.

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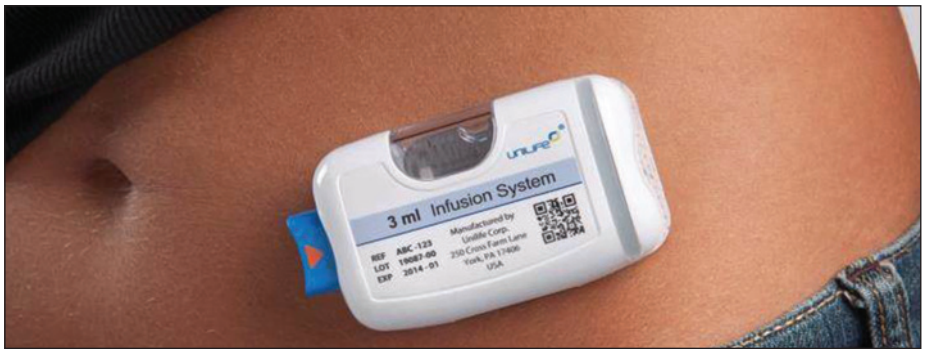

Figure 5: Unilife's scalable, flexible portfolio of wearable injectors for large dose-volumes or long duration therapies.

Figure 6: Unilife's broad, innovative portfolio of injectable drug delivery systems.

WEARABLE INJECTORS

Unilife has developed a scalable, flexible portfolio of wearable injectors (Figure 5) to meet the delivery needs of large dose volume or long duration therapies that are unsuitable for use with handheld devices. Unilife's portfolio of ReadyToGo™ wearable injectors utilises standard materials in the primary drug container, and is compatible with standard filling processes and equipment. They are programmable to deliver the measured dose over seconds, minutes or hours at a constant or variable rate based upon the specific requirements of the pharmaceutical customer, their drug and the target patient.

Importantly, the system maintains sterility of all drug contacting and fluid-path components without requiring full terminal device sterilisation. Other proprietary features include an on-body safety lock to avoid premature activation, and the automatic insertion of a flexible catheter for patient comfort. Multiple customisation options are available to pharmaceutical companies.

SUMMARY

All these factors uniquely position Unilife to serve as a long-term partner to pharmaceutical companies seeking to enable and enhance the delivery and commercial success of their injectable biologics, drugs and vaccines.

TEN POINTS OF DIFFERENTIATION FOR UNILIFE

1. A Broad, Differentiated Portfolio
We have a broad, innovative portfolio of injectable drug delivery systems that customers can leverage to differentiate their injectable therapies and out-perform the competition (Figure 6).

2. Platform-Based, Customisable Technologies
Our platform approach allows us to leverage an array of established base technologies to customise each product rapidly to specific customer, therapy and patient needs.

3. Enhancing and Extending Product Lifecycles
The safety, simplicity and elegance of our products have the potential to build therapy compliance and drive preference amongst patients, payers and prescribers to enhance or extend commercial lifecycles.

4. Dedicated, High-Performance Teams
We select and organise the best industry leaders with deep scientific and technical expertise into vertically integrated, cross-functional teams that can respond to customer needs with unparalleled speed and agility.

5. Compatible with Standard Fill-Finish Processes
Our products are designed for compatibility with standard pharmaceutical industrialisation processes and equipment to help streamline the filling, packaging and shipment of our pharmaceutical customers' products to end-users.

6. Modular Design and Manufacturing Approach
All products are engineered for modular manufacturing to enable efficient customisation and the fast, efficient scale-up of production to support a customers' pathway from clinical trials to commercial launch.

7. Advanced US-Based Production Facilities
Our FDA-registered facility has advanced development and commercialisation capabilities including highly automated precision manufacturing to facilitate the supply of high-quality products in accelerated timeframes.

8. Best-in-Class Quality Management System
So that our products meet the highest quality standards, our Quality Management System is in compliance with, and certified to, ISO 13485 to design, develop, produce and sell ready-to-fill syringes and active and non-active drug injection systems.

9. Flexible Supply Chain Framework
We have the flexibility to identify and select preferred materials and coatings for components, including those within the primary drug container, from an extensive network of established industry suppliers.

10. A Fast-Growing, Protected Patent Portfolio
We aggressively protect our novel intellectual property. Our extensive, fast-growing patent portfolio covers all device platforms and associated technologies to provide unrestricted freedom to operate.

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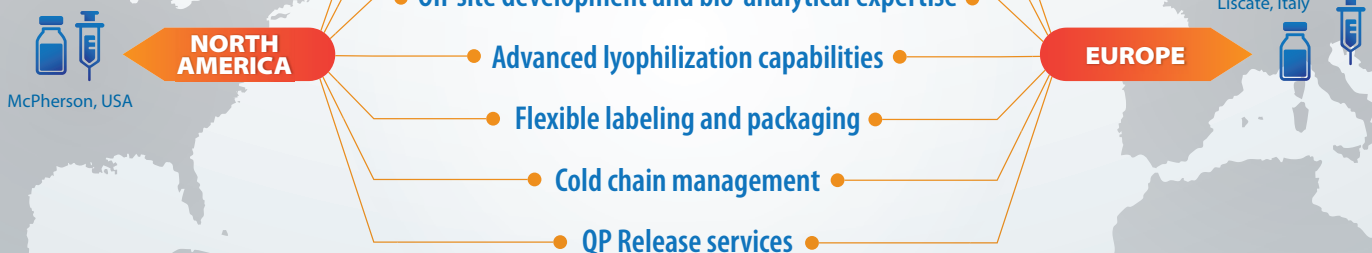

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HIGH VOLUME PRODUCTION: INJECTABLE DEVICES ON THEIR PATH TO SUCCESS

In this item, Reiner Zeidler, Sales Manager Medical Systems, teamtechnik Group, summarises the benefits of the company's modular TEAMED device production system, and its application and ready scaleability from prototype/Phase I clinical trials up through to Phase III to market.

The demand for new solutions to automate the manufacturing of medical products from Phase I clinical trials to a successful high-volume production is increasing. teamtechnik Group is one of the leading suppliers developing and implementing turnkey production systems for medical devices. With its TEAMED platform system (shown in Figure 1) the company offers an upgradeable linear production system for assembly and test.

PHASE I TRIALS: PROTOTYPE PRODUCTION WITH TEAMED POP

Assembly of injectable devices normally includes a number of complicated processes. These must be monitored during the ongoing assembly, or the result must be verified after the process. To speed up time to market, the customer ideally needs a complete final assembly line for the device from the outset – i.e. when the device enters Phase I clinical trials. Due to cost and risk factors, this was previously, generally, impossible. However, teamtechnik Group now offers exactly this option for injectable devices. The company is one of the leading suppliers developing and implementing turn-key production systems for medical devices.

With its TEAMED platform, teamtechnik now offers the possibility to perform and monitor the critical processes with fully automatic solutions at a very early stage. The machine is a small, manually operated unit. Some selected processes and tests are performed automatically.

Customers often approach teamtechnik with their device still under development. In cases like this teamtechnik offers the TEAMED PoP (Proof of Principle) machine (Figure 2a). This machine is designed for 1-5 operators working at the same time. The number of operators depends on the desired output of the machine. In our case study the output is one device per minute with one operator and up to six per minute with five operators. The operator loads all parts manually into the nests of the carrier or directly into the device. For a refined assembly process, the operator moves the carrier manually into the process station where the fully monitored assembly process is performed automatically. After a successful process, the operator pulls out the carrier and pushes it to the next station where other assembly operations are done by the next (or the same) operator(s).

> "THIS IS MADE POSSIBLE ONLY WITH A VERY STRONG MODULAR DESIGN OF THE TEAMED PLATFORMS, USING INDIVIDUALLY REPLACEABLE PROCESSES AND A MACHINE CONCEPT WITH PRE-VALIDATED SERVO-ACTUATED MOTIONS AND CAM-DRIVEN UNITS"

Before finalising the injectable device (another monitored automatic process), a camera system checks (Figure 3) for completeness

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and correct settings of all parts (e.g. counter recognition). As a next process, the cover is assembled automatically to avoid any operator intervention after the completeness check. In addition, the cover assembly is also monitored with respect to path-force.

PHASE III CLINICAL TRIALS: SMALL-VOLUME PRODUCTION WITH TEAMED STAND-ALONE

Thanks to the flexible modular TEAMED platform design, the same process units are integrated into the TEAMED Stand-Alone machine at the next level: a semi-automatic assembly line with material input by one or two operators (Figure 2b). The process stations are linked by a carrier transport system. The carrier features have the same design as in the PoP machine, but with some additional nests for manually pre-loaded parts. Almost all assembly operations are performed by automatic stations, the refined process stations are still the same as in the TEAMED PoP prototype machine.

MARKET SUCCESS: HIGH VOLUME PRODUCTION WITH TEAMED

The next level is a fully automatic high-volume line with all parts fed by bowl feeders or palletising systems (Figure 2c). For a high output the machine is running 24/7 with one or two operators. The carrier design is again like the carrier of the prototype machine. The refined processes like dosing, gluing or welding have been validated at the TEAMED PoP machine. They are still identical in design and function. This saves significant time along the entire route to market. Due to the earlier introduction to market, the ROI time is reduced significantly also.

This benefit is made possible only with a very strong modular design of the TEAMED platforms, using individually replaceable processes and a machine concept with pre-validated servo-actuated motions and cam-driven units.

ABOUT TEAMTECHNIK GROUP

Based in Freiberg, Germany, teamtechnik Group has been making intelligent and reliable automation solutions for the medical, pharmaceutical and other industries. teamtechnik is considered an international leader in highly flexible automation technology. With a total of 800 employees throughout the world, the company achieves sales of over €145 million annually. teamtechnik Group has production sites in Germany, Poland, China and the US, and a global network service.

Figure 1: The TEAMED platform system.

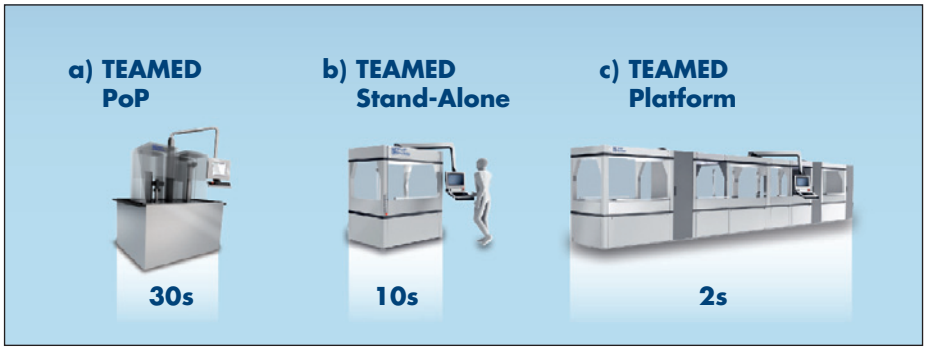

Figure 2: The modular nature of the TEAMED system means it can be applied at a) proof-of-principle/Phase I, b) at small volume production levels/Phase III, and c) and at full high volumes for market production.

Figure 3: A camera system checks for completeness and correct settings of all parts.

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HASELMEIER

Haselmeier is dedicated to meeting the self-injection needs of pharmaceutical manufacturers and patients.

In 1920, Wilhelm Haselmeier established a medical device company in Stuttgart, Germany. Since that time, Haselmeier has continued to develop and create injection devices designed for patient comfort and ease-of-use.

Today, Haselmeier is one of the leading designers and manufacturers of pen and auto-injector systems. Many of these systems feature Haselmeier's patented hidden needle system, which is designed to help patients overcome the fear of self-injection, provide a more comfortable injection and help increase compliance of the patient's medication.

PRODUCT DESIGN

Our capabilities include design and development from concept to finished device using Haselmeier's strong IP portfolio or tailoring of existing Haselmeier designs to meet customer and therapeutic needs.

All designs undergo comprehensive testing, in addition to risk management, risk analysis and FMEA design review. Three-dimensional CAD designs are utilised for creation of customer-specific concepts or customisation of existing designs.

MANUFACTURING AND QUALITY

As a specialist in the manufacture of complex system assembly, product integrity is assured by Haselmeier's manufacturing processes. All new device concepts are created with an "Integrated Design Approach" which focuses on both, the device and the efficiency of manufacture and assembly.

All manufacturing is within compliance with applied standards EN ISO 13485:2003 and Annex ll, Section 3 of the European Directive 93/42/EEC on medical devices. CE certification is certified by TÜV SÜD Product Service (Munich, Germany).

PLATFORM & PRODUCTS

Axis Pen System: variable-dose injection device

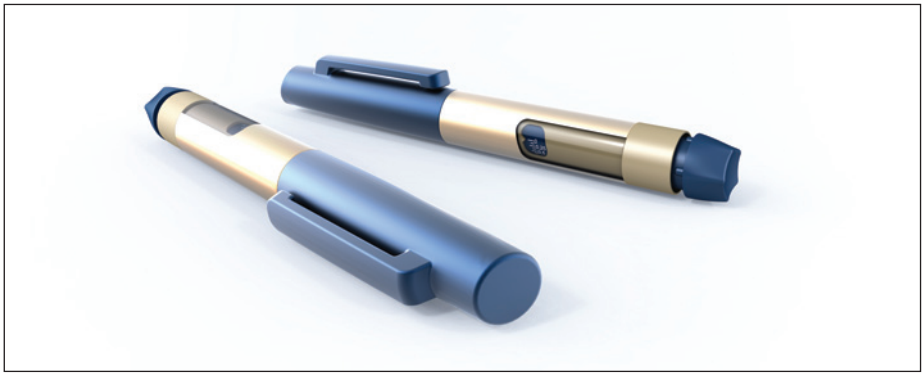

Figure 1: Axis Pen System – variable-dose injection device.

The Axis Pen System is a variable-dose injection device for manual injection. It is available in a disposable or re-usable presentation. The Axis-D and Axis-R Pen Systems (Figure 1) provide a new, unique technical function.

Figure 2: i-pen: re-usable – variable dose injection device.

Figure 3: i-pen²: re-usable – variable dose all-plastic injector device.

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Technomics

THE NEW i-pen②

- All plastic reusable pen
- Dose increments from 0,01ml to 0,6ml
- Easy and safe dose correction
- Large and easy-to-read dose indicator
- Haselmeier quality at economic cost

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The Axis pens feature:
- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale

i-pen: re-usable, variable dose injection device

The Haselmeier i-pen is a re-usable, variable-dose injection device for use with a standard 3 ml cartridge. The i-pen (see Figure 2) features an elegant non-medical design which is the result of extensive research and patient testing.

The i-pen is available as a standard Haselmeier design or can be customised to your specific requirements. It features:
- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body

i-pen²: re-usable, variable dose all-plastic injector device

The i-pen² (Figure 3) is a reusable, variable dose injection device for use with a standard 3ml cartridge. The i-pen² was specifically created to provide a high-quality pen at economic cost.

The i-pen² is available as a standard Haselmeier design or can be customised to your specific requirements. It features:
- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components

Softpen – reusable injection device

The Softpen (Figure 4) is a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution. The Softpen features:
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3 ml cartridge

Figure 4: Softpen – a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design.

Figure 5: The disposable Penlet is a fully automatic, fixed-dose injection device designed for use with a standard 3 ml cartridge.

Penlet – disposable, fixed-dose injection device

The Haselmeier disposable Penlet is a fully automatic, fixed dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue which is followed by delivery of the solution. The Penlet features:
- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection

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TUNGSTEN RELEASE QUANTIFICATION: A PREDICTIVE TOOL TO IMPROVE COMPATIBILITY WITH BIOMOLECULES

In this paper, Dr Daniele Zuccato, R&D Department, Dr Andrea Sardella, R&D Engineer, and Dr Alberto Chillon, R&D Department, all of Nuova , Stevanato Group, and Dr Emanuel Guadagnino, Scientific Advisor to Stevanato Group, describe the development of their method for the analysis of tungsten levels in glass prefilled syringes at sub-ppb levels, and detail the method itself.

INTRODUCTION

Prefilled Syringes (PFS) are recognised worldwide as the most appropriate container for the delivery of new biopharmaceutical drugs such as recombinant proteins, monoclonal antibodies (MAb) and other bio molecules. These complex molecules require the highest possible level of inertness from all different parts of the PFS system that may otherwise have a marked impact on the protein products over their shelf life. Container closure integrity, surface state of the glass barrel after silicone oil treatment, extractables and leachables from the whole system are critical factors to be kept under strict control.

For this reason the concept of chemical inertness of a PFS system must be reconsidered, as the glass barrel is subject to a specific transformation process to form the cone and the flange, the wall surface is modified by the silicone-oil treatment and the cone by needle gluing. Extractables & leachables from any component or material may impair the integrity and therapeutic efficiency of biopharmaceuticals, meaning that they must be substantially minimised.

THE TUNGSTEN ISSUE

This paper is focused on the development of an analytical procedure intended to estimate the tungsten contamination level in a glass syringe. Recent studies have shown that soluble tungsten polyanions may cause the precipitation and/or aggregation of biomolecules [1] such as MAbs to form visible particles. It is also reported that

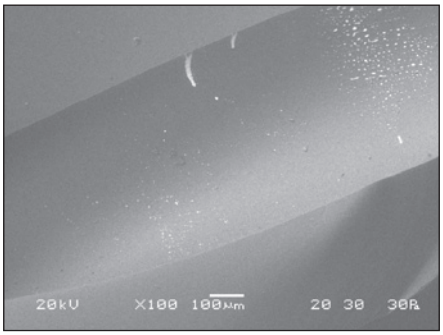

Figure 1: SEM image of the syringe funnel inner surface.

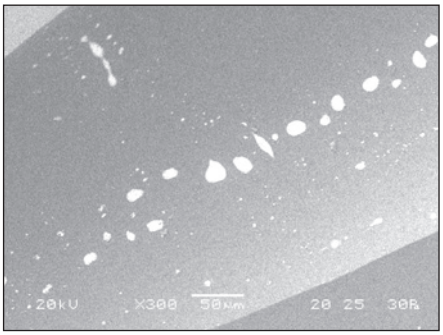

Figure 2: Magnified SEM image of tungsten deposits found on the inner surface of the syringe funnel.

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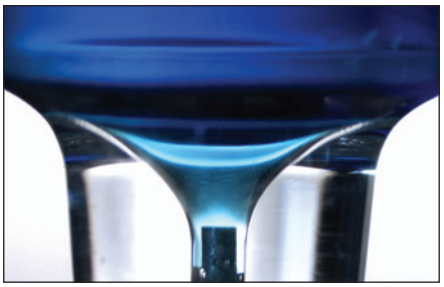

Figure 3: Evidence of the contact between the filling liquid and the tungsten contaminated area on a staked needle syringe.

exposure of proteins to increasing concentrations of tungsten polyanions in acidic pH strongly favours aggregation and may induce reduced activity and increased immunogenicity.[2,3,4]

The native borosilicate glass does not contain tungsten, arising from the contamination of the raw materials for instance, in a significant amount likely to induce protein aggregation. On the other hand it is well known that during the cone formation of glass syringes a tungsten containing pin is kept in contact with the glass tip to form the bore where the needle shall be accommodated in a later stage. The use of pins at elevated temperatures favours the formation of tungsten oxides (WO_3 and WO_4) which evaporate and interact with the outermost glass surface of the funnel to form soluble sodium tungstate polyanions that become easily extractable. Figures 1 and 2 are scanning electron micrographs of the inner surface of the funnel, the white spots represent deposits of sodium tungstate, as confirmed by punctual EDS analysis (results not shown here).

Several experiments have been carried out to estimate the maximum permissible concentration of tungsten which is deemed not to cause an adverse effect to biopharmaceuticals. It was found that the typical tungsten concentration which may cause a detrimental interaction with proteins is about one order of magnitude higher than the one which is found in PFS systems[3] and that 500 ppb is a reasonable estimate of the mean tungsten concentration that is extractable from glass syringes.[5]

CHALLENGES IN DEVELOPING A RELIABLE METHOD FOR TUNGSTEN ANALYSIS

From a regulatory point of view, a worldwide established procedure for the extraction and detection of tungsten from a PFS system does not exist.

The lack of a commonly established method results in a confusing market situation: each pharmaceutical company established its own acceptable limit for tungsten release and a proprietary extraction method to verify the compliance with its own specifications.

This uncertainty also generated an unclear situation from the syringe producers' point of view, for each customer has its own in-house method and compliance with its own specifications.

SGLab, the research laboratory of Nuova Ompi – Stevanato Group, has developed a reliable method for the measurement of tungsten, based on a trial and error approach.

The following factors soon appeared to be critical: ensuring the wettability of the funnel area by an appropriate filling procedure; selecting the most appropriate extraction conditions; and developing a digestion procedure that could guarantee complete tungsten extraction, possibly in one single run.

FUNNEL WETTABILITY

The tungsten salts are mostly present on the syringe funnel, the small gap which is purposely created by a tungsten pin where the needle will be assembled.[4] This area is typically in contact with pharmaceutical formulation during the vacuum plunger placement process, exposing the solution to the highest possible concentration of tungsten. From an extraction method perspective, this means that it is mandatory to force an intimate contact between the extraction solution and this small area of the syringe.

In principle any operation, either manual or automatic, that guarantees the full contact between the contaminated area and the extracting solution may be used. At SGLab, a manual procedure is used. The effectiveness of the procedure for the complete wetting of the small funnel area has been verified with a colouring solution. Figure 3 shows that an intimate contact between the extraction liquid and the contaminated area has been achieved.

EXTRACTION METHODS

Several extraction procedures were tested using two different approaches: a) dissolution of the outmost inner surface of the funnel by a mixture HF/HCl; and b) extraction by water of the soluble tungsten salts.

The surface attack by a cold mixture of HF/HCl is well described in the literature [6,7] and at room temperature is known to produce the dissolution of glass layers about 1 μm thick by per minute of contact. This method is well reproducible, goes to completion within ten minutes and no further extractions are required, but regulations concerning the safe use of HF in the lab means that this procedure is not recommended in most laboratories.

Comparable results were obtained using a two-stage water extraction at 75°C for 1h in a ultrasonic bath. During the second run the extraction of tungsten was always less than 10% of the total amount extracted during the first run.

In Figure 4, average inductively coupled plasma, optical emission spectroscopy (ICP-OES) results from the two methods are compared.

As expected, tungsten from HF/HCl is higher because the dissolution method guarantees the complete removal of tungsten that conversely is only partly extracted by water. As the coefficients of variation are comparable, it was concluded that both methods were able to reveal the presence of tungsten peaks that sometimes may occur due to an uncontrolled forming process. On the other hand pharmaceutical companies are conscious that the extraction ability of any buffer solution intended to go in contact with the funnel will never produce extraction values by far comparable with those obtainable by HF. This first screening, and subsequent discussions with pharmaceutical companies gave us confidence that the use of an aqueous solution at high temperature is sufficient to simulate the extractability produced by any parenteral preparation over its shelf-life.

	Dissolution (HF/HCl mixture)	Extraction (aqueous solution)
Average (n=50) ppb W	440±128	321±90
% RSD	28	31

Figure 4: Comparison of Tungsten ICP-OES results from different extraction methods.

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TUNGSTEN MEASUREMENT

Extraction solutions can be analysed by either ICP-OES (Figure 5) or inductively coupled plasma, mass spectroscopy (ICP-MS) (Figure 6), depending on the expected tungsten concentration.

Tungsten detection limits by ICP-MS are typically approximately 0.1 ppb while the corresponding LOD by ICP-OES is two orders of magnitude higher (typically around 60 ppb). One of the major advantages of using ICP-MS is due to the smaller volume which is required to perform a single analysis. Syringes of 0.5 mL capacity can successfully be analysed one-by-one using ICP-MS, while ICP-OES would require extracts from several syringes to be combined to reach at least a 2 mL volume.

The increasing sensitivity of biomolecules to foreign contaminants combined with continuous improvements in the forming process over the years, has dramatically reduced tungsten levels in syringes. The ICP-MS technique is therefore the most eligible to measure tungsten and other contaminants at ppb and sub-ppb levels.

DESCRIPTION OF THE SGLAB METHOD

Syringes are filled with distilled water taking care that the funnel is completely wetted by the solution, plunger and needle shield are inserted manually. Syringes are placed in a metallic rack, heated up to 75°C and treated in an ultrasonic bath for one hour. After cooling at room temperature each syringe is washed with 1 mL of aqueous solution and then measured with both ICP-OES or ICP-MS, depending on the expected tungsten level. A second extraction is performed as a validation step to guarantee the completeness of each single extraction, whereas routine analyses are performed by one single extraction.

Figure 5: SGLab equipment, ICP-OES.

NUOVA OMPI SYRINGE SCREENING CURRENT PRODUCTION

The production of an EZ-fill™ syringe (sterile syringe, ready to be filled) requires a sequence of different stages: the bulk syringe production, the needle assembly, the washing + siliconisation + sterilisation finish.

The impact on the tungsten deposition due to each single stage was evaluated. Compared to the bulk, the staked needle syringe showed a considerable masking effect due to the reduced glass surface exposed to water extraction when the needle is in place (see Figure 7).

The washing step performed before the siliconisation is not sufficient to substantially reduce the tungsten content. In agreement with previous studies,[4] results obtained from syringes before and after the washing step are nearly the same (see Figure 8).

Further research showed that three different tungsten concentrations can routinely be achieved depending on the final tuning of the process conditions. The standard production of 1mL long EZ-Fill syringes shows typical tungsten values below 1,000 ppb. The so-called "low tungsten" production that is obtained using a particular care on the cone forming step, shows typically tungsten values below 500 ppb. For pharmaceutical products which are known to be very sensitive to tungsten, the use of pins made of tungsten-free material can allow to reach tungsten levels well below 10 ppb (Figure 8).

CONCLUSION

The development of a procedure to be used as a rapid, reproducible method for the determination of extractable tungsten from a PFS system is described. Several methods were tested. The method proposed here simulates the extractability obtainable with parenteral preparations over their shelf life and shows high efficiency combined with a good reproducibility.

The ready availability of a wide selection of analytical instruments at SGLab allowed the systematic screening of the current syringe production at Nuova Ompi – Stevanato Group. As a follow-up a substantial improvement of the syringe-forming process was achieved, that is now capable of producing on an industrial scale batches of prefilled syringes compatible with the most sensitive biomolecules in the market.

A close collaboration between the pharmaceutical companies and the PFS producers is highly recommended in order to maintain the complete therapeutic efficiency of the new biomolecules in contact with the primary glass packaging.

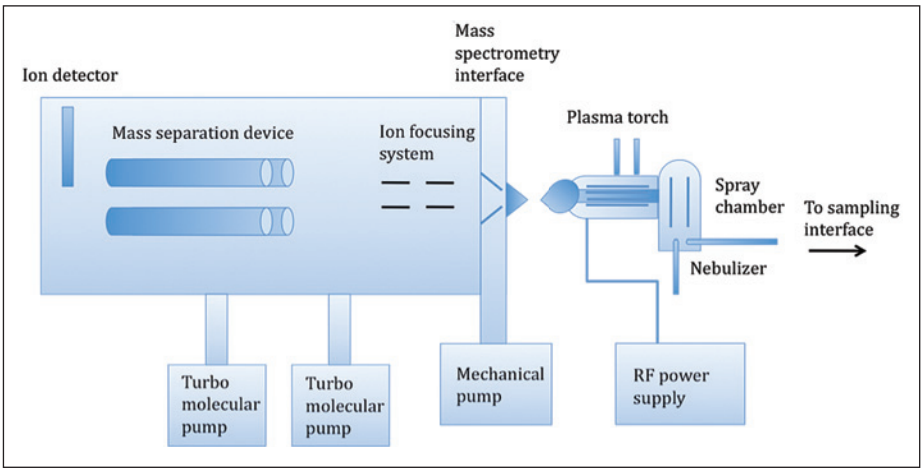

Figure 6: Schematic view of an ICP-MS system.

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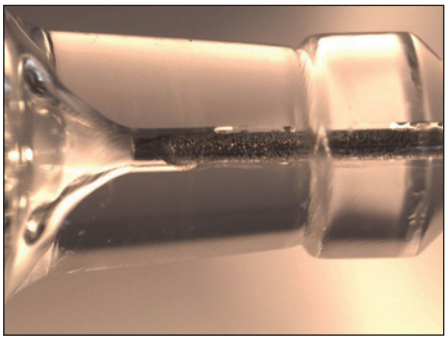

Figure 7: Reduced exposed surface due to the needle's presence.

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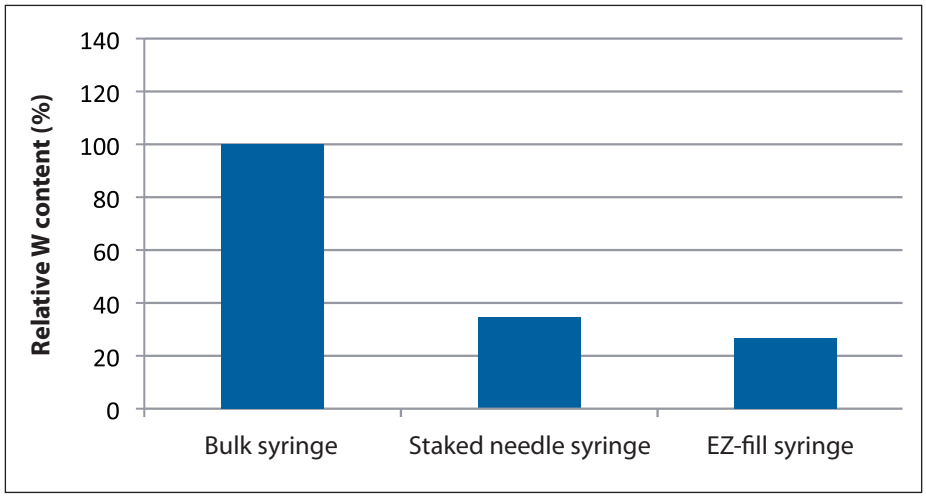
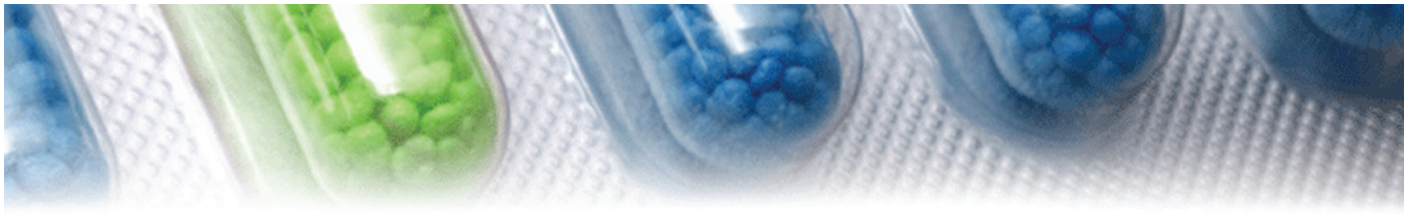


Figure 8: Impact of the syringe-forming stages on the final extracted tungsten.

Process type	Extracted W (in ppb)
Standard	<1000
Low-tungsten	< 500
Tungsten Free	< 10

Figure 9: Typical tungsten extraction values of the current EZ-fill™ syringes process.



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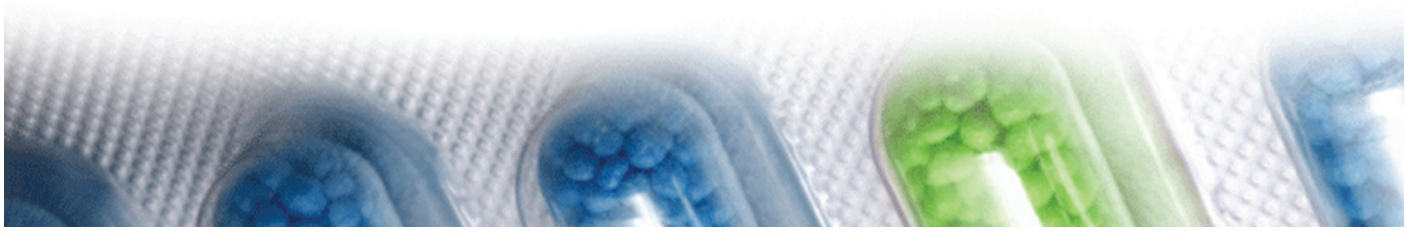

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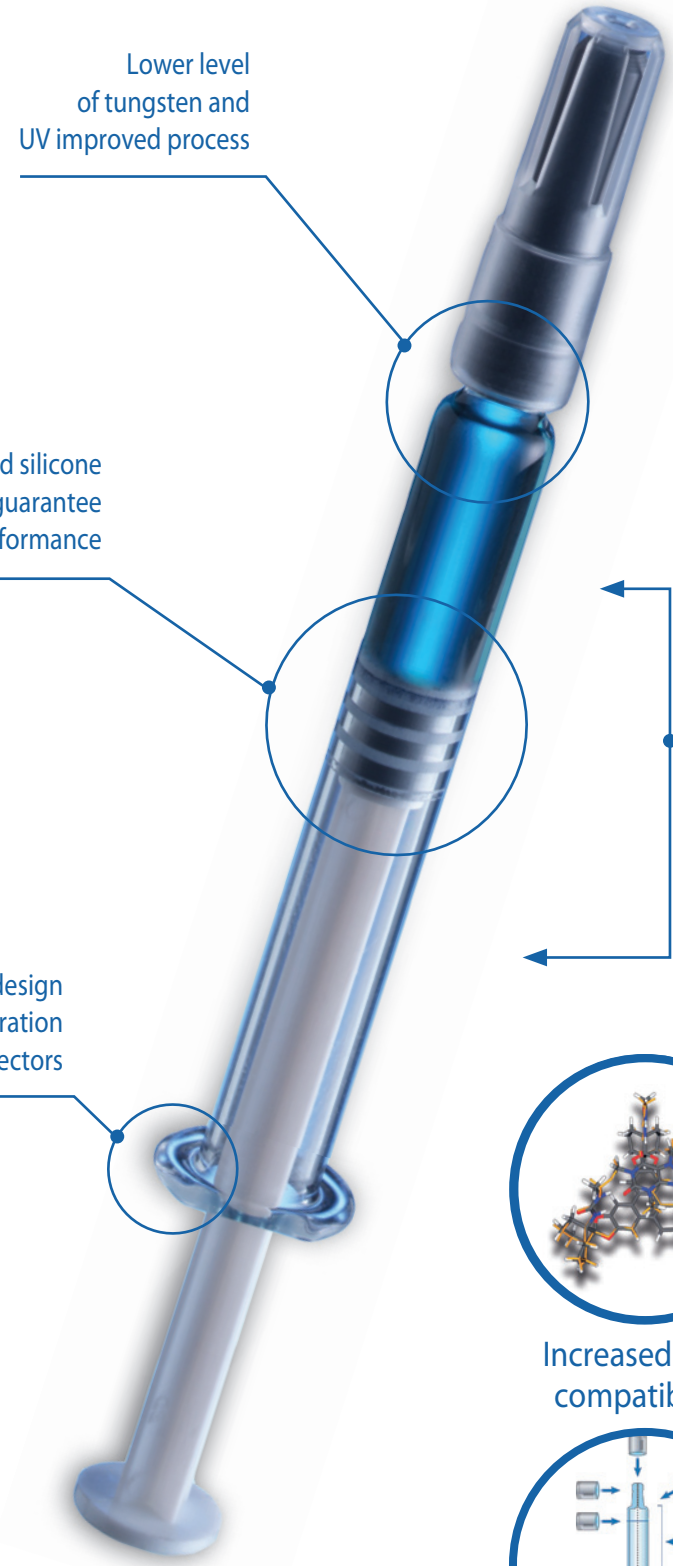
Syringes for Biotech



Lower level
of tungsten and
UV improved process

Optimized silicone
distribution to guarantee
high gliding performance

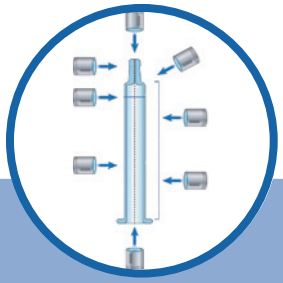
Optimized design
for perfect integration
with auto-injectors

Washing
treatment
before
annealing

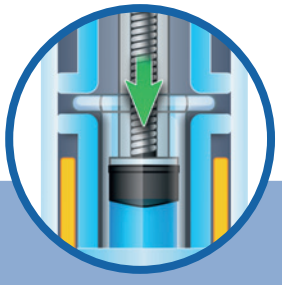
100% dimensional
and cosmetic
inspection
by camera

Increased drug
compatibility

Increased compatibility
with AI



Increased cosmetic
quality



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A NEW ELECTRONIC MULTIUSE AUTO-INJECTOR: THE FLEXI-Q EMU

In this article, Menachem Zucker, PhD, Vice-President and Head of the Injectable Drug Delivery Devices (I3D) Division at Elcam Medical, provides insights into the world of biological drugs and Elcam Medical's innovative drug delivery solutions.

Elcam Medical, a world leader of OEM disposable medical devices and a provider of solutions for flow control needs, provides its customers with unique, innovative and differentiating solutions that create a significant competitive advantage in their markets.

Elcam emphasises end-to-end customer experience, excellent and seamless customisation and integration of its devices in the customers' end products. The company has 30 years of experience within the medical device industry, leveraged into all its drug delivery solutions.

"ELCAM BELIEVES THAT PHARMACEUTICAL COMPANIES WILL HAVE A SIGNIFICANT AND GROWING NEED FOR DIFFERENT AUTO-INJECTORS. EACH PHARMA COMPANY WILL REQUIRE A UNIQUE DESIGN AND SHAPE OF THE DELIVERY DEVICE TO FIT THEIR SPECIFIC DRUG AND USERS."

Biotechnology drugs are on the rise in the pharmaceutical market. While only a few of these drugs are currently approved for use in the US, many more are in use in clinical trials, and still others await FDA approval. The majority of these drugs are very fragile proteins that can only be administered by injection. These injections are typically performed using conventional syringes and needles. Drug delivery systems can elevate both the therapeutic and commercial value of a drug and the growth of alternative injection devices is driven by these three factors: improved patient compliance; improved patient quality of care; and the trend toward self-administered drug therapy.

The selection of drug delivery devices depends on several factors, including formulation, primary package, dosing and usage. The devices available range from prefilled syringes (PFS) to auto-injectors such as pen injectors, needleless injectors and patch pumps.

Elcam Medical, a leading provider of disposable medical devices to the US and European OEM markets, has developed a new and innovative line of drug delivery devices designed for the administration of biotechnology drugs.

In recent years, Elcam Medical, and more specifically its Injectable Drug Delivery Devices (I3D) Division, have focused on developing and manufacturing high-quality, patient-compliant auto-injectors for biologic drugs.

Elcam believes that pharmaceutical companies will have a significant and growing need for different auto-injectors. Each pharma company will require a unique design and shape of the delivery device to fit their specific drug and users. Thus the company continues to invest in

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Figure 1: The electronic Flexi-Q eMU, the newest auto-injector in the Flexi-Q line.

"ELCAM MEDICAL DELIVERS NOT JUST A PRODUCT, BUT A PROMISE: TO COMBINE EXCELLENCE WITH COMMITMENT; TO WEAVE TOGETHER RELIABILITY WITH INTEGRITY; AND TO OFFER COMPETITIVE PRICING FOR SUPERIOR RESULTS"

this market to increase its portfolio and enable it to provide solutions to meet a variety of requirements.

Among its drug delivery solutions are: auto-injectors for drugs in vials, in prefilled syringes and in cartridges; auto-injectors for high viscosity drugs; reusable auto-injectors that enable dosing; and devices compatible with emerging market needs.

THE FLEXI-Q LINE

The Flexi-Q drug delivery line includes a range of disposable auto-injectors and multiuse auto-injectors. The devices are designed to maximise user compliance in self-administration of injectable drugs. They suit a wide range of patient populations, including those suffering from rheumatoid arthritis (RA) and multiple sclerosis (MS), and provide a wide range of customisation options such as delivery volumes, viscosity range, injection time, primary packaging selection and more.

NEWEST AUTO-INJECTOR: FLEXI-Q EMU

Elcam Medical's newest auto-injector under development is the Flexi-Q eMU, shown in Figure 1. An electronic multiuse auto-injector, it comprises a reusable driving unit and a disposable cassette, compatible with standard PFSs containing biologics or cartridges suitable for variable dosing.

The Flexi-Q eMU is intended for use with chronic diseases that require frequent injections, such as MS, diabetes, and growth hormone disorders. The reusable design lowers the cost per injection and reduces the volume for storage and disposal.

Flexi-Q eMU advantages include:

- Reusable, electronic driving unit
- Unique disposable cassette incorporates cartridge for variable dosing or PFS for biological drugs
- Easy-to-use interface features LCD screen and operating buttons
- Automatic needle insertion
- Controlled injection time: 3-100 seconds
- Controlled needle penetration depth: 6-12 mm
- Fixed or variable delivery volumes: 0.1-1.0 mL (PFS), and up to 3 mL (cartridge)
- Compatible with injection of high-viscosity drugs
- Drug delivery begins only after full needle penetration
- Very quiet operation
- Incorporates safety features with needle protection before and after injection, preventing needle-stick injuries
- Includes calendar software for injection reminders and logs
- Easy communication with PC (through micro USB) for loading injection programs and reading injection logs
- Smartphone design, Pocket size: 120 L x 60 W x 20 H mm
- Rechargeable batteries: 30 injections per battery charge.

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FLEXI-Q PFS

A fully disposable auto-injector for PFSs

This single-use auto-injector features passive needle shielding, allows better patient safety and encourages patient compliance in self-injection.

The ultimate differentiating vehicle when considering the launch of a new drug or as a life cycle management tool for an existing drug.

FLEXI-Q DV

A fully disposable auto-injector for drugs in vials (both lyophilized and liquid forms)

The only commercially available device that provides a unique, user-friendly solution for self-administration of these drugs.

This single-use auto-injector allows simplified reconstitution and aspiration from conventional vials, features safety needle shielding throughout the process, provides life cycle management capabilities for new and existing drugs, encourages better patient compliance and improves safety.

FDA 510(k) cleared

FLEXI-Q HV

A fully disposable auto-injector for low to high viscosity liquid drugs in PFSs

This single-use auto-injector features passive needle shielding, allows better patient safety and encourages patient compliance in self-injection.

The ultimate differentiating vehicle when considering the launch of a new drug or as a life cycle management tool for an existing drug.

FLEXI-Q MU

A Multi-use auto-injector for drugs in prefilled syringes and vials

Features a reusable driving unit and a cost-effective, automatic needle protection disposable cassette for use with standard PFSs and vials. For use in chronic diseases that require frequent injections (e.g., MS).

The partially reusable design lowers the cost per injection and reduces the volume for storage and disposal.

Figure 2: The rest of the range of products in the Flexi-Q line of auto-injectors.

Summarised in Figure 2, Elcam Medical's Flexi-Q Auto-Injector Line for Self-Administration of Drugs, Biologics and Biosimilars are:

- Safe and simple
- Reduced pain perception
- Injection starts only after full needle penetration
- Easy, safe drug reconstitution and aspiration from vials
- Drug viscosity range
- Unique life cycle management tools (DV → PFS)

A PROMISE, NOT JUST A PRODUCT

Elcam Medical delivers not just a product, but a promise: to combine excellence with commitment; to weave together reliability with integrity; and to offer competitive pricing for superior results.

Elcam Medical is a world-class producer of disposable medical devices for the OEM market and provider of innovative solutions for specialised flow control needs. Working with the medical industry's leading companies, Elcam Medical has particular expertise in the areas of fluid management and IV therapy, vital sign monitoring and drug delivery.

The company's long-term partnerships within the medical industry have taught it that flexibility and customisation are key ingredients for success. This flexibility can be found in Elcam's teams with their customer-centric approach, in products that adapt easily to meet customer needs and in a flexible, open business attitude.

Elcam Medical is experienced in working under tight deadlines without compromising quality. The company operates in strict compliance with ISO 9001:2008 and ISO 13485:2003 standards. The quality system is in full accordance with the US FDA QSR.

Elcam Medical has production sites in Europe, the United States and Israel.

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NEW APPLICATIONS AND MARKET TRENDS FOR PREFILLABLE CARTRIDGE COMPONENTS

Here, Tibor Hlobik, Global Director, Marketing, for Prefillable Syringe Technologies, West Pharmaceutical Services, details some of the technical specification options of cartridges for injectable drug delivery, and describes the applications of cartridge-based injectable drug delivery systems. An overview of market and quality drivers in this space is also provided.

Cartridge-based administration using injection device systems has dominated the insulin market for many years. In 2011, the insulin market for cartridge-based container closure systems was at an estimated 1 billion units. Additional applications for cartridge-based container systems include dental, at more than 450 million units per year, and therapies such as human growth hormone, interferon and epinephrine. In fact, thanks to lower production costs when compared with vial and syringe systems, cartridge-based delivery has found a widespread and growing market.

As the healthcare market continues to evolve and administration in the home-care setting increases, cartridge-based delivery has made inroads into a variety of markets. Today, systems are in use or under consideration for such therapeutic categories as anaemia, rheumatoid arthritis (RA), dermatology, oncology and hepatitis. In addition, insulin use is increasing due to the growth in population and higher demand in emerging countries, so the diabetes market is evolving to provide more accurate and reproducible dosing. Insulin pen injectors, which commonly employ a 3.0mL cartridge, provide convenience and ease of use to patients, which may in turn help to improve compliance.

As the global market moves toward home-based care and multi-dose delivery systems for select therapeutic categories, pharmaceutical manufacturers are now seeking sterile components, including cartridges, plungers and other high-quality components, that are capable of offering ready-to-use quality and high functional performance in a variety of delivery systems and devices. Such quality is essential to the functionality, safety and efficacy of pens, injection devices and cartridge-based delivery systems.

SELF-INJECTION IN THE HOME

Over the years, cartridge-based pen and custom drug delivery devices have made significant advances in new markets, brand differentiation and self-administration. New categories include MS, RA, hepatitis, osteoporosis, haemophilia, reproductive health, anaemia, haemolytic disease, antithrombotic therapy and oncology. Additionally, the types of devices marketed by manufacturers have become more diverse. Pen injectors have evolved to accommodate liquid or lyophilised formulations, an advantage over other types of devices that are limited to liquids. Newer developments in pen devices include the use of: needle safety devices; automated needle insertion and injection; needle-free; small and large volume dosing capabilities; and electronics.

Cartridges use solid elastomeric plungers and elastomer-lined aluminium seals to maintain drug product purity and function to deliver precise doses with combination product devices. A broad spectrum of different cartridge formats, as well as formats for solid plungers and lined seals, is available.

The glass bodies (see Figure 1) are usually produced from neutral borosilicate glass, type I. The common standards are ISO 11040-1 glass cylinders for dental local anaesthetics cartridges and ISO 13926-1 glass cylinders for pen injectors for medical use. Standard sizes produced are 0.6, 1.5, 1.8, 2.2 and 3mL, but special sizes can also be manufactured. Cartridges can be used with pre-printed or with plain glass bodies that are later labelled.

Plungers and seal liners are available in a variety of different elastomeric formulations that meet the standards of European, Japanese

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Figure 1: Cartridge Body and Components Examples.

and US Pharmacopoeias. Discs for lined seal technology can be a monolayer for single dose applications or a dual material laminate (layer of halo butyl for drug contact and layer of isoprene for needle puncture fragmentation resistance) for multi-puncture applications.

While a number of different brands and models are available, most insulin pens fall into one of two groups: reusable pens and disposable pens.

Before using a reusable insulin pen, a patient must load a cartridge of insulin (sold separately in boxes). Cartridges typically hold 150 or 300 units of insulin. Depending on the size of the doses, a cartridge may provide enough insulin to last for several days. When the cartridge is empty, it is thrown away and a new one loaded.

Disposable insulin pens are preassembled with insulin-filled cartridges and thrown away when empty. Most disposable pens used today hold 300 units of insulin. Disposable pens are generally more convenient than reusable pens because cartridges do not need to be loaded, but usually cost more to use than reusable pens.

In most cartridge applications, plungers and lined seals are created custom to the pharmaceutical manufacturer. High-quality components must not only perform and run at acceptable speeds on feeder bowls, tracks and assembly hardware, but should also be backed by the expertise and technical knowledge of the component manufacturer. Strong partnerships between component and pharmaceutical manufacturers ensure that components are properly adapted to existing and new fill-finish lines. Consistent and predictable quality can also ensure that there will be minimal processing variation during filling and assembly.

For pharmaceutical manufacturers, selection of a high-quality component helps to ensure that the elastomeric formulation does not negatively affect a drug product's efficacy and safety profile. Components manufactured with known design space can help minimise the risk of drug product contamination from particulates, and help to ensure the reliability of component functionality when used in a device or delivery system. For example, plunger dimensions and design characteristics, as well as siliconisation consistency play a key role in accuracy of plunger movement for precise dosing. Finally, all components must meet regulatory compliance and industry standards intended for safe drug delivery (e.g. ISO standards). Selection of solid plungers and lined seals in modern formulations, in the latest designs, in ready-to-use or ready-to sterilise quality, can help to ensure that components move through fill-lines smoothly, whilst adding value and mitigating risk for pharmaceutical manufacturers.

MARKET DRIVERS

As the worldwide market grows for insulin, biotechnology companies, PFS/cartridge manufacturers, innovative adaptive filling technology and pharmaceutical manufacturers will require high-quality components. Steady growth in the diabetic population and the longevity of the disease is expected to drive the insulin delivery market.

The insulin delivery market consists of insulin jet injectors, insulin pens, insulin pumps and insulin syringes. Insulin pens will remain the dominant market segment, and the insulin pumps segment will continue to grow at a high rate.

"COMPANIES ARE USING LARGER DELIVERY VOLUMES AND AVOIDING HIGHLY CONCENTRATED PROTEINS TO PREVENT AGGREGATION"

In the biotechnology market, recombinant proteins and advances in biotechnology are driving the evolution of injection devices and innovation for drug delivery. Companies are changing drug formulation formats by using larger delivery volumes and avoiding highly concentrated proteins to prevent aggregation. Customer product-specific strategies now include combination product concepts that provide brand positioning, safe and reliable administration and self-administration. Many of these strategies are incorporating cartridge-based delivery systems.

A specific autoimmune drug segment is already established with blockbuster drugs such as Humira (Abbott/Takeda) in prefilled syringe systems, Enbrel (Amgen/Pfizer/Takeda) in vial and prefilled syringe systems, and Remicade (J&J/Merck/Tanabe) in vial, but has a very strong pipeline segment of Phase II-III subcutaneously delivered drugs being considered for delivery in cartridge based devices. Growth of biologics in the autoimmune space is forecast to grow to US$55 billion (£34 billion).

Prefilled syringe and injection device units will continue to grow at a fast rate over the coming years, but growth is set to decline in 2016 and beyond. Volume is expected to rise from 3.16 billion in 2012 to 5.73 billion units in 2018, as reported by Greystone Research Associates.

New fill-finish technology is being developed by all the major machine manufacturers including Groninger (Crailsheim, Germany), Inova (part of Optima Packaging Group, Schwaebisch Hall, Germany) Bosch Packaging (Crailsheim, Germany) and Bausch & Ströbel (Ilshofen, Germany), that allows flexibility for filling of small campaigns and with multiple container-closure systems. This is driven by high growth in biotechnology and the need to provide multiple container closure/device systems for the same drug based on patient population and or geographic location. These systems use sterile components including: vials/stoppers/seals; syringes/plungers and cartridges/plunger/lined seals; and filled under RABS or barrier isolator technology conditions.

QUALITY DRIVERS

Cartridge-based drug delivery is complex as the container closure system must function with 100% reliability and in harmony with a pen device or a more sophisticated integrated device. The plunger and seal components play a key role in drug administration, which in most cases is performed by the patient. Modern elastomer formulations that meet global pharmacopeia compliance with low extractables, and those that are free of dry natural rubber will help to mitigate patient safety risk when used in cartridges.

Selecting elastomer closure configurations in market-proven designs and to quality standards required for regulatory submission can minimise drug development time to market.

Elastomer components delivered in a ready-to-sterilise or ready-to-use format can help a pharmaceutical company avoid quality risks associated with internal preparation of components, particularly during handling, washing, siliconising and packaging operations. Components that are supplied washed and rinsed in Water for Injection (USP) meet bioburden, endotoxin and particulate requirements, and are siliconised to controlled levels. The process is validated and documented and meets all relevant global regulatory requirements as listed in the US FDA's 21 CFR 211.94, Drug Product Containers and Closures.

Partnerships early in the drug development process between pharma companies and component manufacturers can help ensure a smooth transition to cartridge-based applications, and provide high-quality components that may help with the functionality, safety and efficacy of drug product delivery to the patient.

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SHL GROUP

UNDERSTANDING WHICH TYPES OF DESIGN SHOULD BE DRIVING INNOVATION AT DRUG DELIVERY DEVICE SUPPLIERS

As market demand for self-injection devices, such as auto-injectors, continues to grow at a rapid pace, greater emphasis is now being placed on how device companies can innovate. This innovation centres on fulfilling the device needs of biopharmaceutical companies today and helping them bring their combination products to market. Steven Kaufman, Global Marketing Director, SHL Group, writes here about the importance of design innovations that are required to make a drug delivery device by focusing on the areas of mechanical design, industrial design and manufacturing design.

OVERVIEW

Innovation continues to be a word that is frequently used throughout various industries today. However, when taking into consideration the conservative nature of the biopharmaceutical industry and the device companies that work within that industry, introducing new and innovative technologies can take a significant amount of time to implement. Safety is always a priority and as a result, technologies that are proven on the market are generally preferred.

When launched, the DAI disposable auto-injector (shown in Figure 1) set a new standard within the industry. Not only was it easier to use and more intuitive than any other such device on the market, it incorporated some innovative safety solutions. A safety needle shield extended out after the injection was completed to help prevent needle-stick injuries. A larger viewing window gave patients the ability to check the biologic prior to injection and also see the coloured plunger rod when the injection was compete. A patented interlock also helped to ensure that the device would only inject when the patient was ready.

Drug delivery devices need to suit the unique needs of various patient groups. Safety, intuitive-

Figure 1: The DAI disposable auto-injector incorporates a safety needle shield, large viewing window, a coloured plunger rod and a patented interlock.

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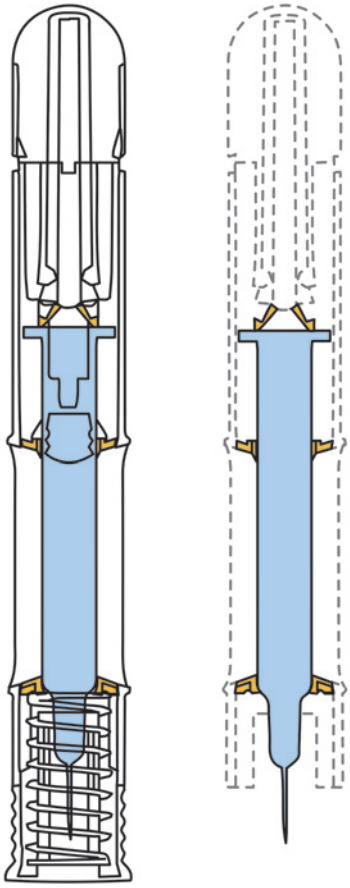

Figure 2: The Molly™ auto-injector holds the PFS firmly in place by the neck instead of at the flange allowing for more injection force absorption and reducing the chance of syringe breakage.

ness and ability to customise are often top priorities for biopharmaceutical companies. Close partnerships with various players in the device infrastructure are needed, from filling companies, human factor consultants, and automation equipment suppliers, to regulatory experts that help to get market approvals for combination products. Effective communication and the sharing of key learnings have increasingly become vital.

Companies that produce devices need to anticipate changes in primary container preference, injection volumes and of course, viscosities. Auto-injectors, in particular, remain in high demand with the increasing number of injectable biologics coming to market, including generic injectables and biosimilars. Biopharmaceutical companies are looking more closely at new technologies, whether it is plastic prefilled syringes (PFS) or talking auto-injectors, but at the same time they face increasingly short timelines and related regulatory scrutiny.

Nonetheless, it is possible for device companies to innovate effectively now by focusing on mechanical, industrial and manufacturing design solutions to ensure that suitable devices are available at an earlier stage. Thus, how device suppliers can better prepare their companies and product lines to meet this demand is worth highlighting.

MECHANICAL DESIGN

Although electronics have become a fundamental part of our lives with the adoption of smartphones and tablets, the vast majority of single-use, disposable auto-injectors continue to use mechanical solutions, not electro-mechanical, at this time. These mechanical solutions are the foundation of most auto-injector programs and the preference for any new device or device platform is to have it based on a "proven" mechanical design. This design will still require extensive testing and must be vetted and reviewed carefully. Such designs can take many years to develop and involve the investment of millions of dollars and sometimes starts 5-10 years in advance.

In the past, such mechanical designs were typically enhanced and perfected with follow-on funding from biopharmaceutical customers. This would also allow for specialised device customisation that would relate directly to the primary container, type of drug, usage of the device and the patient group. These biopharmaceutical companies were typically large and could thus offset these investments when the drug launched on the market. More recently we are seeing a trend towards shorter timelines and reduced investments both from big biopharma companies and smaller speciality biotech firms. The level of knowledge and experience can differ greatly between companies, which is why experienced consultants are becoming increasingly important.

More than ever, the drug delivery device supplier is being relied upon to step-up investments in technology and device platforms and to ensure that mechanical designs have proven functionality in place at a much earlier stage. Investments in related IP are considered to be crucial and, when the device is soon ready to be produced, Freedom To Operate (FTO), has to be demonstrated. Given the changing landscape, especially in the area of auto-injectors, it is one thing to develop a new technology, but quite another to ensure that the proper patents are put into place. With drug valuations moving from millions to hundreds of millions to several billions of US dollars for injectables, nothing can be left to chance.

One of the most effective innovation strategies device companies should consider is to have a range of proven mechanical design solutions developed and tested in advance. Then, these designs can serve as the basis for several different types of self-injection systems that can be offered to biopharmacuetical companies.

Figure 3: SHL's latest auto-injector, Amber™, is a two-step "push-click" device.

SHL, for example, has mechanical engineers work closely with our design and technical teams to develop proven mechanical designs that address several key challenges in the world of auto-injectors. One challenge is increased viscosity and we currently have two internal programs that provide solutions for highly viscous injectables. Another key development relates to where the primary container is supported within the device. Some areas of a PFS handle force and stress better than others. Devices such as the Molly™ auto-injector hold the PFS firmly in place by the neck instead of at the flange to allow for more injection force absorption and reduce the chance of syringe breakage (see Figure 2).

The design of the Molly™ auto-injector provides an example of a device based on a proven and patented mechanical design. It was the first ever pre-configured auto-injector to be made available to biopharmaceutical companies. Molly™ was designed to be more compact based on studies that showed patients wanted more discreet devices, it was optimised for assembly, the primary container was, as mentioned above, supported in a manner that placed less stress on the PFS itself and, also based on market feedback, the device was designed to have two steps rather than a three-step handling process.

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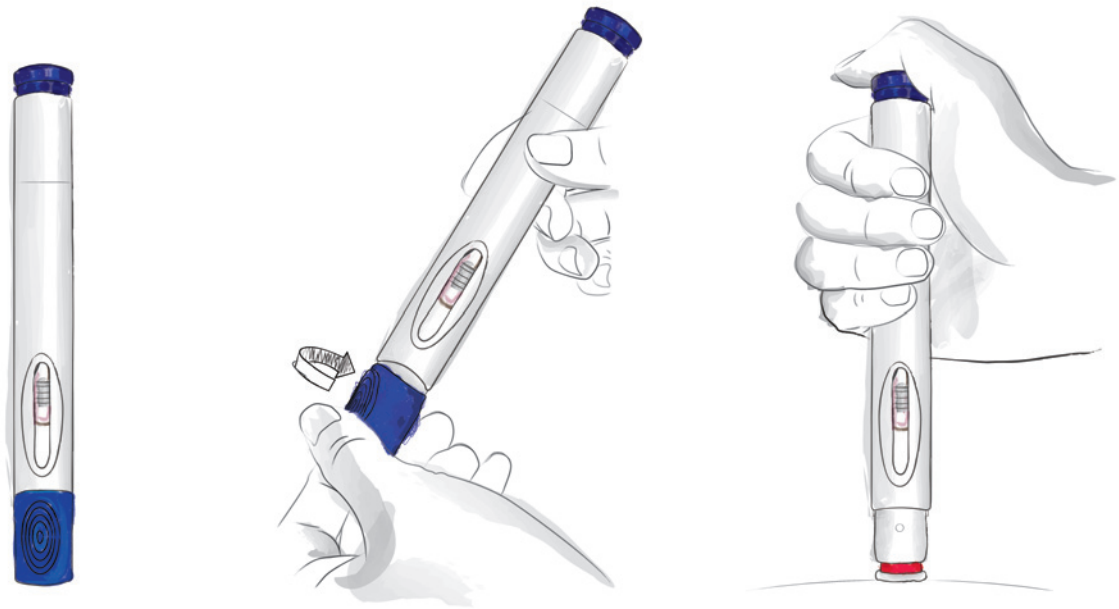

Figure 4: The cap of the auto-injector pictured here was designed with a fingerprint-like extrusion to help patients with dexterity issues to enhance their grip. Different ways of uncapping offer the user increased flexibility with cap removal.

INDUSTRIAL DESIGN

The importance of working with talented industrial design experts in-house or externally as consultants has become a very hot topic over that last few years. With the spotlight now clearly on the importance of human factors engineering, the ergonomics of device designs to enhance user experience and ultimately to improve patient compliance, has become crucial. Regulatory guidelines, such as those provided from the US FDA and related authorities, state that human factors studies are no longer a nice extra to have, they are a must-have.

Again, device companies should be expected to do some of the preliminary industrial design work, if not the majority, before the customer even evaluates the auto-injector that they are considering. For example, preconfigured devices such as the Molly™ are already suitable for mass production and can be used for a number of patient groups. The same can be said of the DAI, disposable auto-injector, which is on the market throughout the world and is used with several different injectable products.

The most recent example of a preconfigured device would be SHL's latest device, Amber™, which is shown in Figure 3.

Amber™ is a two-step "push-click" device that has been developed in close cooperation with a cross-functional team of industrial design experts. This new device will be shown at SHL's innovation bar near booth 64 at the forthcoming PDA Basel event. It is optimised for grip and handling, has an enhanced viewing window, has a transparent cap with a unique shape that allows for ease of removal, provides a large area for mass production labelling, and much more.

The Amber™ auto-injector is a device that demonstrates how device companies can do much for the industrial design of a device at even the initial stage. Such devices, once confirmed by customer-sponsored human factor studies involving their patient groups, can then be more quickly commercialised with minimal or perhaps even no changes to the shape of the auto-injector itself.

However, even when industrial design staff are actively involved with the initial designs of these devices, biopharmaceutical companies must still conduct their own human factors studies with the patient group for their injectable. These studies must be conducted independently of the device companies to ensure the results are objective. Then, the feedback from the study should be taken into consideration to modify or further enhance the industrial design for the marketed device if required.

Detailed usage analysis is performed on the targeted patient group and rigorous verifications and validations are integrated into corresponding design control processes. Conducting the study as soon as possible is vital. Time-to-market is being pushed across the board at this time. If further changes to the shape of a device really are needed, additional investments will be required in a redesign, including tooling, assembly, test equipment and more.

As highlighted by the FDA, combination products are unique in that their safety profile and product efficacy depend on user interaction. Therefore, as we review the results of formative studies on devices, so-called early-stage human factors studies, we see how industrial design is becoming increasingly important to biopharmaceutical customers.

The sketches in Figure 4 shows how an auto-injector cap was designed with a fingerprint-like extrusion to help patients with dexterity issues to enhance their grip. The cap also offers different ways of uncapping – twisting or pulling – giving the user increased flexibility with cap removal.

Changes to the industrial design of a device can also help strategically to ensure differentiation from other similar devices. Biopharmaceutical companies can invest in more extensive industrial design development

"ONE OF THE MOST EFFECTIVE INNOVATION STRATEGIES DEVICE COMPANIES SHOULD CONSIDER IS TO HAVE A RANGE OF PROVEN MECHANICAL DESIGN SOLUTIONS DEVELOPED AND TESTED IN ADVANCE. THEN, THESE DESIGNS CAN SERVE AS THE BASIS FOR SEVERAL DIFFERENT TYPES OF SELF-INJECTION SYSTEMS THAT CAN BE OFFERED TO BIOPHARMACUETICAL COMPANIES"

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and bear related costs, and will then benefit by having a shape or look that is distinctively theirs. This strategy can be very effective if the company plans to launch more than one injectable, but with the same primary container. Now, their device will have a distinctive look and feel that is more closely associated with their company and brand. As a result of increased demand for services, the number of human factor consultants and industrial design firms working in the combination product industry has increased dramatically in the last few years. In addition, some device companies have enhanced their own industrial design teams to help keep such services in-house.

Customised shapes for devices can only be effective if vetted by the target patient group or the clinicians that will be using the device. During the early stages of the industrial design, 2D drawings (Figure 5) will be transferred into 3D files, which in turn will be used to make "block" models of a device. Several block models can then be used in a study to help narrow down user preferences. Once the design is confirmed, it is reviewed by tooling experts to ensure the mouldability of the device. Materials for the device are chosen, including colours, and biocompatibility is performed.

"AS HIGHLIGHTED BY THE FDA, COMBINATION PRODUCTS ARE UNIQUE IN THAT THEIR SAFETY PROFILE AND PRODUCT EFFICACY DEPEND ON USER INTERACTION. THEREFORE, AS WE REVIEW THE RESULTS OF FORMATIVE STUDIES ON DEVICES, SO-CALLED EARLY-STAGE HUMAN FACTORS STUDIES, WE SEE HOW INDUSTRIAL DESIGN IS BECOMING INCREASINGLY IMPORTANT TO BIOPHARMACEUTICAL CUSTOMERS"

MANUFACTURING DESIGN

Device companies should create innovative manufacturing processes to ensure quality and maximise the production output for drug delivery devices. To achieve this, all critical manufacturing capabilities such as moulding, tooling and automation are ideally maintained in-house to maximise efficiencies at each development stage.

When producing auto-injectors, investing in the best equipment, streamlining processes and customisation are always priorities (Figure 6). SHL utilises top-of-the-line Krauss Maffei (Munich, Germany) moulding machines and Fanuc (Rochester Hills, MI, US) robotics. Customised thermoformed trays for device components are made by SHL. Customised end-of-arm tools ensure a precise grip and auto-stackers that are located beside each moulding machine to enhance production flow are also produced in house.

Capacity, scalability and efficiency are vital when it comes to manufacturing and this can be achieved a number of ways. For example, at SHL production sites we have developed automated stackers that are located next to each moulding machine. When plastic components are moulded, they are inserted directly into a tray that sits on the stacker. When the tray is full, the stacker will automatically switch to a new tray, minimising the number of handling steps required before the parts move into assembly and to prepare the components for the next manufacturing step. We also put careful thought into how our sub-assemblies are positioned in trays, not only to minimise dead space in the shipping cartons, but to also maximise handling efficiency at the final assembly site.

Another way that we can increase efficiency is by simply improving communication between the biopharmaceutical company and the device company. For example, the device company should be watchful of tooling life and back-up tooling for risk mitigation purposes. They should keep their partner up to date and also make them aware of the lead-time for key services like tooling. Biopharmaceutical companies can assist

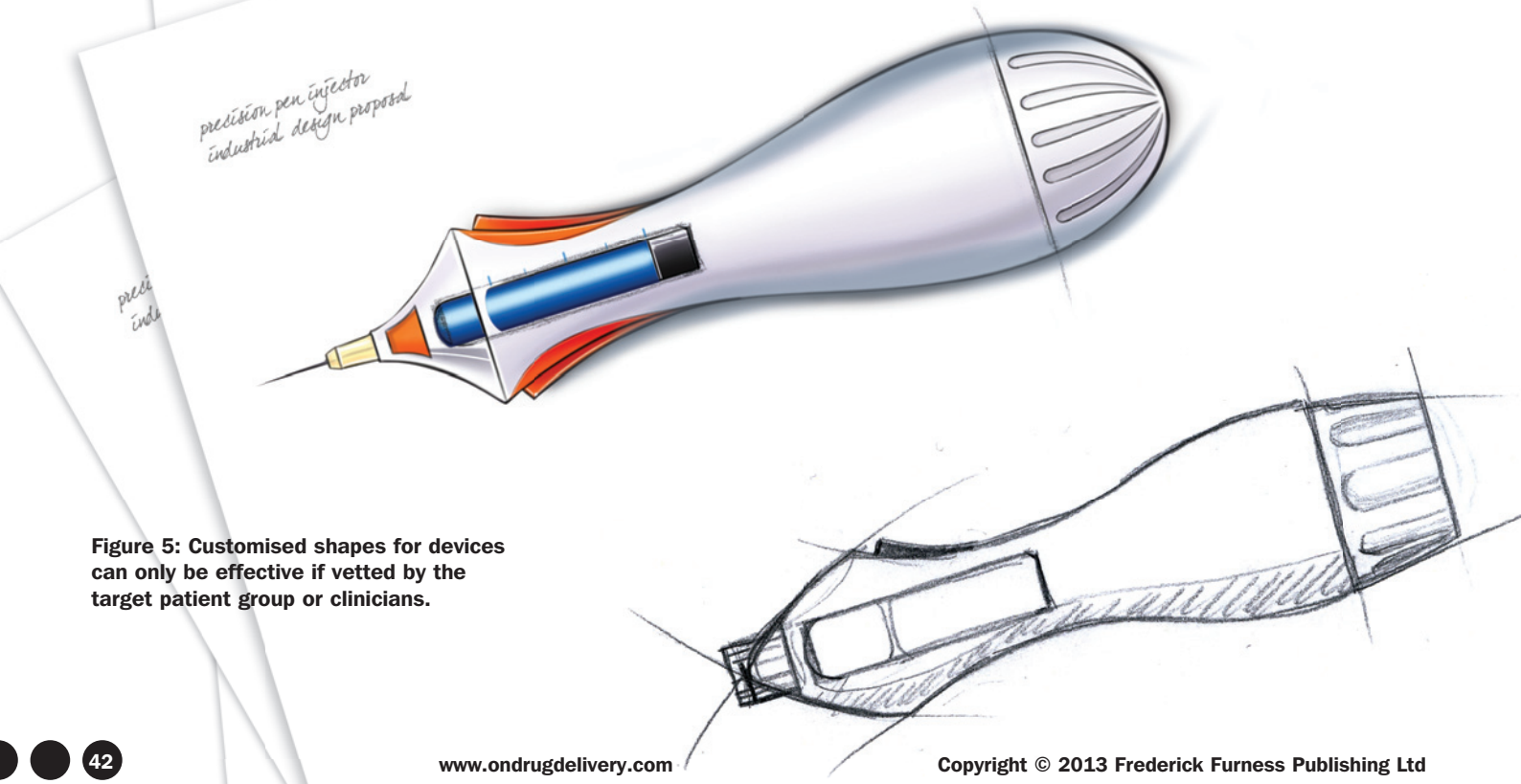

Figure 5: Customised shapes for devices can only be effective if vetted by the target patient group or clinicians.

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Figure 6: Investing in the best equipment, streamlining processes and customisation are always priorities for SHL.

Figure 7: SHL's TRIO injection test surface.

device companies by making them aware of launches into new markets and marketing pushes.

TRENDS, OPPORTUNITIES & CHALLENGES

When looking at ways to innovate it is important to understand the trends in the market. For auto-injectors the market trend is currently leaning towards "proven" mechanical designs that utilise standard primary containers such as ready-to-fill or SCF 29G thin-walled PFS RNS (rigid needle-shield). Electro-mechanical solutions and needleless solutions are available, and are quite intriguing, but more time is needed to see how broadly they will be used, especially for the single-use disposable devices. Injection time continues to be a hot topic with a target of less than 10 seconds being ideal, but with some viscosities this is very challenging. Reduced development times and enhanced speed to market are also clearly in demand with some companies expecting to take a device to market in less than 18 months.

The opportunities for device companies and related service companies are boundless. As stated in the overview of this article, several device companies can better serve the needs of their customers by focusing on developing a range of proven mechanical designs that be utilised in a range of devices with different primary containers. Auto-injectors work with prefilled syringes and also a growing range of cartridges. Investments on the side of device companies will be significant, but this will pay significant dividends in the long run with so many injectables coming to market.

Strengthening resources around the area of industrial design can only benefit all parties. In addition, remember the importance of supporting human factor studies with instructions for use (IFUs), devices with placebo/water for injection and even being careful with the type of injection pad that is provided.

For example, the TRIO injection test surface (Figure 7) was an internal SHL project developed to respond to the need for a versatile injection pad or fixture that could be used during auto-injector usability or related testing. The TRIO allows for a range of needle extensions, is reusable, has a grip-friendly non-slip surface, and more.

Manufacturing design can be described a number of ways, but the main point here is to ensure that is a device partner has developed a structured approach to producing your combination product. As demand increases, the supplier will be able to ramp up production and proactively plan for such changes. Quality is built into production throughout the entire value chain and devices are now being designed with mass production in mind.

Coming forward and finding new ways to innovate can take many forms. With specialised needles, using cartridges instead of PFS for auto-injectors, plastic PFS 1ml with staked-on needle becoming more mainstream in the coming years, and customised training devices, innovation abounds. But by focusing on mechanical, industrial and manufacturing design, device companies can strengthen their partnership roles with biopharmaceutical companies. These are exciting times in which to innovate and there is certainly more to come.

ABOUT SHL

SHL is the world's largest privately-owned designer, developer and manufacturer of advanced drug delivery devices. We have more than 2,500 staff globally, with our primary design centres located in Sweden and the US, and manufacturing centres located in Asia. Final assembly, labelling and packaging services for drug delivery devices are offered at our newest facility in the US.

SHL supplies auto-injectors, pen-injectors and inhaler systems to global biopharmaceutical companies. Significant investment in R&D has enhanced our broad pipeline of next-generation drug delivery systems. These innovative devices include a range of disposable and reusable injectors with fixed or variable dosing, enhanced precision and the ability to accommodate high viscosities.

ACKNOWLEDGEMENT

INSPIRING NOVATION

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NEOPAC

THE TUBE

MEETING THE GAP IN PARENTERAL PACKAGING

The primary packaging market for parenteral formulations is dominated by a few established and well characterised containers, says Ralf Künzi, Medical Business Development, Hoffmann Neopac. Here, he outlines the benefits and drawbacks of each container type, revealing a clear gap in available parenteral packaging options.

MEETING THE GAP IN PARENTERAL PACKAGING

When overlaying the pros and cons of the available container types for parenteral packaging, a clear gap in parenteral packaging options becomes obvious. Fleximed® is a new parenteral packaging option from Hoffmann Neopac designed to fill this gap by addressing the unmet needs centered on ease of use and cost of goods.

AMPOULES

Ampoules are available in many different sizes and shapes and also made from several materials, however specifically for parenteral applications glass is by far the most common material. The main benefit of ampoules is their low cost of goods. Especially in developing economies the glass ampoule is therefore the most common type of primary packaging for parenteral formulations. Due to the good barrier properties of glass, ampoules provide a high level of protection at minimum cost.

The main disadvantage is user handling as ampoules have to be cut and broken to be opened and the drug has to be transferred into a syringe using a transfer needle. In addition to this being a cumbersome procedure, cutting and breaking glass creates small glass particles which may enter into the blood stream and if the break is not clean, dangerous glass sharps are generated. Moreover, ampoules are mostly made from thin-walled glass which easily breaks when dropped. Due to their tall narrow shape ampoules easily fall over leading to costly and sometimes dangerous spillage of contents once the ampoule has been opened. Furthermore, the contents of the container are exposed after it has been opened, posing a significant risk of contamination if not handled with utmost care.

Ampoules should thus only be considered as a viable packaging option if cost of goods is the only selection criterion. Ampoules are not ideal if the drug is administered to patients very frequently due to high time consumption for the caregiver. In the case of drugs requiring particular care when handled, such as cytotoxic drugs, ampoules should be ruled out as a primary packaging option altogether.

CRIMP VIALS

As with ampoules, crimp vials exist in many different sizes. The main difference to ampoules is the rubber septum used to close the vial. This design aspect resolves the main disadvantages of ampoules and in addition allows for multiple administrations from the same container. Cost of goods is higher due to the additional number of components and the thicker glass required ensuring that the crimp-sealing process does not cause the glass to break.

Crimp vials are predominantly made from glass except for the rubber septum, with the latter component leading to more challenging drug compatibility characteristics compared with ampoules. Crimp vials entirely made from plastic are becoming more popular for parenteral applications and are predominantly made from cyclic olefin copolymer (COC). This material does however not provide the same barrier properties as glass especially for oxygen and water vapour permeation.

The handling procedure for crimp vials is clearly improved compared to ampoules but still requires numerous steps as the drug has to be transferred into a syringe requiring a dedicated transfer needle.

Crimp vials are thus a viable packaging option for many types of drugs. But as for ampoules, the complex handling procedure is a limiting characteristic of this primary packaging option. Crimp vials are therefore a suboptimal choice for drugs administered very frequently and/or to a very large number of patients.

PREFILLED SYRINGES

Over the last 20 years the popularity of prefilled syringes has increased significantly. The main reason for this trend is the substantially higher level of convenience for the user. If equipped with a staked-on needle a prefilled syringe requires minimal preparation and can easily be used by care givers as well as patients themselves. As for crimp vials, prefilled syringes are to-date also mainly made of glass with COC versions slowly gaining market acceptance. There are however also some clear drawbacks of prefilled syringes, the main ones being comparatively high unit costs especially for delivery volumes above 2 ml, and the other being the need for silicone lubrication. Also the fact that a rubber plunger is required poses challenges for certain ingredients. And tungsten residues on the inner glass surface have caused some undesirable interactions in the past.

Prefilled syringes are thus a viable packaging option for drugs which are frequently administered. To compensate for the comparatively high cost of goods, prefilled syringes are mainly used for high-priced pharmaceutical preparations; this is especially true for larger delivery volumes. In addition, special attention needs to be paid to compatibility aspects related to rubber materials and silicone oil.

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CARTRIDGES

A cartridge is basically a combination of a prefilled syringe and a crimp vial. The cartridge is typically used for multi-dose applications, such as for administering anaesthetics in dental care and for the self-administration of hormone replacements such as insulin, growth hormone etc. They allow for accurate deliveries of small amounts of liquids (<0.5 ml). Like the other parenteral containers, glass is by far the most widely used material for the cartridge barrel. Similar to the prefilled syringes the drawbacks are mainly related to comparatively high unit costs, the need for siliconisation inside the barrel, and compatibility aspects due to the use of rubber components.

Cartridges are thus a viable packaging option for drugs which are frequently administered in small doses and which have a sufficiently high price tag to absorb the higher total cost of goods. As for pre-filled syringes, special attention needs to be paid to compatibility aspects related to rubber materials and silicone oil.

MATERIAL CONSIDERATIONS

As already stated in this article, glass is by far the most common material used for parenteral packaging. This is for good reason as the barrier properties of glass are unmatched by anything else and the material is inert to a wide range of ingredients. However, besides obvious drawbacks of glass such as the risk for breakage, glass can pose substantial challenges such as delamination e.g. due to acidic pH or protein adsorption for biologic APIs. Therefore, polymer-based packaging materials such as COC, Cyclic Olefin Polymer (COP) and polypropylene are becoming more widely accepted as primary packaging materials for injectable drugs. However, these materials provide insufficient barrier properties for a large range of sensitive ingredients. And especially for larger containers the cost of goods is prohibitive for many applications.

LIQUID UNSTABLE DRUGS

Formulation scientists are confronted with special challenges if drugs are not stable in liquid form over prolonged periods. The goal for any new drug must be to achieve liquid stability as this is always the better option in terms of cost of goods, packaging complexity and logistics and most of all user handling. However, despite all modern formulation technologies, liquid stability cannot be achieved in many cases. Therefore, the primary packaging should reduce the formulation-related challenges and drawbacks.

Unfortunately, to date very few viable primary packaging options exist. In most cases the dry component is filled either as a powder or granulate into a crimp vial, or as a liquid followed by lypholisation. The liquid components have to be stored in a separate crimp vial resulting in a particularly complicated and time-consuming handling process. To simplify this process special add-on devices are available, but these devices are not reducing the actual number of steps but still add further delivery costs. The most convenient options to date are dual chamber cartridges and syringes, which clearly reduce the number of steps and makes drug delivery almost as easy as for liquid stable drugs. But for many applications the resulting high total cost of goods is prohibitive, and in addition due to their comparatively large-size dual chamber cartridges and syringes are rarely used for delivery volumes greater than 1ml.

FLEXIMED® FILLING THE GAP

From the above considerations it becomes clear that current parenteral packaging options do not fully cover current market needs. The greatest need is apparent for frequently administered drugs which cannot be sold at a sufficiently high price to absorb the costs for a prefilled syringe. In addition, certain characteristics of drug ingredients can also be problematic with today's primary container selection – for example, if ingredients are interacting with silicone lubrication or causing glass to delaminate.

Even more dramatic is the need for suitable packaging options if parenterally administered drugs cannot be formulated as liquids for stability reasons. To-date, most such drugs are therefore packed in suboptimal primary containers.

To meet this substantial need Hoffmann Neopac has developed the innovative Fleximed® tube. Fleximed® provides a combination of packaging characteristics which is absolutely unique in the field of parenteral packaging:

- Ease of use: requiring substantially fewer handling steps compared with ampoules and crimp vials, no need of a transfer needle
- Multi-layer laminates for tailor-made barrier properties
- Different protein adsorption behaviour compared with glass
- Packaging does not break when dropped.
- Low cost of goods, especially for larger fill volumes >3 ml.
- By adding a frangible middle seam two or more components can be stored in one tube.
- State-of-the-art bulk freeze drying technologies also allow Fleximed® to be used for lyophilised drugs.

The following illustration (Figure 1) visualises how Fleximed® completes the gap for parenteral containers when considering the key challenges and demands in the parenteral world.

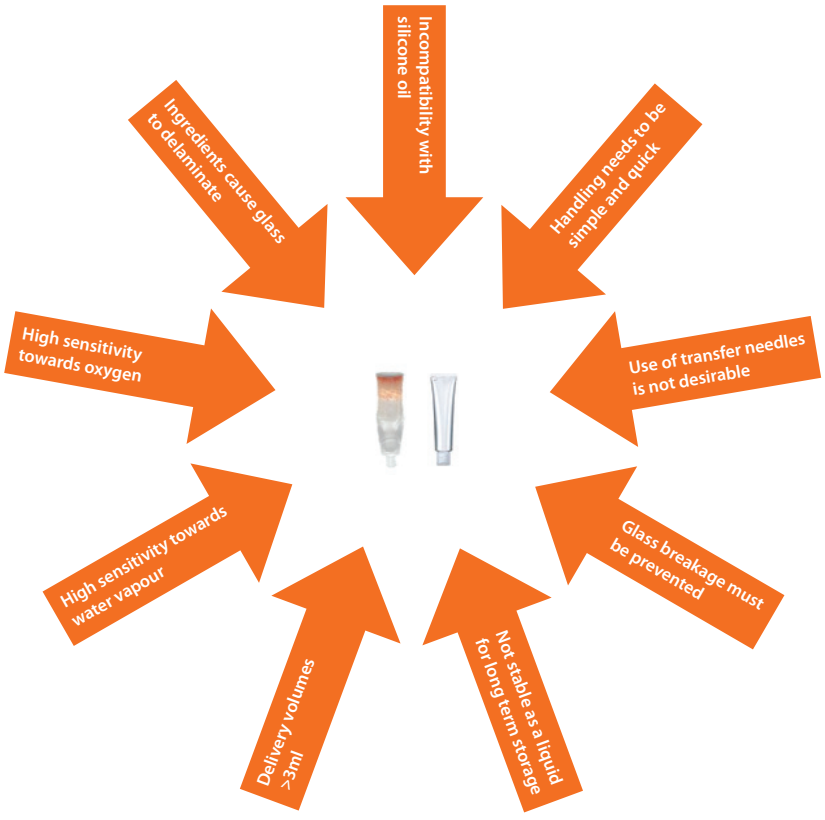

Figure 1: Key demands for primary parenteral containers which are ideally met with Fleximed®.

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SiO2 Medical Products
SCIENCE INSIDE™

PART I OF II: IMPROVED PARENTERAL CONTAINERS THROUGH PLASMA DEPOSITION OF HIGH PURITY GLASS

In this piece, the first of a two-part article, Kevin Turney, Senior Applications Development Scientist, and Peter Sagona, Vice-President and Secretary, both of SiO_2 Medical Products, and Shawn Kinney, consultant to SiO_2 Medical Products, describe the company's plasma coating technology that allows a nanometres thin layer of glass (in fact, pure silicon oxide) to coat plastic (cyclic olefin polymer) parenteral drug containers and delivery systems, thus imparting the barrier properties and other advantages of glass with the benefits of polymer devices within the same device. We're pleased to confirm that part two will appear in the February 2014 issue of *ONdrugDelivery Magazine*.

INTRODUCTION

SiO_2 Medical Products (SiO) is a vertically integrated manufacturer of high-quality, high-volume pharmaceutical and medical device components formed to develop and commercialise precision-moulded plastic products lined with thin, transparent silicon-oxide based coatings. The coating layers are applied using plasma enhanced chemical vapour deposition (PECVD). A precision polymer container with a technically advanced coating system creating an inert, glass-like product contact surface, is ideally suited for packaging of injectable biopharmaceuticals and high purity drug compounds. Together, this allows SiO to offer primary parenteral containers with superior performance when compared with current glass or plastic containers.

"A NEW PARADIGM IN MATERIALS OF CONSTRUCTION FOR PARENTERAL CONTAINERS HAS EMERGED FROM SIO: PLASTIC CONTAINERS BASED UPON MEDICAL GRADE POLYMERS (CYCLIC OLEFINS) COATED WITH A VERY THIN, TRANSPARENT LAYER OF PURE SILICON OXIDE"

BACKGROUND ON EXISTING CONTAINERS

For decades, glass has been the most commonly used material for manufacturing parenteral containers. Glass is readily available, strong, mouldable to typical container shapes and sizes, easy to clean and sterilise, and relatively inert. Despite these positive attributes, glass has shortcomings that make it a less than ideal material of construction for parenteral containers.

Borosilicate glass is not pure silicon dioxide. Glass manufacturers incorporate inorganic additives into the base raw materials to improve

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handling and manufacturability of molten glass; these additives include oxides of boron, calcium, sodium, and aluminium. Fundamentally, the raw material used to manufacture glass is still naturally derived; the raw sand contains low levels of impurities, including iron, that vary with the location of the source. Raw material control is variable and has the potential to impact extractables, and the integrity of the container.

Glass delamination is an important topic in current pharmaceutical trade literature leading to the drafting of a USP general information chapter, USP 1660.[1] Under specific conditions, glass particles may flake off from the inner surface of parenteral containers due to delamination mechanisms, many of which relate to inorganic additives within the glass formulation. Delamination has been suggested as the root cause for US FDA product recalls due to glass particulates (i.e. lamellae).[2]

Glass products are prone to breakage, which can occur upon receipt of the incoming container, filling of the product on manufacturing lines, transport, usage within auto-injector assemblies, and during administration. Each instance of breakage of a parenteral package causes a cascading effect, as it results in potential contamination of other containers and equipment, possible breach of sterility, as recalls of the product due to visible particulates, and safety risks. Within the manufacturing environment glass bruising, caused by vial to vial contact, introduces flaws and stresses which later can result in cracking and breakage following small stresses to the container. In essence, when a glass container is dropped or exposed to certain mechanical stresses, it should be discarded from risk mitigation alone. Combination products, such as auto-injectors, pose an added concern when glass containers may not be visible to examine breakage.

In traditional moulding methods, glass containers are produced with large dimensional variance. These deviations can cause issues in auto-injectors and speciality delivery devices that require very tight and reproducible dimensions. Failure to maintain specific tolerances can lead to non-obvious failures or jams of devices and auto-injectors, potentially underdosing an unknowing patient. Glass is limited in its ability to be moulded into non-standard shapes and sizes limiting the use of glass in future applications.

An additional contaminant in borosilicate glass syringes, tungsten, was found to cause precipitation and aggregations in some protein-based products. The source of the tungsten was traced to the forming pins which are used to form the lumen of the tip.[3] Tungsten deposited in the lumen as tungsten oxide interacted with some protein formulations leading to precipitation.

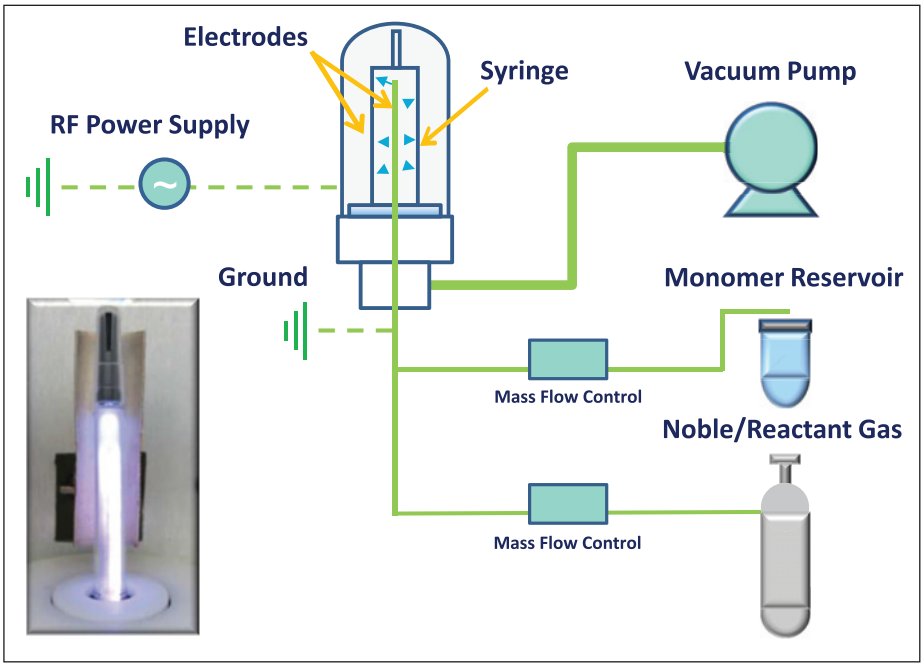

Figure 1: Plasma-enhanced chemical vapour deposition (PECVD) process for coating parenteral containers.

The shortcomings of the use of glass as described above are intrinsic to the material and cannot be eliminated, they can only be reduced. Glass will always be prone to breakage. Metal oxides must be added to improve melting, flow, and moulding of borosilicate glass. Hence, it will be present as a potential extractable and source of initiation of delamination. Glass manufacturers have put a great deal of time and effort into trying to mitigate the problems, but glass will always be glass.

Plastic has been offered by some as a better material for parenteral containers, but plastics also have their shortcomings. Plastic does not break or shatter as easily as glass, it is not prone to delamination, and it offers superior dimensional tolerances. Yet, polymers have extractables and leachables not found in glass. Plastic does not have the barrier properties of glass and can allow migration of label adhesives into the drug product. Further, plastics lack the excellent gas barrier of glass and, therefore, are unacceptable containers for oxygen-sensitive compounds. Plastic, like glass, is not the perfect material for parenteral storage containers.

PLASMA DEPOSITION TECHNOLOGY

A new paradigm in materials of construction for parenteral containers has emerged from SiO: plastic containers made of medical grade polymers (cyclic olefins) coated and incorporating a very thin, transparent layer of pure silicon oxide. Pure silicon oxide lacks metal oxide additives implicated in glass delamination; it also blocks extractables/leachables, oxygen and even label adhesive from migrating into the drug product. Plastic containers coated with silicon oxide, promise to be the ideal materials of construction for parenteral containers. The ultrathin silicon oxide is flexible, and not prone to breakage or delamination under mechanical or thermal stresses.

An innovative plasma deposition process has been developed (see Figure 1) that deposits a pure, ultrathin layer of silicon oxide on plastic containers. This process creates parenteral storage containers that have all of the advantages of both glass and plastic without many of the shortcomings of either.

Plasma deposition of glass is not new; it has been used for many years to coat items from bottles to computer chips to artificial lenses. What is novel is the plasma process, the thinness of the coating, a discrete coating to provide a broad range of pH stability in parenteral products, and the use of individual containers as the vacuum chamber for the plasma. By depositing the coating via individual containers versus batch processing the system is scalable for production and offers a consistent and uniform coating of the containers, delivering consistent performance.

The plasma process utilises pure organosiloxane monomers and gases. The container to be coated is sealed in a puck that provides an electrode and a gas inlet (see Figure 1). A vacuum is applied to the container through the puck and then the process reactants (e.g. hexamethyldisiloxane (HMDSO), argon, and oxygen) are introduced through the gas inlet tube. Once a steady state is achieved, the gaseous mixture is then excited by radio frequency (RF) energy to establish a plasma inside the container. The plasma deposits a uniform silicon oxide coating layer on the inside surface. By controlling pro-

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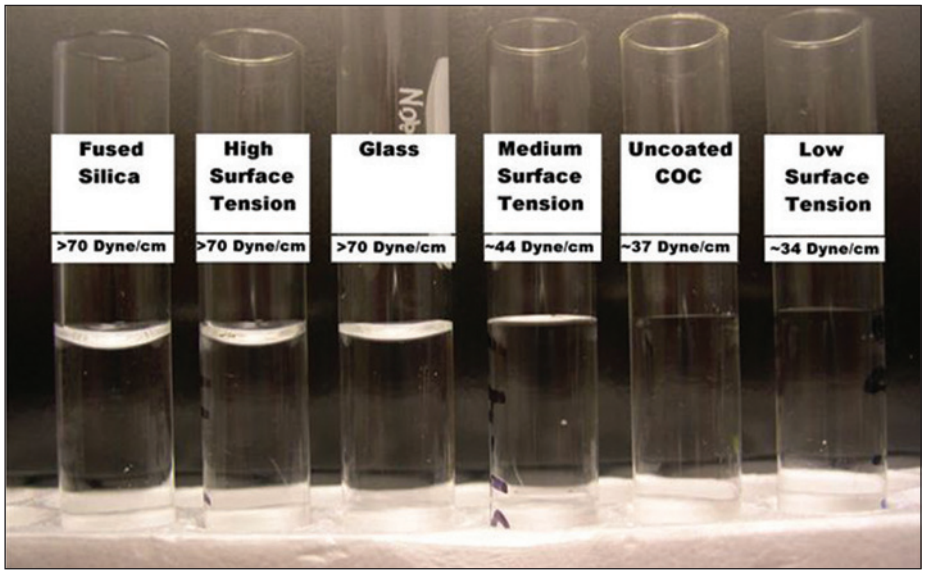

Figure 2: Surface energy of the coating can be controlled through the PECVD process.

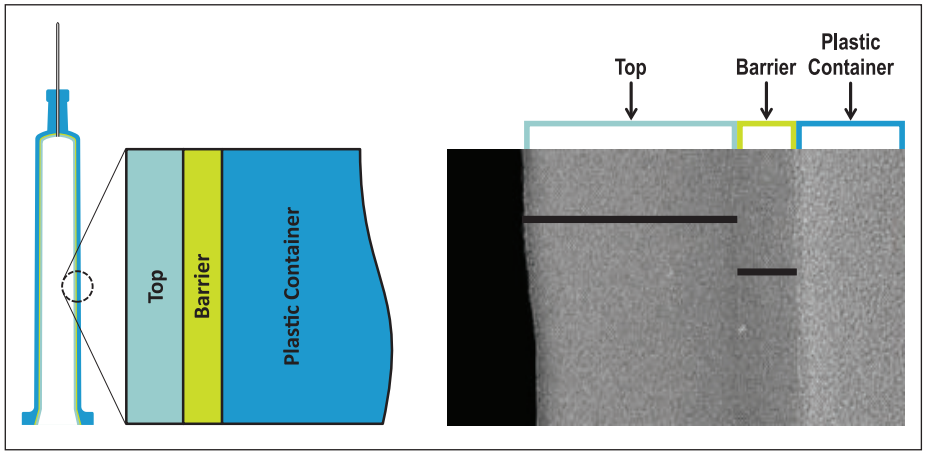

Figure 3: Transmission electron microscopy (TEM) image of the barrier coating system for staked needle syringe.

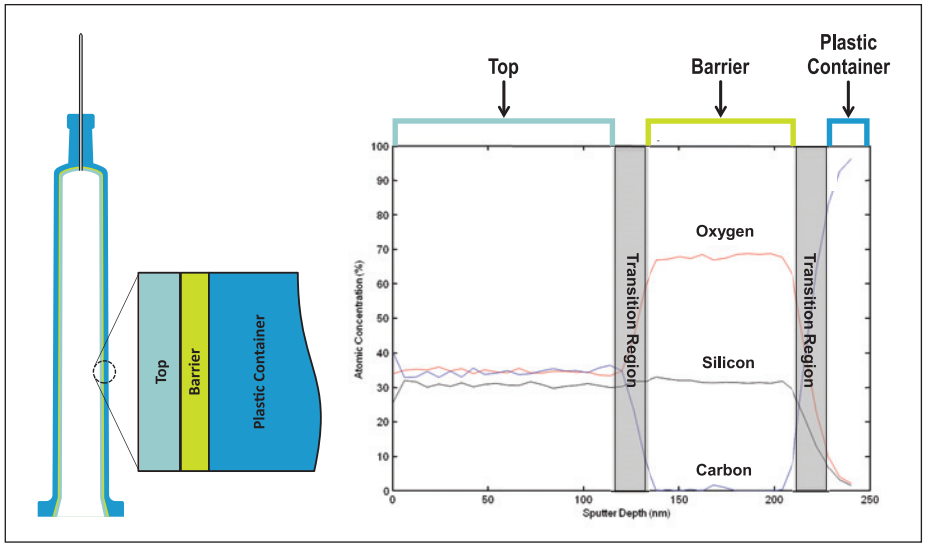

Figure 4: XPS of the barrier coating system.

cess parameters the chemistry, uniformity and deposition rate allow for consistent thickness and barrier properties. Spectroscopic process analytics have been established to monitor the plasma for each unit produced.

This coating process produces a container with an ultrathin layer of pure silicon oxide that is just nanometres thick. Thickness is very important because thin layers of glass are flexible and consequently give under strain rather than resist and break as do thick layers of glass. We have shown that these plasma-coated polymer surfaces can withstand a deflection, which would cause a glass container to shatter, with no loss of coating adhesion. In fact, we have found that the glass coating integrity and adhesion is maintained even to the point that the plastic itself is permanently deformed.

BARRIER COATING SYSTEM

After deposition of the thin silicon oxide coating layer, other plasma coating layers can be applied. Changes to the plasma processing conditions, including changes to the gases and monomers, allow the customisation of coatings. An example of a barrier coating system is the addition of a top coat over the silicon oxide coating providing protection from hydrolytic attack. In SiO_2 Medical Products' barrier coating system, each coating layer is applied in a separate PECVD process. First a silicon oxide layer is applied to the container. After the silicon oxide layer is applied, the container is transferred to a second coater where the top (pH protective) layer is applied. Alternative processes can be employed to tailor hydrophobicity. The coatings can be customised dependent upon the contact surface needs, as shown in Figure 2.

An example barrier coating system (a barrier layer and top hydrolytic attack protection layer) for a staked needle syringe is shown in Figure 3. Transmission electron microscopy (TEM) is used to image the coatings inside the syringe barrel.

This coating system was developed to provide a barrier to high pH injectable formulations. Glass dissolves in water at high pH. With a borosilicate glass container a few microns of the glass surface are dissolved. Under no circumstance would the entire glass container be dissolved, due to saturation of the solution, yet contaminates, silicon and other metals within the glass do migrate into the drug formulation. Being only nanometres thick, the silicon oxide coating, which provides the barrier properties to oxygen and potential leachables, must be protected from hydrolytic attack. Protection is provided by the top layer coating system. In Figure 3, from left to right in the TEM one can see the protective layer, the silicon oxide barrier layer and polymer

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container surface. The elemental composition of each coating is shown in the XPS (x-ray photoelectron spectroscopic) within Figure 4. The top layer has a composition of silicon, oxygen, and carbon in a ratio of 1:1:1. The barrier coating has a composition of silicon and oxygen in a ratio of 1:2. Each layer's composition is uniform throughout until the discrete transition to the next layer on the container surface. By XPS and other techniques, each layer has been shown to be bonded to the underlying layer.

We have demonstrated that the silicon dissolution rate of our coating system is approximately 100-fold less than that of standard borosilicate glass. Long-term stability studies with solutions ranging in pH from 3.5-8, with surfactants, a variety of different buffer types and ranges of salt concentrations have shown years of shelf life, determined by maintenance of the barrier layer's barrier performance.

CONCLUSION

The innovative material described here is a combination of plastic with a pure glass barrier coating system to produce a new parenteral container material that has optimal properties of clarity, pH stability, resistance to breakage, dimensional tolerances, improved barrier properties to gas and solutes, and increased purity. This blend of plastic and glass creates the ideal parenteral container material for drugs and biologics.

This article has focused on the details and explanation of our barrier coating system describing the plasma process, composition of the resulting coatings and purpose of the layers that comprise the coating system. We have discussed the benefits of this barrier coating system over glass and plastic from a purity, barrier and breakage perspective. The second part of this article, which will appear in the February 2014 issue of *ONdrugDelivery Magazine*, will describe the characterisation of the barrier coating system from a performance perspective with physical, chemical and thermal stresses that a parenteral storage container must be able to withstand. It will also feature additional detailed evidence of the benefits of our barrier coating system.

"THIS PROCESS CREATES PARENTERAL STORAGE CONTAINERS THAT HAVE ALL OF THE ADVANTAGES OF BOTH GLASS AND PLASTIC"

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ABOUT THE AUTHORS

Shawn Kinney:
A consultant to SiO_2 Medical Products (SiO) on the parenteral drug market, Shawn Kinney, PhD, is the founder of Hyaluron, a contract manufacturer of injectable therapeutics. Dr Kinney has presented at many conferences and authored numerous articles relating to pre-filled syringes. He provides technical and marketing assistance to SiO regarding the design of parenteral containers, secondary packaging and coating stability. He holds a Doctorate in Chemistry from the University of Massachusetts at Amherst.

Peter Sagona:
SiO Vice-President and Secretary, Mr Sagona is responsible for programme management, including overall project coordination of deliverables and timelines. Mr Sagona also oversees the intellectual property strategy associated with the program. Prior to joining SiO, Mr Sagona spent 11 years with CV Holdings LLC, and seven years at SmithKline Beecham Clinical Laboratories managing automation development projects. Mr Sagona received an MS in Engineering Management from Drexel University.

Kevin Turney:
Senior Applications Development Scientist at SiO_2 Medical Products, Dr Turney is responsible for technical evaluation and implementation of plasma coated parenteral containers. He coordinates customer development activities through internal and external scientific resources. Dr Turney has a PhD in Analytical Chemistry from the University of Florida. Prior to joining SiO_2 Medical Products he was a Senior Scientist within R&D at Amgen, where he was Group Leader for Structure Elucidation.

ABOUT SIO_2 MEDICAL PRODUCTS

SiO_2 Medical Products (SiO) is a manufacturer of plastic primary containers, with a thin glass coating on the interior surface. SiO is a privately held company located in Auburn, Alabama USA. SiO was founded and is supported by CV Holdings, LLC, an organisation with 90 years of manufacturing experience, developing and manufacturing packaging for diagnostic applications, food and dairy worldwide. SiO's R&D and manufacturing facilities are housed in a pilot facility in Auburn, with professionally staffed, fully equipped analytical and mechanical laboratories. SiO will move to its newly constructed 160,000 square foot headquarters nearby in first quarter 2014. The state-of-the-art facility contains three ISO Class 7 clean rooms, each spanning 10,500 square feet and dedicated to SiO's glass coating and packaging lines. Plans are in place to build a second manufacturing plant in Strasbourg, France to provide duplicate manufacturing capabilities.

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COMPANY PROFILE – SPECIALTY COATING SYSTEMS

SPECIALTY COATING SYSTEMS™

Nowhere are leadership, experience and proven technology more crucial than in the medical and pharmaceutical industries. Specialty Coating Systems (SCS) has been developing and applying ultra-thin, pinhole-free Parylene conformal coatings to essential devices and components for more than 40 years.

As the global leader in delivering innovative Parylene coating solutions for advanced medical technologies, manufacturers have continually turned to SCS for planning, development, engineering and application of thin-film Parylene polymer coatings to their critical components.

Our team consists of the world's foremost Parylene specialists working in state-of-the-art laboratory facilities. Our strict quality control systems across eleven coating facilities worldwide ensure that all SCS customers experience the most innovative, precise and consistent coating processes.

OUR HERITAGE

SCS dates back to the 1970s when Parylene conformal coatings were first commercialised due to William F Gorham's work at Union Carbide Corporation (UCC), now a subsidiary of Dow. In 1971, Nova Tran Corporation was established in Clear Lake, WI, US, having purchased a license agreement from UCC to be one of the world's first Parylene service providers. Union Carbide Corporation purchased Nova Tran in 1984 and in 1991, Nova Tran, along with several other companies, were combined into a new company called Specialty Coating Systems (SCS). Union Carbide transferred all of the original information and patents regarding the development of Parylene to SCS. With our global headquarters now located in Indianapolis, IN, US (see photo), we are proud of our heritage, which has afforded us unprecedented coating and applications expertise.

INNOVATIVE PRODUCTS FOR THE MEDICAL & PHARMA INDUSTRIES

Ultra-thin and pinhole-free, SCS Parylenes offer exceptional properties for medical device protection. We couple the properties of Parylene with our years of experience, vast technology and worldwide resources to provide the industry with coatings and services it can rely on. The benefits of SCS Parylene include:

- Biocompatibility and biostability
- Controlled thickness down to 500Å
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- Micro-encapsulation capabilities
- Dry-film lubricity
- Superior chemical, moisture and electrical barrier.

Specialty Coating Systems' worldwide headquarters in Indianapolis, IN, US.

SCS Parylenes N, C and Parylene HT® comply with biological testing requirements for ISO-10993 and USP Class VI Plastics. Specialty Coating Systems maintains Device and Drug Master Files with the US FDA. These files, which include the results of biological studies on SCS Parylenes, are available for reference by SCS commercial coating service customers.

HOW WE CAN HELP YOU MAKE SAFER AND BETTER DEVICES

SCS can apply Parylene coatings to virtually any surface material, including metal, elastomer, plastic, glass, ceramic and paper. The thickness of a Parylene coating can range from a few hundred angstroms to several mm. Parylene polymerises as a uniform, thin-film coating that conforms to all surfaces, edges and crevices of a substrate, including the interior of tubing, without blocking orifices, adding dimension or weight. Because Parylene is not a liquid, the coating suffers none of the meniscus and edge effects of conventional liquid coatings. As a result of its ultra-thin application, Parylene adds very little dimension or mass to critical, weight-sensitive components.

Numerous medical devices and device components benefit from Parylene coatings, including syringe components, needles, stents, electrosurgical tools, cochlear and ocular implants, ingestible devices, pacemakers, and elastomeric components, to name only a few.

PHARMACEUTICAL APPLICATIONS: WHY PARYLENE STANDS OUT

Shelf-life is important for all medications, for prefilled syringes as well as pharmaceuticals in vials and bottles. For these, the more aggressive chemicals tend to attack not only the containers, but can cause unwanted chemicals to be extracted from the container material into the drug itself. Parylene can prevent this. It is an excellent barrier coating, protecting the container, including caps and seals, and also

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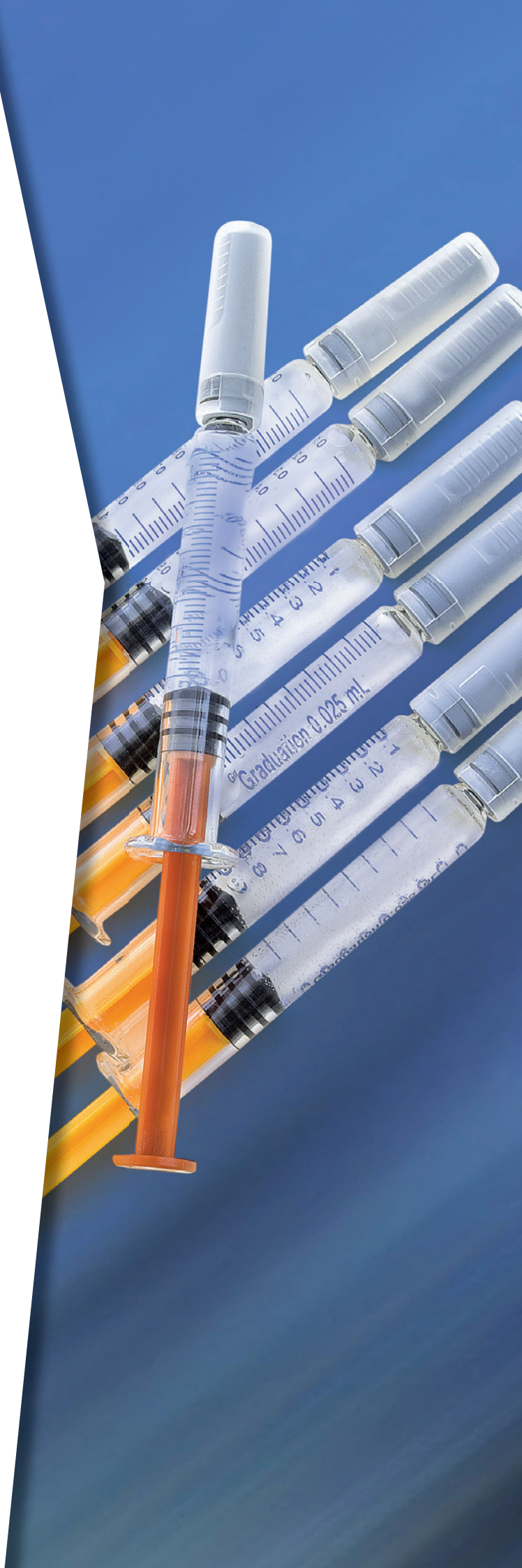
SPECIALTY COATING SYSTEMS™

When it comes to reliability, nothing protects like Parylene.

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

With 11 locations around the world (6 in the Americas, 3 in Europe, 2 in Asia), Specialty Coating Systems is the leader in Parylene coatings and maintains comprehensive FDA Drug and Device Master Files for customer reference.

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



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COMPANY PROFILE – SPECIALTY COATING SYSTEMS

protecting the drug from any unwanted leaching or extractions.

Some prefilled syringes have sealing mechanisms to ensure needle sterility and to prevent premature drug dispensing. These seals can occasionally form a very tight bond as it sits on the shelf. The self-seal can be difficult to break. Coating these components with Parylene before assembly helps prevent seal bonding. In this case, Parylene acts as a release agent allowing the sealing material to release easily when needed.

AT SCS, EVERY CUSTOMER MATTERS

Our worldwide resources include highly experienced sales engineers and expert manufacturing personnel working in eleven state-of-the-art coating facilities around the globe. The following is an overview of the activities, standards and certifications to which SCS and/or SCS Parylene coatings comply:

- AS9100C certification
- US FDA Device and Drug Master Files
- Notified Bodies and Accredited Third Parties co-ordination
- ISO 10993 biological evaluations and certifications
- USP Class VI certification
- ISO 14644 cleanrooms.

Every customer has unique product and performance specifications that must be met. Our experience and expertise are leveraged on every project in order to meet the most challenging specifications and quality requirements.

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PATIENT CENTRIC DESIGN OF A NOVEL ANTI-NEEDLESTICK SAFETY DEVICE

This article, by Sarah Baer, Marketing Product Manager, BD Medical – Pharmaceutical Systems, Safety, describes the incorporation of a patient centric design approach to adapt a clinically proven safety device to meet increasingly complex biotechnology drug requirements.

Historically, safety devices have been primarily added to prefilled syringes to meet anti-needlestick legislation around the globe. Today, we see a growing number of biotechnology drugs in pharmaceutical company pipelines that require devices to meet both healthcare practitioner and self-injecting patient needs. For example, patients with chronic diseases often suffer from impaired dexterity, making it difficult to perform an injection. And, many biologics have more complex properties which make them harder to inject subcutaneously. Therefore, the design of a safety device to support biotechnology drugs must be able to address these requirements.

NEEDLESTICK SAFETY TODAY

The exposure of healthcare practitioners to blood-borne pathogens as a result of injuries caused by needlesticks are a significant public health concern. The US Centers for Disease Control and Prevention (CDC) has estimated the number of sharps injuries in healthcare to be approximately 600,000 each year, [1] with about half of those injuries occurring in US hospitals.[2]

Given the high incidence of needlestick injuries, we have seen an increase in legislation on a global scale. In 2000, the US enacted the Needlestick Safety and Prevention Act,[3] in 2008 the Province of Ontario, Canada, passed 474/07,[4] Brazil passed rule Norma Regulamentadora NR32 in 2005 and Portaria MTE N° 939 in Nov 2008, with a deadline to implement in Oct 2010.[5] The EU passed a mandate, 2010/32/EU, which required all EU member countries to address the danger of accidental sharps injuries (including needlesticks) by enforcing this legislation beginning May 13, 2013, and as a result many member countries have passed new legislation.[6] For example, Austria, Belgium, Finland, Germany, Hungary, The Netherlands, Norway, Poland, Slovenia, Spain, Sweden and the UK have all subsequently finalised and passed needlestick safety legislation to support the May 2013 deadline.

It is also anticipated that this increase in legislation will impact the presentation of injectables, especially those in prefilled syringes as, although it does not specifically target the pharmaceutical manufacturer, many pharmaceutical companies are using this as an opportunity for brand differ-

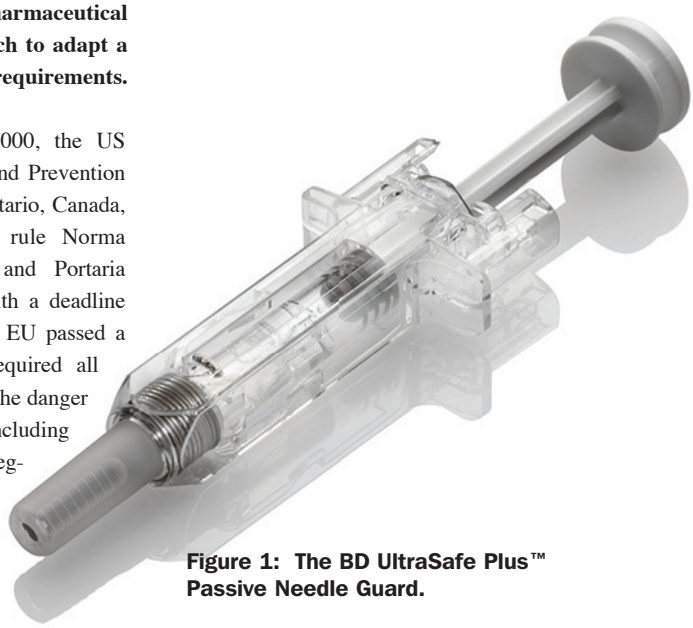

Figure 1: The BD UltraSafe Plus™ Passive Needle Guard.

"WE CONSULTED WITH LEADING AUTOMATION MACHINE BUILDERS TO ENSURE ASSEMBLY OF THE BD ULTRASAFE PLUS™ PASSIVE NEEDLE GUARD WAS COMPATIBLE WITH MINIMAL MODIFICATIONS TO EXISTING OR PLANNED SECONDARY PACKAGING LINES"

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entiation as they are seeing value in offering safer injection presentations for end-users.

During a recent onsite seminar, at the headquarters of BD Medical – Pharmaceutical Systems in Le Pont de Claix, France, Mrs. Stephanie McCarthy, a registered nurse from the Derby Hospitals NHS Foundation Trust in the UK, emphasised the importance of hospital worker safety legislation to protect both healthcare workers and patients. Mrs. McCarthy also spoke regarding the costs for implementation of needlestick safety in the workplace and how they far outweigh the monetary and psychological costs of not introducing safety engineered medical devices in the hospital.

INTUITIVE SAFETY DEVICE DESIGN

Several studies have confirmed that the safety aspect of an injection device is highly valued with nurses and self-injecting patients, and preferred over a bare prefilled syringe.[7] However, it is very important that the correct device is selected. A passive safety technology has been shown to be the most effective as demonstrated by the 2010 Tosini study, conducted by GERES (Groupe d'Etude sur le Risque d'Exposition des Soignants), which confirmed that passive, fully automatic safety devices offer better protection against accidental needlestick injuries.[8]

The BD UltraSafe Passive™ and Plus™ Needle Guards as shown in Figures 1 and 2 use an innovative passive safety technology. The superiority of the passive safety technology arises because most needlestick injuries happen in the few moments after needle withdrawal.[9] Because of this, it is critical that the needle is shielded right after the injection. Any extra steps required by the user may result in no activation of the safety mechanism resulting in an unshielded and potentially infectious needle until disposal.

SUPPORTING BIOLOGICS

The growth in the biologic segment, estimated at US$176.4 billion (£109.5 billion) in sales for 2012,[10] is driving the need for novel delivery systems. The majority of the over 550 biologics in development are monoclonal antibody therapies targeting chronic and autoimmune diseases such as rheumatoid arthritis (RA), psoriasis, and multiple sclerosis (MS).[11] These biologics are typically administered by subcutaneous injection by the patient or caregiver at home rather than at a clinic or doctor's office. This provides convenience for the patient while also reducing healthcare costs.

Many self-injecting patients suffering from chronic diseases may also suffer from reduced dexterity, making self-administration especially difficult. Self-injecting patients are trained when they receive treatment for the first time. However, intuitiveness and ease-of-use are essential factors in overall injection device design. To address this, many devices are provided in a variety of designs and different activation mechanisms to suit patient requirements.

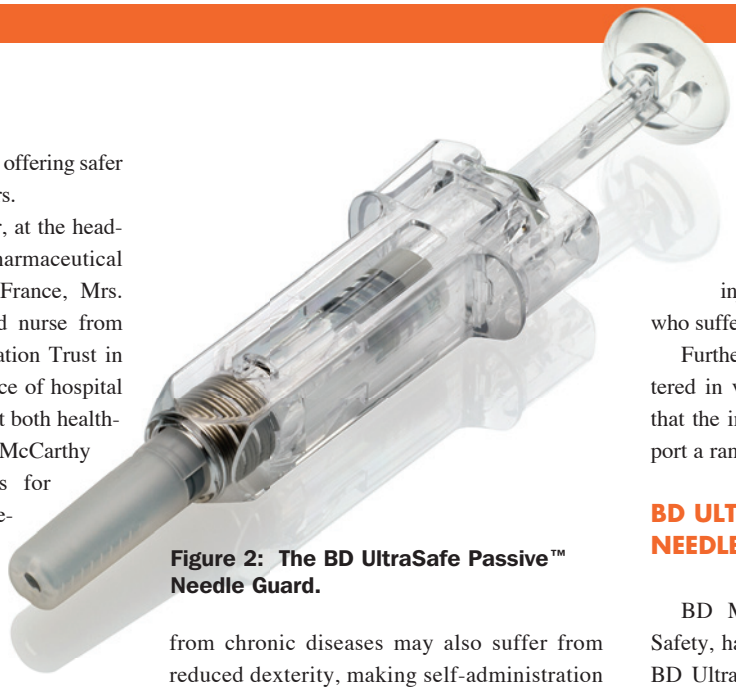

Figure 2: The BD UltraSafe Passive™ Needle Guard.

In addition formulations of biotech drugs, in particular monoclonal antibodies, can be viscous, which can then make them even more difficult to inject. This is especially true for patients who suffer from debilitating disease such as RA.

Furthermore, biologics often are administered in varying doses and volumes, requiring that the injection device design be able to support a range of fill volumes.

BD ULTRASAFE PLUS™ PASSIVE NEEDLE GUARD

BD Medical – Pharmaceutical Systems, Safety, has developed a novel injection device, BD UltraSafe Plus™. The design is based on the clinically proven BD UltraSafe Passive™ Needle Guard platform, primarily for use in a clinical setting, which has been marketed for over 12 years and successfully commercialised with more than 30 different drugs.

The design of the BD UltraSafe Plus™ Passive Needle Guard (see Figures 2 and 3) is specifically to support biotechnology drugs and

Figure 3: The BD UltraSafe Plus™ Passive Needle Guard is intuitive and easy to use.

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Figure 4: The ergonomic features of the BD UltraSafe Plus™ Passive Needle Guard provide injection support.

provide improved handling especially for those patients who prefer manual injection control. Specific features are:

- Extended built-in finger flanges and ergonomic plunger head provide a better feel for manual injection by the self-injecting patient (Figure 4)
- Robust plunger rod supports injection of viscous drugs
- Larger drug inspection window improves drug visibility.

PATIENT-CENTRIC DESIGN

Many patients have different requirements depending on their technique, injection site and dexterity impairment. Therefore, there is not always a single device that meets all end-user requirements. BD offers many options for self-injecting patients including the BD Physioject™ autoinjector for patients who prefer automatic injection as well as the new BD UltraSafe Plus™ Passive Needle Guard for patients who may prefer more manual control over their injection. BD incorporates a rigorous human factors and patient-centric design approach to meet the needs of healthcare providers, patients, payers and pharmaceutical companies.

The overall design of the BD UltraSafe Plus™ Passive Needle Guard was validated by performing handling studies with both nurses and self-injecting patients. In June 2012, a large clinical focus group was performed which included 500 injections by self-injecting patients and nurses. Patients in this study suffered from RA, MS, cancer, Crohn's disease and asthma. These diseases can have very different effects on dexterity so it was important to test the design with a broad range of patients.

Results from the user study confirmed that the BD UltraSafe Plus™ Passive Needle Guard was intuitive and easy to use with a 100% activation success rate for all 500 injections.[12] In addition, the added design features such as the wider finger flanges and ergonomic plunger rod were positively received by all users in providing additional injection support.

"MRS. STEPHANIE MCCARTHY, A REGISTERED NURSE FROM THE DERBY HOSPITALS NHS FOUNDATION TRUST IN THE UK … SPOKE REGARDING THE COSTS FOR IMPLEMENTATION OF NEEDLESTICK SAFETY IN THE WORKPLACE AND HOW THEY FAR OUTWEIGH THE MONETARY AND PSYCHOLOGICAL COSTS OF NOT INTRODUCING SAFETY ENGINEERED MEDICAL DEVICES IN THE HOSPITAL"

The results of the user study not only supported the added design features but also the ability of BD UltraSafe Plus™ Passive Needle Guard to provide additional support in injecting drugs of higher viscosity. All users preferred to inject viscous solutions using BD UltraSafe Plus™ Passive Needle Guard than a standard prefilled syringe.[13]

ADD-ON FINGER FLANGES FOR INJECTION SUPPORT

The BD UltraSafe Plus™ Passive Needle Guard was designed with extended finger flanges to accommodate one full finger on each side of the device. There are, however, some patients who may prefer even wider finger flanges to support their injection. Given this requirement, BD Medical – Pharmaceutical Systems will offer specific add-on finger flanges to support the BD UltraSafe Plus™ device. Moreover, the design of this add-on finger flange will take into consideration particular shapes and textures that are perceived differently across various patient populations allowing for more disease-specific designs.

SUPPORTING MANUFACTURING CAPABILITIES

After the design of the BD UltraSafe Plus™ Passive Needle Guard was confirmed, we consulted with leading automation machine builders to ensure assembly of the BD UltraSafe Plus™ Passive Needle Guard was compatible with minimal modifications to existing or planned secondary packaging lines for the BD UltraSafe Passive™ Needle Guard device.

The BD UltraSafe Plus™ Passive Needle Guard is designed to be used in conjunction with 1.0 mL long prefilled syringes with staked needles, such as the BD Hypak™ or BD Neopak™ Glass Prefillable Syringe.

The BD UltraSafe Plus™ Passive Needle Guard received US 510(k) clearance as an anti-needlestick safety device in April 2013 and will be commercially launched by a pharmaceutical company in 2013.

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SUMMARY

The market for biotechnology drugs continues to grow and there is a need for pharmaceutical companies to offer injection devices that support both the complex properties of the biologic as well as the needs of the end-user who will be performing the injection. Patients, especially those with limited dexterity, have very specific needs and requirements for the injection device. Providing a prefilled syringe with a safety device specifically designed for patients who prefer manual injection control and for drugs with higher viscosity provides pharmaceutical companies with a viable option that supports both of these requirements.

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ABOUT BD

BD is a leading global medical technology company that develops, manufactures and sells medical devices, instrument systems and reagents. The company is dedicated to improving people's health throughout the world. BD is focused on improving drug delivery, enhancing the quality and speed of diagnosing infectious diseases and cancers, and advancing research, discovery and production of new drugs and vaccines. BD's capabilities are instrumental in combating many of the world's most pressing diseases.

Founded in 1897 and headquartered in Franklin Lakes, NJ, US, BD employs nearly 30,000 associates in more than 50 countries throughout the world. The company serves healthcare institutions, life science researchers, clinical laboratories, the pharmaceutical industry and the general public. For more information, please visit www.bd.com.

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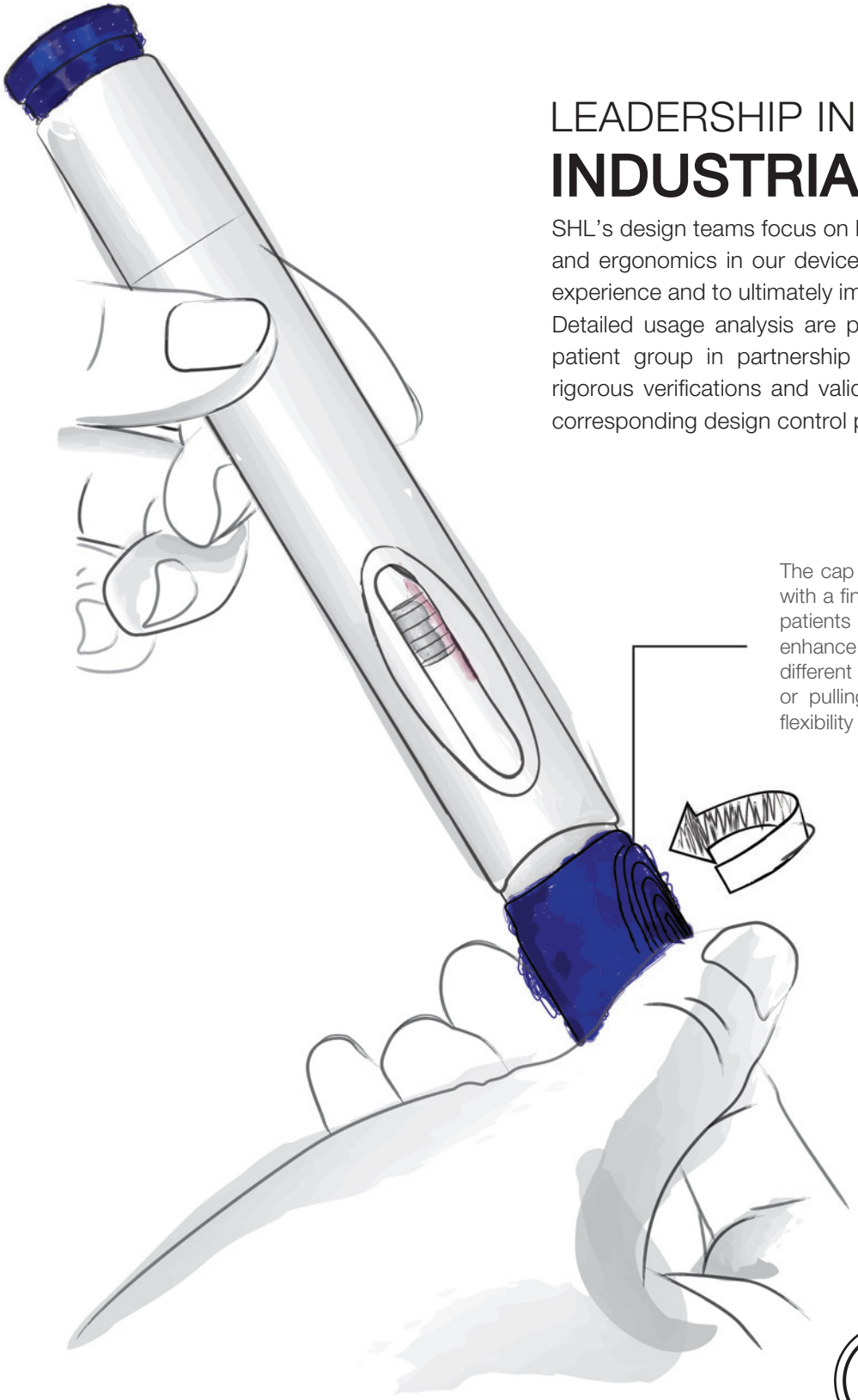

LEADERSHIP IN
INDUSTRIAL DESIGN

SHL's design teams focus on human factors engineering and ergonomics in our device designs to enhance user experience and to ultimately improve patient compliance. Detailed usage analysis are performed on the targeted patient group in partnership with our customers and rigorous verifications and validations are integrated into corresponding design control processes.

The cap for this device was designed with a fingerprint-like extrusion to help patients with dexterity issues to enhance their grip. The cap also offers different ways of uncapping - twisting or pulling, giving the user increased flexibility with cap removal.

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