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Mar:	Transdermal Patches, Microneedles & Needle-Free Injectors
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May:	Injectable Drug Delivery: Devices Focus
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July:	Novel Oral Delivery Systems
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Front cover image "Gloved Hand Holding a Prefilled Syringe", supplied by West Pharmaceutical Services, whose article appears in this issue, page 32. Reproduced with kind permission.

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MEDICAL TECHNOLOGIES

OVAL'S AUTO-INJECTOR PLATFORM FOR THE DELIVERY OF HIGH-VISCOSITY DRUGS

Drug development pipelines are tending towards increasing numbers of injectable products, and amongst these an ever larger proportion are viscous biologics and sustained-release formulations. Set against this backdrop, Susanna White, Mechanical Engineer, Oval Medical Technologies, and Louisa Harvey, Director, Harvey Medical, and Consultant to Oval, provide an overview of some of the considerations and challenges faced when designing delivery systems for viscous formulations, and describes Oval's unique high-viscosity drug delivery device platform.

INTRODUCTION

Drug development pipelines are showing an increasing trend towards injectables including biologics, peptides and sustained-released formulations. Many biologics have better patient outcomes, with enhanced patient safety and efficacy that are starting to contribute to personalised and targeted medicine. The injectables market is growing rapidly (see Figure 1) with many new formulations being viscous.

The viscosity of a formulation is influenced by the size and concentration of the molecule; many biologics are large molecules [2] and have to be given in high concentrations to achieve efficacy. These factors result in either highly viscous formulations, typically up to 100cPs (water has a viscosity of around 1cP at room temperature), or large volumes, both of which pose challenges for delivery by existing technology.

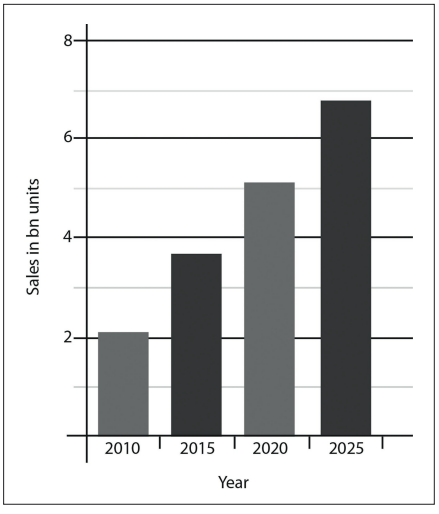

Figure 1: Prefilled syringes market sales growth projections / bn units.[1]

SUSTAINED-RELEASE FORMULATIONS

Many sustained-release injectable formulations are being developed, as part of life-cycle management strategies, to reduce dosing frequency, and to increase the barriers to entry for generic competition. Sustained-release formulations can have very high viscosities (up to 250,000 cPs), which are extremely difficult to inject manually, owing to the high injection forces required, and cannot be delivered by conventional auto-injectors.

Sustained-release formulations commonly work by forming a bolus of drug within the subcutaneous or muscular tissues, which slowly release drug over time. High-viscosity formulations are required to prevent the drug from dissipating into the bloodstream where it has rapid bioavailability and the sustained-release functionality is lost. It is important that these formulations are delivered to the right area of the body, and that the form of the drug bolus is maintained. If for instance the drug bolus is significantly spread out within the tissue it will have a much larger surface area, which can result in an

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initial spike in drug availability followed by too little in later stages of the dose duration.

Various methods are used to achieve sustained release, and all of these methods are invaluable in enabling a patient to take their chronic medication less frequently. However, there is a significant trade-off between frequency of delivery, and the ability to deliver viscous formulations.

Important issues for consideration when specifying drug delivery devices for viscous formulations include:

- Human factors such as physical usability, patient pain and emotional discomfort
- Mechanical reliability and consistency of performance.

In order to deliver viscous injectables, a fundamentally different approach to the design of auto-injectors is required. Oval Medical Technologies has considered each one of these issues, and has developed a new approach to the design of auto-injectors that brings benefits to the patient, the pharmaceutical company and healthcare providers.

MEETING THE CHALLENGES FOR VISCOUS DRUGS

Usability, Patient Preference & Compliance

Pharmaceutical companies and healthcare providers are concerned with patient compliance for obvious reasons, and compliance can be heavily influenced by usability (ability for the user to use the device) and preference (a desire by a user to use a device). Most patients when required to practice self-injection can use a manual syringe to inject an orange, but needle phobias, or the fear of pain, may prevent the same person from injecting themselves for real.

Highly viscous drugs can be particularly painful to inject as the needle diameters are often larger and injection times longer. Ideally the user interface of a device should be designed for the target population. By considering the needs and preferences of the patient, from the beginning, products are much more likely to succeed in the market than devices that are not intuitive to use and do not address specific user preferences such as needle phobias.

High syringe plunger forces may make the injection very uncomfortable for the patient or even be too high for manual injection altogether. Forces can be reduced by using a larger diameter needle but this can be unacceptable to patients, particularly if the needle is visible,[3] and can cause bleeding and bruising at the injection site. The limit of comfortable force for manual injection depends on factors such as the user, the delivery device and the injection site. According to the WHO the maximum force requirement for delivery should not exceed 30 N,[4] but based on Oval's previous experience, a comfortable limit to enable those with limited dexterity to operate a syringe can be as low as 20 N (4.5lbf).

As an example, 1mL of a 90cPs formulation administered through a 27 G needle can require more than 70 N to deliver, when using a "1 mL Long" manual prefilled syringe. A reasonable size auto-injector based on Oval's technology can provide 400N (90lbf) allowing small needles to be used. Auto-injectors are therefore the delivery system of choice for highly viscous formulations.

Reliability & Variability

Viscous formulations pose the greatest challenge to the delivery device designer in terms of reliability.

There are numerous issues that make conventional auto-injectors, which include a 1 mL glass syringe, unsuitable for use with viscous formulations. These include:

- tendency of glass to break under high injection forces
- variation in glide forces owing to incomplete siliconisation of glass and the propensity of rubber to stick
- propensity of rubber plungers to leak under high pressures.

For non-Newtonian formulations, small variations in injection force from device to device can lead to very wide variations in injection time.

Plunger stiction in auto-injectors has caused significant problems for the pharmaceutical industry. A number of devices have been subject to batch recalls. For example, in 2006 the Neulasta® SureClick™ auto-injector was recalled for failing to dispense the proper dosage due to sticking plungers. The product was subsequently withdrawn from the market in an auto-injector.[5]

Another related failure mode is juddering of the plunger during delivery, which can cause the user to remove the device before the entire dose has been dispensed.

OPPORTUNITIES FOR DELIVERING HIGH-VISCOSITY FORMULATIONS

Better Syringes

The difficulty in the application of conventional auto-injectors for viscous formulations is resulting in a number of companies choosing prefilled syringes as the delivery device of choice. However users including patients can have difficulty producing high actuation forces, resulting in very lengthy and variable delivery times, use of larger needle diameters, and greater pain and discomfort.

"THE USE OF A POLYETHYLENE CUP SEAL THAT PUSHES OUT THE DRUG DURING DELIVERY, REDUCES THE RISK OF LEAKAGE UNDER THE HIGH INJECTION FORCES THAT ARE REQUIRED"

Dilute the Formulation

While many sustained-release formulations require viscosity to function, biologics can be diluted. However, there are limits to the rate at which large volumes of injected drug can be absorbed by the body, so infusion (with associated costs and inconvenience) may be required.

Patch pumps (such as the micro infuser from BD and the SmartDose® from West) allow slow delivery of higher volumes in a home environment and offer an alternative to infusion, but can be costly and less convenient than auto-injectors, and are limited in the volumes that they can deliver compared with infusion.

Use a Larger Needle

Changes to the needle bore have a big impact on the force needed to deliver a drug. However large needles have certain disadvantages:

- They can increase needle phobia
- They can cause trauma at the injection site, including bleeding and bruising
- The drug can escape by flowing out of the hole left at the injection site.

Smaller needles require much higher pressure to administer the drug, which has an impact on usability and comfort for the patient. The injection will inevitably take longer, and the carer may not be able to keep the needle as steady.

There are cases where 18 G needles are used where no alternative options for

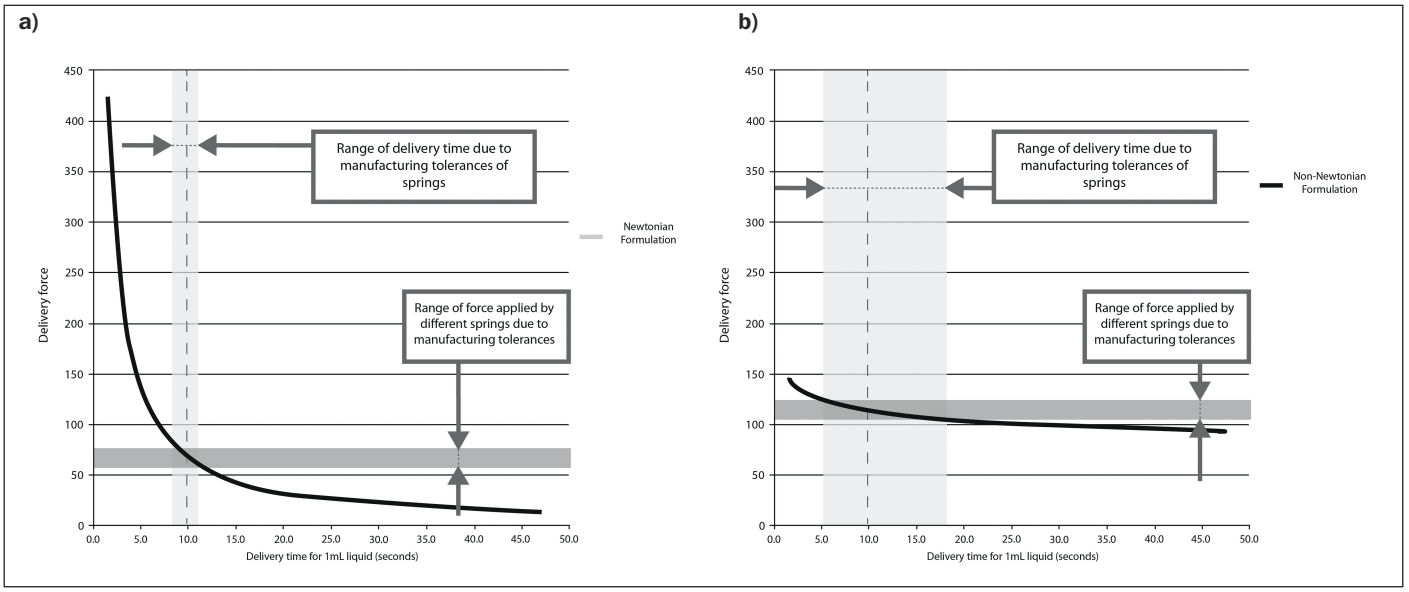

Figure 2: Delivery times calculated for a) non-Newtonian and b) Newtonian fluids.

delivering high viscosity product are available. However increased market and regulatory pressure to address device usability issues make the use of large needle bores unacceptable since they are painful and can cause large puncture wounds.

Use a Self-Powered Delivery Device

These can offer significant opportunities, and fall into two main categories:

Auto-injectors:

Auto-injectors can provide much higher delivery forces than those achievable by use of a manual syringe. This allows smaller needles, quicker delivery and potentially a much less disconcerting delivery experience for the patient. They can also make self-injection by patients much easier.

Patch pumps:

Patch pumps are suitable for the delivery of viscous biological drugs. They work by delivering the drug slowly, for example over a period of 20 minutes. The main advantage of pumps is their ability to hold larger volumes. The maximum volume that can be delivered subcutaneously using a syringe/auto-injector is dependent on many factors (injection site, depth, speed, absorption rate, level of acceptable pain etc) but is considered by some to be typically around 1.5 mL.[6]

Pumps are useful for biologics which should be delivered evenly into the blood stream. However, pumps may not work for those drugs with a sustained-release profile because you will not achieve the bolus form that is often needed. An auto-injector is therefore more appropriate for sustained-release formulations.

OVAL'S VISCOUS DRUG DELIVERY PLATFORM

Oval has developed a unique auto-injector platform technology capable of handling highly viscous drugs. It is fundamentally unique and has been shown to be capable of delivering a variety of 1000 cPs solutions (the thickness of motor oil) through a 25 G thin wall needle, in less than seven seconds, using a high viscosity primary drug container. Oval has a technology that has successfully delivered a 250,000 cP non-Newtonian formulation which gave equivalent results to a manual injection in a pharmacokinetic study in dogs.

Oval's design philosophy is to address Human Factors, device mechanical reliability and consistency of performance to produce devices that are best in class. Glass and rubber are not used in Oval's high viscosity devices; the primary drug container is cyclic olefin that has been shown to have very high burst strength. The use of a polyethylene cup seal that pushes out the drug during delivery, reduces the risk of leakage under the high injection forces that are required. The spring force is optimised for a given formulation viscosity and volume, the needle diameter and length and the target delivery time. Oval has developed methodologies to optimise these parameters and works with pharmaceutical companies to provide auto-injectors designed specifically for the target patient population.

Non-Newtonian viscosity

The definition of viscosity was quantified by Newton who realised that for some fluids the rate of flow (y) was directly related to the applied stress (σ): the constant of proportionality is the coefficient of viscosity (η). Fluids that work to this equation are described as Newtonian fluids, and those which do not are described as non-Newtonian.[7] Many highly viscous formulations are also non-Newtonion in character, and these can lead to specific issues around drug delivery (see Figure 2). Oval has direct experience of delivering highly non-Newtonian fluid formulations, and has developed specific delivery technology and test methods to optimise the performance of devices intended to be used to deliver these formulations.

In order to model the behaviour of non-Newtonian drugs, Oval uses a power law relationship between shear stress and shear rate known as the Ostwald–de Waele relationship. This is shown in equation 1 below where K and n are both physical properties of the fluid in question.

$$1)\ \tau = K\left(\frac{\partial u}{\partial y}\right)^{n}$$

In the case of a Newtonian fluid n would be equal to 1 and K would be the viscosity. Using this model, the relation between pressure drop and flow through a circular tube is given by equation 2.

$$2)\ Q = \frac{\pi r^{3}}{\frac{1}{n}+3}\left(\frac{\Delta p \cdot r}{2LK}\right)^{1/n}$$

Here Q is the volume flow rate, Δp is the pressure difference and L and r are the length and radius of the tube respectively. This equation must be simplified, reordered and have logarithms taken to turn it into a form that can be compared to experimental results.

$$3)\ \log\left(\frac{\Delta p \cdot r}{L}\right) = n\log\left(\frac{Q}{r^{3}}\right) + \log\left(2\mathrm{K}\left[\left(\frac{1}{n}+3\right)\frac{1}{\pi}\right]^{n}\right)$$

The experimental method involves using a force gauge to push the drug out of a container

through a needle of known length and diameter at a number of different velocities. These force and velocity data are used to calculate the pressure drop and volume flow rate through the needle, which is then analysed graphically and compared with equation 3 to determine the physical properties, K and n, of the drug.

The same tests are run on the drug whilst it is heated (40°C) and cooled (5°C) to understand its temperature dependency. This is important as, if a drug's physical properties are highly sensitive to temperature; this may result in an extremely variable delivery time if left unaccounted for in the design, and many biologics are stored at 4°C.

Once the parameters of the drug have been established its behaviour can be predicted, and it is possible to calculate appropriate spring forces required to deliver it. The parameters K and n and equation 2 are then used to determine the force required to optimise delivery time and needle gauge. From this, the most appropriate delivery method can be decided upon.

In some cases the non-Newtonian performance of a formulation can render it unsuitable for conventional auto-injectors altogether. Small changes in spring forces or viscosity due to manufacturing tolerances or temperature etc can have a very significant impact on delivery time, so that one injection may take tens or even hundreds of times longer than another of the same product.

This effect is explained in Figure 2. The two curves show the relative delivery time for different delivery forces of Newtonian and non-Newtonian formulations. Oval has resolved this issue through use of a novel power mechanism which helps to control the rate of drug delivery.

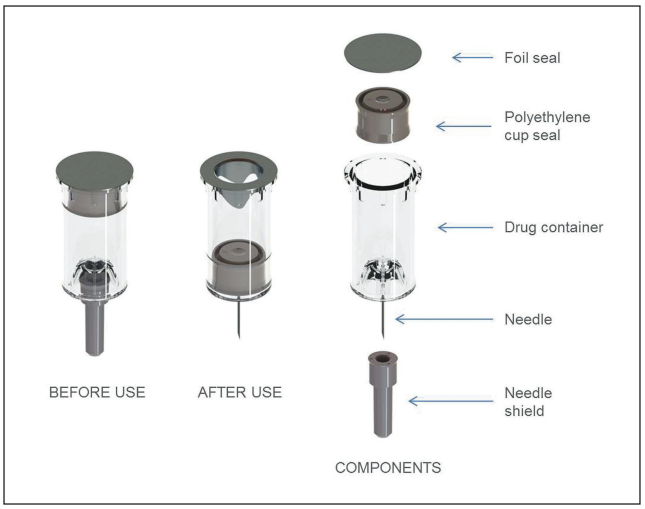

Figure 3: Oval's cup seal and foil technology.

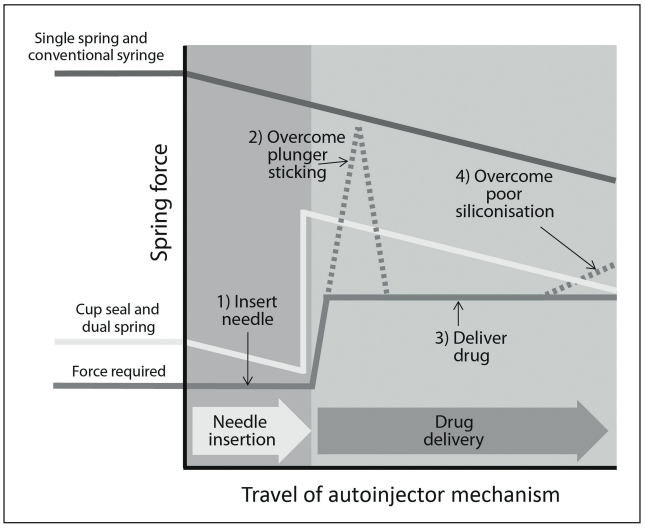

Figure 4: Drive system.

Material selection

As stated earlier, Oval decided to move away from a glass primary drug container to achieve a much higher burst strength, and after careful consideration chose Topas® cyclic olefin copolymer (COC) for their primary drug container. Cyclic olefin is a well-characterised material, used to produce many syringes around the globe. Topas® COC has been in production since 2000. COC was chosen due to its good leachable performance, very high water vapour barrier, excellent chemical resistance, its compatibility with various sterilising processes, and excellent optical properties.[8]

Oval took a revolutionary approach to eliminate rubber, which is traditionally used in glass syringes to create the plunger. Rubber has a propensity to stick to glass and requires lubrication with the silicone oil. Silicone oil can degrade biologics and can act as an adjuvant with some products, which could potentiate an immune response.[9] Rubber plungers have two distinct roles in a glass syringe namely to form the liquid seal of the primary drug container and to push the drug out at point of administration. This design is a compromise since the choice of rubber is not optimal for both functions. High injection forces required for viscous formulations, cause rubber plungers to leak. Oval's major innovation is the choice of polyethylene cup seal and foil (see Figure 3).[10] The two functions have been split between the polyethylene cup seal (for delivery) and the aluminium foil laminate seal (for container closure integrity). These materials are commonly used for similar functions in many other products. For instance, some dry-powder inhalation devices use aluminium foil to seal the primary container, and many products such as spray cleaner use polyethylene cup seals. Oval has brought these commonly used materials together to resolve the issues with rubber plungers in glass syringes.

In the same way that we viewed the rubber plunger as fulfilling a dual role, thus representing a compromise, the spring in an auto-injector can also be viewed as having two distinct functions. Both concern powering the device but one is to provide the power for the needle to pierce the skin and the other is to drive the plunger and deliver the drug. So, the Oval device uses a two-spring system to actuate the device; the first spring uses a lower force appropriate for piercing the skin. This then activates a stronger spring to provide the force required to deliver the drug. Figure 4 shows the spring force in the Oval device compared with conventional systems.

Customisation

Oval has the ability to customise many aspects of its device, enabling flexibility to build better auto-injector mechanisms. For example, the primary drug container wall thickness can be tailored to make it stronger. Features can be inserted to support the primary drug container. The power source can be modified in accordance with the viscosity. For generating the highest forces, with the most viscous drugs,

"THE OVAL DEVICE USES A TWO-SPRING SYSTEM TO ACTUATE THE DEVICE; THE FIRST SPRING USES A LOWER FORCE APPROPRIATE FOR PIERCING THE SKIN. THIS THEN ACTIVATES A STRONGER SPRING TO PROVIDE THE FORCE REQUIRED TO DELIVER THE DRUG"

Oval has developed safe and reliable power systems that are extremely compact. Where a more expensive power source is required technologies that allow for reuse are available. For example, the power pack can be retained for the next dose with the rest of the device being single-use.

CONCLUSION

Many biological drugs and sustained-release drugs cannot be satisfactorily delivered using current technologies. A number of devices and technologies in development are claiming viscous delivery, but none quite achieve the properties of the Oval device, particularly for sustained-release drugs.

Oval's technology has enabled the delivery of previously undeliverable solutions, in a user-friendly device. The delivery of viscous drugs was successfully achieved due to a change in materials, a fundamental change in the plunger by using cup-seal and foil, and the ability to customise many aspects of the device including power source.

Usability is imperative in the design of auto-injectors and even more so where high viscosity drugs are involved as they create additional challenges. At Oval usability is integrated in the design from the outset. In addition to providing a solution to the delivery of viscous formulations, Oval has developed a technology platform that improves delivery performance and product reliability for the widest range of formulation viscosities.

Oval is able to test the rheological properties of drugs in-house, and using mathematical modelling can give clients a good indication of how their drug may perform using its technology.

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INNOVATIVE INJECTABLE DRUG DELIVERY SYSTEMS

In this article, Thomas Jakob, PhD, Director, Business Unit Moulding, Pharma Solutions, RAUMEDIC AG, describes innovative injectable drug delivery systems together with a broad range of know-how and experience of polymer technologies. The most common starting point of all innovative injectable drug delivery systems is a customer idea.

Innovative and complex ideas in the field of polymer injectable drug delivery systems need a capable partner to succeed in realisation. For customised products such as new and innovative Injectable Drug Delivery Systems it needs a wide range of polymer technologies including injection moulding, extrusion and assembly. Starting with a first idea through prototyping, design studies, risk analysis, research and development up to mass serial production under clean room conditions, packaging and sterilisation the complete supply chain is more than just complex.

INNOVATIVE INJECTABLE DRUG DELIVERY SYSTEMS

With a share of approximately 25%, injectables were the number two in the global pharmaceuticals market in 2010, preceded only by oral medication. Double-digit growth rates, for example, in the areas of biotech products and injectable generics show the importance of this market segment. Besides standard prefilled syringes, vials and containers, more customised and innovative injectable drug delivery devices, such as safety syringes, customised

Figure 1: Fully automatic needle gluing, using UV LED lamps for the curing process

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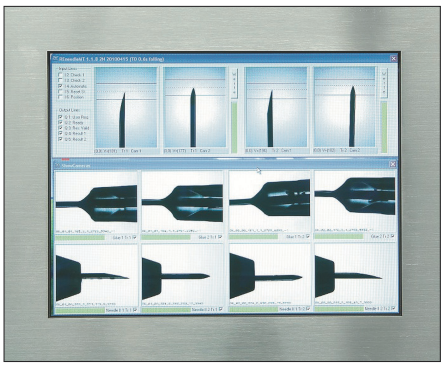

Figure 2: 100% vision inspection of the needle glue process as well of the quality of the needle tip.

Figure 3: UV-fluorescent glue enhanced visual inspection process.

Figure 4: High precise injection moulding parts from the polymer material polycarbonate, produced from a 64-cavity tool with hot runner system.

pen systems, needle-free or intradermal injectors are required by the market. Currently in the injectable drug market an estimated 2.7 billion prefilled syringes are used annually (Greystone Associates, 2009). In particular, polymer systems are estimated to undergo double digit growth rates in the coming years, especially those custom-developed for new drugs.

"WITH A SHARE OF APPROXIMATELY 25%, INJECTABLES WERE THE NUMBER TWO IN THE GLOBAL PHARMACEUTICALS MARKET IN 2010, PRECEDED ONLY BY ORAL MEDICATION. DOUBLE-DIGIT GROWTH RATES, FOR EXAMPLE, IN THE AREAS OF BIOTECH PRODUCTS AND INJECTABLE GENERICS SHOW THE IMPORTANCE OF THIS MARKET SEGMENT"

TECHNOLOGIES FOR INNOVATIVE DRUG DELIVERY SYSTEMS

A common stage in the manufacture of most injection devices (with the obvious exception of needle-free systems) is that a needle, which comes in a range of differing dimensions, is embedded in an injection-moulded polymer component. Three principal technologies are used for the connection: gluing, over-moulding and welding and the most appropriate process is dependent on the one hand on the needle size and surface, and on the other hand on the polymer type, size and geometry of the injection moulding part. Furthermore factors such as the required needle-holding forces, its final intended use in practice, and of course economic considerations, are relevant.

Figure 1 shows an example of a fully automatic needle-gluing process. The glue is cured with UV LED lamps followed by 100% vision control of the result, and an additional 100% needle force control according to standard norms (Figure 2). A UV-fluorescent glue system is used in order to enhance the visual inspection. The glue is visualised under a UV light as shown in Figure 3.

In addition to absolute precision in the fully automated needle handling process, there are also very narrow tolerances for the manufacture of injection-moulded parts. High-precision injection-moulded polycarbonate components are shown in figure 4. The specialities in this case are on the one hand the small size of the injection moulding part and on the other hand the tooling concept. The size of these parts is in the range of one pellet of polycarbonate before injection moulding. The second highlight in the development is the injection tool concept, where a 64-cavity tool was built with a highly innovative melt-disc hot runner system. One of the benefits for the customer is that precision injection moulding results in accurate holding forces for the embedded and glued needle.

For the handling system, different production systems are possible, starting from manual needle handling to fully automatic handling with linear or six-axis robot systems, where needles can be directly over-moulded with a polymer injection moulding part.

Another available manufacturing technology is multi-component injection moulding, which allows hard and soft thermoplastic polymers to be combined in one product without post-assembly. Especially for applications such as sealing and connecting combinations of different thermoplastics this technology can perfectly be applied. The soft component reacts chemically with the hard component and can only be separated through destructive force. This makes the product perfectly safe - an important factor in the pharmaceutical industry. Furthermore, the reduction of individual parts contributes to reduce costs.

A multi-component technology can even be enhanced by combining it with metal insert tech-

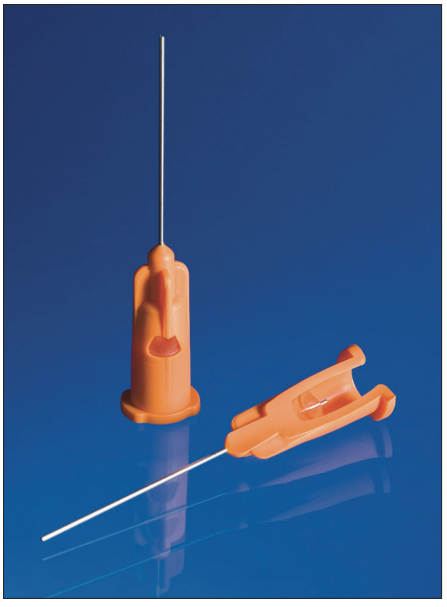

Figure 5: Metal cannula directly moulded with a two-component injection-moulding technology.

Figure 6: RauSafe™ provides safe protection against needle stick injuries.

nology. Figure 6 shows a metal needle directly moulded with a two-component injection moulding technology, first with a soft polymer and subsequently with a hard polymer. In the two-component luer cannula, the soft component has an additional sealing function. The adhesion between the metal insert and the polymer is comparable with gluing processes. Applications can be found in all kinds of injection systems.

In the pharmaceutical/drug delivery devices market there is a growing demand for new devices with directly over-moulded needles. Especially with regard to extractables and leachables, the advantage of an over-moulded needle is that the drug is only in direct contact with the polymer and the needle but not with any glue. Over-moulding technology in combination with fully automatic needle-handling in particular is growing in popularity and one reason for this is that the sophistication of injection device design, using new polymer materials, is increasing.

One area where the industry is able to take advantage of the availability of more sophisticated injection moulded polymer components, for the benefit of their customers, patients and healthcare workers alike, is in the development of needle-safety technologies.

"ONE AREA WHERE THE INDUSTRY IS ABLE TO TAKE ADVANTAGE OF THE AVAILABILITY OF MORE SOPHISTICATED INJECTION MOULDED POLYMER COMPONENTS, FOR THE BENEFIT OF THEIR CUSTOMERS, PATIENTS AND HEALTHCARE WORKERS ALIKE, IS IN THE DEVELOPMENT OF NEEDLE-SAFETY TECHNOLOGIES"

EFFECTIVE NEEDLE-STICK PROTECTION: RAUSAFE™

Worldwide, there are an estimated 3.5 million needle-stick injuries annually in doctors' clinics, hospitals and in the home-care setting. Associated with this is a risk of infection with dangerous viral diseases such as HBV, HCV or HIV. The resulting health and financial consequences after an infection are risk factors that have to be taken seriously.

In May 2013, the new EU Directive 2010/32/EU for the prevention of needle stick injuries came into force in all Member States of the EU. It dictates that employers in the medical field should provide systems with an integrated safety mechanism.

For this reason RAUMEDIC has developed a new safety device for injection systems. RauSafe™ (see Figure 6) can be adapted to a variety of existing injection systems on the market and provides reliable protection whilst being simple and intuitive to use.

The RauSafe™ needle safety device is activated after an injection by simply pushing it forward. As soon as the needle is completely enclosed, you can hear and feel the system click into the end position.

ABOUT RAUMEDIC

Innovative customised innovative injectable drug delivery systems are one example of the development and manufacturing expertise of RAUMEDIC and its customer-oriented conversion into high-quality medical and pharmaceutical products. RAUMEDIC meets all the requirements for generating tailor-made solutions in the areas of rapid prototyping, material development, precision and multi-component injection moulding, injection of moulded parts onto tubes, extrusion, micro-extrusion, multi-layer extrusion, part assembly as well as end packaging, sterilisation and certification. With its in-house laboratory RAUMEDIC can provide for all customers a broad range of different chemical, physical and individual test methods. RAUMEDIC creates complex concepts and developments for its customers and is consistently putting these into practice.

RAUMEDIC, a family owned company, is a spin-off of REHAU AG + Co, providing customer-specific polymer products and complete assembled systems on fully automated manufacturing machines, all manufactured from biologically suitable and approved materials under clean room conditions according to ISO 14644 class 7.

RAUMEDIC provides customer service worldwide through local subsidiaries and the development and processing competence centre in Münchberg, Germany. RAUMEDIC has established a comprehensive quality management system encompassing all processes within the company. The quality management system is process-oriented and certified in compliance with ISO 13485.

COMPANY PROFILE PHILLIPS-MEDISIZE

Phillips Medisize

Partnerships Built on Innovation

Phillips-Medisize is a leading global outsource provider of design and manufacturing services to the medical device and diagnostics, drug delivery and commercial markets, and has a history of manufacturing complex drug delivery devices such as inhalers, injection pens and safety syringes. The company has produced dry-powder inhalers (DPIs) since 1985, and has been involved in the development of about ten different inhaler programmes. Phillips-Medisize was the development partner for the first DPI, but since then our speed of turning a new inhaler platform design into clinical trials has increased significantly.

Large pharmaceutical companies require functioning inhalers before they make decisions concerning new inhaler platforms. Good ideas and drawings are not enough.

The company's strategy has been to develop its services continuously in order to keep up with these challenges. To deliver speed in all the development phases, it has invested in the very fast manufacturing of both one and multicavity tools.

As this service is combined with the best metrology service available on the market, the customer gets components and devices in record time. Having all the critical services in-house – such as design and development, tool manufacturing, metrology and injection moulding – alongside a long experience of assembly automation, has been a resoundingly successful strategy.

Customers are satisfied with seeing their new devices turn into full production in a continuously shorter time period.

Thanks to Phillips-Medisize's successful implementation of the strategy of delivering fast development programmes, customers have awarded it with new business. This is why the company added a 6,000m^2 expansion to its facility in Kontiolahti, Finland, in February 2013. This state-of-the-art facility focuses on the production of complex drug-delivery devices such as inhalers, injection pens and safety syringes, manufacturing various products from multicomponent drug delivery devices in prototype form to finished drug-delivery devices in a high-speed automated production environment.

The expansion was driven by new opportunities that Phillips-Medisize has been presented with over the past 12 months, as well as, to support increased global demand for devices with precise dosage drug-delivery requirements.

Phillips-Medisize has annual sales of more than $500 million (£325 million), with 75% of the total revenue coming from drug delivery, medical device and diagnostic products such as disposable insulin pens, glucose meters, speciality inhalation drug-delivery devices, single-use surgical devices and consumable diagnostic components.

COLLABORATION

When product launch success depends upon speed to market, drug and device companies benefit by joining forces. Such partnerships can free pharmaceutical and biotech companies to focus on their core competencies, while leveraging their suppliers' existing, proven, regulatory compliant manufacturing processes and infrastructure. Early collaboration, from initial design concept phase, allows the device company partner to help anticipate potentially problematic areas that can occur during pilot production, clinical trials and eventual high-volume manufacturing.

Project success, and the ability to control the many variables in product development, depends upon the ability of drug companies to select the right device manufacturing partner, with the right mix of development support and commercial manufacturing service offerings, to help guide the project. This target is best met by working with a single supplier able to handle and package drugs, demonstrate complete knowledge of the complexities of medical product development, and offer a full range of engineering and product development services.

By applying adequate due diligence in choosing their partner, pharmaceutical and biotechnology companies can improve the odds of launching a successful new drug product into the marketplace – on time and on budget.

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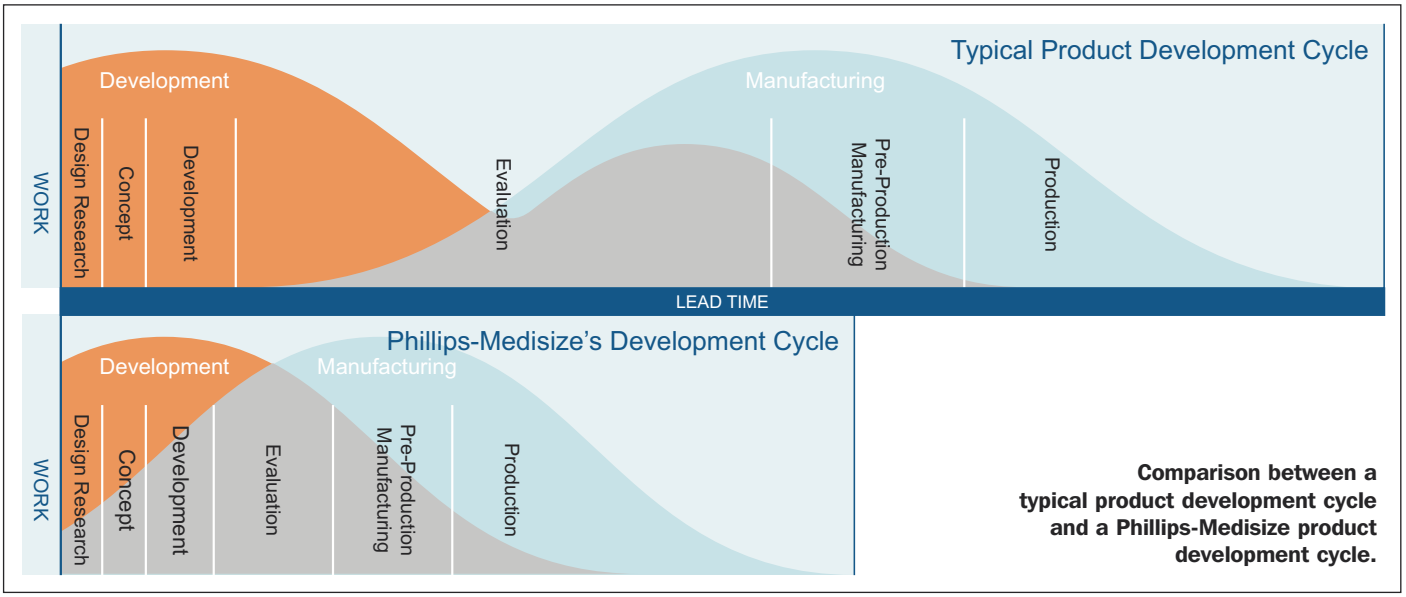

Comparison between a typical product development cycle and a Phillips-Medisize product development cycle.

2014 PDA Universe of Pre-filled Syringes and Injection Devices

October 6-7, 2014 | HUNTINGTON BEACH, CALIFORNIA

CALL FOR POSTERS / CASE STUDIES

The 2014 Pre-filled Syringe Program Planning Committee invites you to submit a scientific abstract for poster presentation at the *2014 PDA Universe of Pre-filled Syringes and Injection Devices*. The theme of this year's conference is *Improving Patient Outcomes through Innovation*.

Suggested topics include, but are not limited to:

- **Advances in Primary Container/ Prefilled Syringe Technology:**
  - Analytical Characterization Methods
  - Quality Improvements
  - Protein/Syringe Interactions
  - New Materials/Injector Technologies
  - Multiple Chamber Injector
  - Safety Devices
  - Autoinjectors and Add-ons
- **Factors Influencing the Selection and Development of Delivery Devices:**
  - Human Factors
  - End User Needs and Perspectives
  - Interaction between Device and Syringe
  - Regulatory Filing Process
  - Impact of Drug Characteristics
- **Case Studies: Market and Regulatory**
  - **Global Market Trends**
    - Asia Market
    - Europe Market
    - North/South/Latin America Market
  - Regulatory and Clinical Strategies
  - Combination Products
- **Case Studies: Manufacturing**
  - Vial to Pre-filled Syringe Conversion
  - Integration of PAT and Q8
  - Manufacturing Technologies Based on Disposable Processing Units
  - Material Selection
  - Stability Study Strategies
  - Aseptic Processing and Final Packaging Best Practices
  - Tech Transfer Best Practices
  - Contract Manufacturing Best Practices
  - Clinical Trails with Prefilled Syringes
  - Release Testing
    - Incoming Components
  - Microbial Control
  - Quality Agreements

Abstracts must be received by March 31, 2014 for consideration.
The Committee may also consider abstracts for an oral presentation.

Case studies are particularly desired. Commercial abstracts featuring promotion of products and services will not be considered. Submitters will be advised in writing of the status of their abstract after **June 2, 2014**. Poster presenters are required to register as a paid full conference attendee at the rate of **$1,795 member/$2,044 nonmember**. Exhibit Only registrants are eligible to present a poster by registering as a full conference participant.

In order to be listed in the final program agenda, your full conference registration must be received no later than August 29, 2014. After this date, the prevailing registration fees and policies apply.

QUESTIONS?

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ALL ABSTRACTS WILL BE REVIEWED

All submitted abstracts will be reviewed by the Program Planning Committee for inclusion as a podium presentation or for poster presentation.

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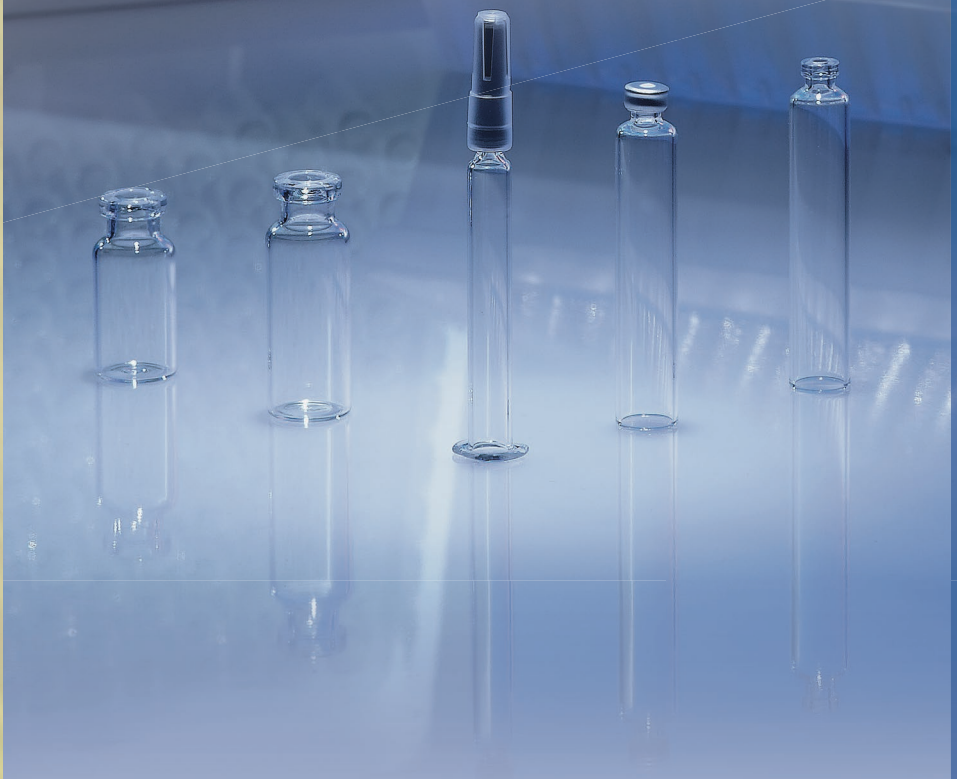

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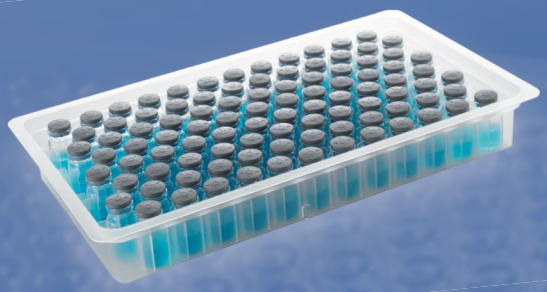

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SiO2 Medical Products
SCIENCE INSIDE™

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

In this article, the second part of a two-part series, Chris Weikart, Director of R&D, and Peter Sagona, Vice-President and Secretary, both of SiO_2 Medical Products, and Shawn Kinney, consultant to SiO_2 Medical Products, showcase the chemical, mechanical, and thermal performance stability of vials and syringes coated with an ultra-thin, high-purity glass barrier coating system. Performance stability studies were conducted with a wide range of liquid formulations intended to simulate what primary containers may experience under long-term aging (i.e. more than two years). Parenteral containers were filled with challenge solutions meant to represent the extremes of pharmaceutical and biological formulations.

INTRODUCTION

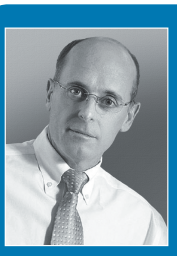
Part I of this article series appeared in the October 2013 issue of *ONdrugDelivery Magazine*.[1] In the first article, SiO_2 Medical Products introduced plastic primary containers with a glass-like, barrier coating system. Furthermore, the patented plasma technology used to deposit the glass layer and some description of the coating composition, architecture, and function were detailed. Data were presented on the barrier coating system thickness uniformity, composition, and surface energy using transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), and contact angle measurement. Here in Part II, we focus on the performance stability of vials and syringes coated with this ultra-thin coating system and report the results.

The barrier coating system incorporates a thin silicon oxide (glass) barrier layer and a cross-linked organosiloxane top layer. The high-purity glass barrier coating system is flexible because of its ultra-thin thickness of several hundred nanometers, and covers the entire interior surface of the primary container. The drug contact top layer protects the underlying silicon oxide layer from hydrolytic attack over the drug's shelf life, especially at higher pH conditions.

BACKGROUND ON LIQUID SOLUTION SELECTION

A range of liquid solutions were used to evaluate the barrier-coated parenteral containers, including extremes of pH (i.e. 3.5 citrate buffer and 8.0 phosphate buffer), water for injection (WFI), and high osmolality phosphate buffered saline solution (~600 mOsm/kg, pH = 7.4) with a surfactant. These liquid solutions were selected because they simulate a range of standard pharmaceutical and biological formulation conditions that are known to provide challenges to glass containers, as follows:

- Citrate has a low acid dissociation constant (referred to as "pKa") and is known to chelate metals, as demonstrated by its use in passivation. However, citrate can present a delamination challenge to standard borosilicate glass.
- pH 8.0 is an upper range found in "typical" parenteral drugs. Higher pH solutions increase



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the silicon dissolution of glass containers.

- Phosphate is a widely-used buffer with biologics and has an acid dissociation constant (pKa) well-suited for pH 8.0.
- Water for injection (WFI) is known to be an aggressive solvent to containers and is commonly the solvent of choice for parenterals, especially for small-molecule drugs.
- A high osmolality phosphate buffer solution (PBS) and WFI will demonstrate the ability of the coatings to withstand from low WFI to high osmolality solutions.

Tween, a common surfactant in biological formulations, was also included in this study at a concentration of 0.2%, which is considerably higher than typical biological formulations.

CHEMICAL STABILTY PERFORMANCE EVALUATION

The shelf-life of barrier-coated plastic cyclic olefin polymer (COP) vials was evaluated through chemical stability studies involving various liquid formulations, as identified above. Barrier-coated 5ml vials were filled with the formulations, incubated at 4ºC, 25ºC, and 40ºC, and tested at various time points for critical performance parameters, including oxygen transmission rates (OTR), amount of dissolved Si, and particulates. If coating debonding was occurring, an elevated dissolved Si and particulates would be expected. If the barrier coating on the coated vials was being dissolved, an increase in OTR and dissolved Si would be expected.

1. Gas Barrier Properties - Oxygen Transmission Rate

An effective method of evaluating the oxygen ingress or oxygen transmission rate (OTR) into a container can be conducted by monitoring the oxygen partial pressure inside the container over time after the oxygen inside is replaced by nitrogen.

To understand the impact of the glass coating on OTR better, all of the non-wall sources of oxygen ingress (i.e. stoppers and tip-caps) were eliminated. For a vial, this was accomplished by sealing the vial opening with a glass slide and epoxy. An oxygen-sensitive sensor inside nitrogen-purged vials was used to measure the oxygen partial pressure over time.

A plot of the oxygen partial pressure over time for 5ml uncoated COP vials, barrier system coated COP vials, and borosilicate glass vials is shown in Figure 1. The data illustrate

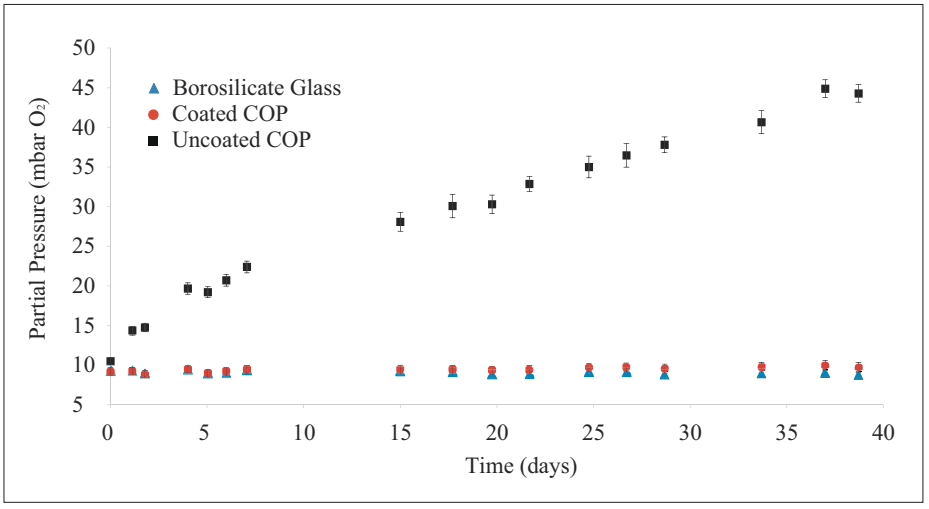

Figure 1: Partial pressure of oxygen inside vials.

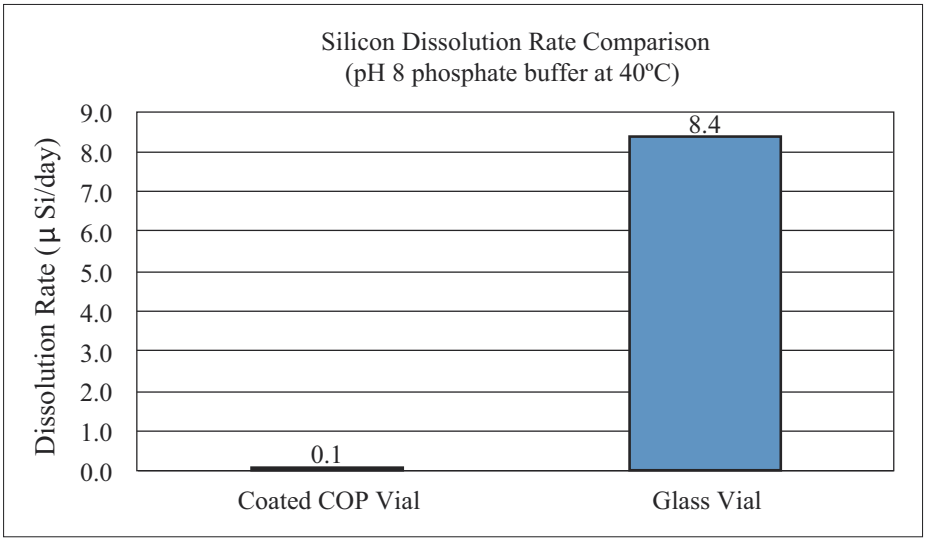

Figure 2: The top-layer reduces silicon extractables from the glass coating compared with traditional borosilicate glass at high pH.

that the glass coating improves the barrier to oxygen significantly and approaches the barrier provided by borosilicate glass. Comparing the relative OTR of the uncoated and coated COP shows at least 30 times lower OTR through the coated COP wall.

2. pH Stability - Silicon Dissolution Rate

The chemical stability of the barrier coating system was also interrogated by monitoring the amount of silicon dissolved over time in vials filled with the liquid formulations that were outlined previously. Silicates are well known to dissolve readily in high pH solutions by hydrolytic attack, which is further accelerated at high temperature.[2] In a high pH environment, a several hundred nanometer thick layer

"THE HIGH-PURITY GLASS BARRIER COATING SYSTEM IS FLEXIBLE BECAUSE OF ITS ULTRA-THIN THICKNESS OF SEVERAL HUNDRED NANOMETERS, AND COVERS THE ENTIRE INTERIOR SURFACE OF THE PRIMARY CONTAINER"

Oxygen barrier performance is maintained over the product shelf life by protecting the silicon oxide layer from chemical attack and dissolution. The OTR, described in this section, is an important performance parameter for the stability of the barrier coating system. The barrier coating system has remained intact, which is further supported by additional data (presented later in this article).

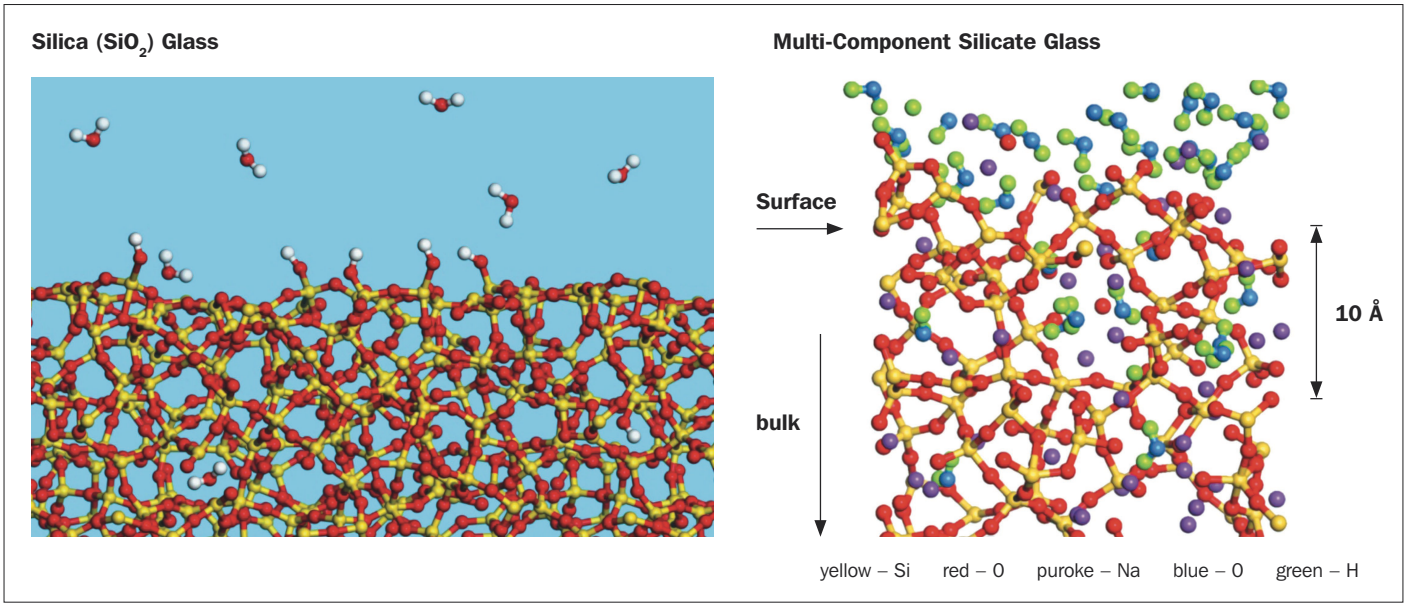

Figure 3: Illustration of pure glass surface *versus* a surface of a multi-component glass.

of silicon oxide or amorphous glass will completely dissolve quickly at 40°C. The purpose of the top layer is to protect the underlying silicon oxide barrier layer for the duration of the product shelf life. The top layer's unique combination of siloxane content, carbon content, and cross-link density provides a barrier to hydrolytic attack by the solution.

3. Extractables Characterisation

Extractables characterisation was conducted on COP vials that had been coated with the barrier coating system to quantify potential extractable chemical species from the coating. Both coated and uncoated vials were subjected to reflux extraction in WFI, water at pH4, water at pH8, and isopropyl alcohol (IPA). Volatile impurities and residual solvents were characterised using headspace gas chromatography-mass spectrometry (HS GC-MS) with electron ionisation, and semi-volatile compounds were characterised using gas chromatography-mass spectrometry. Non-volatile polar compounds were characterised using high-performance liquid chromatography-ultraviolet-mass spectrometry with positive and negative atmospheric pressure chemical ionization. Chemical species attributed to the coatings were not observed in any of the extracts at levels exceeding the analytical evaluation threshold (AET) of 0.13 µg/g and 1 µg/g for volatiles from headspace analysis.

"SiO_2 MEDICAL PRODUCTS' BARRIER COATING SYSTEM APPLIED TO PLASTIC PRIMARY CONTAINERS IS ROBUST UNDER CHEMICAL, THERMAL, AND MECHANICAL CONDITIONS REPRESENTING THE EXTREMES"

The silicon concentration was measured by inductively coupled plasma – optical emission spectroscopy (ICP-OES) in each solution at various time points. The change in silicon concentration over time was converted into a silicon dissolution rate in units of micrograms per day. Figure 2 shows an 80-fold reduction in silicon dissolution rate for vials coated with the barrier coating system compared with borosilicate glass filled with pH 8 solution at 40°C. Further, there was no observed increase in particulates with any of the solutions studied.

Ion exchange reactions, a prevalent mechanism for chemical attack of borosilicate glass (Figure 3), are non-existent in a plasma-deposited barrier coating system because of the absence of alkaline ions and oxides. Consequently, Si dissolution in vials coated with the barrier coating system is not accompanied by the B, Ca, Al, and Na ions known to be a leading cause of glass delamination.

MECHANICAL STABILTY PERFORMANCE EVALUATION

Barrier-coated 5ml plastic (COP) vials were evaluated through a variety of mechanical challenges to determine the robustness of the barrier coating system to maintain barrier properties after the application of simulated forces that a vial may be exposed to during processing.

1. Mechanical Stability – Glass *versus* Plastic

During filling, packaging, and processing, containers can experience varying applied loading forces from equipment placing stoppers into position, crimp cap placement, labelling, and general handling. Glass vials can tolerate a small amount of deformation before they experience a catastrophic failure and shatter, creating glass particles, which can contaminate other containers in addition to the manufacturing line. Plastic containers such as vials manufactured from COP, can withstand considerably higher compression forces than glass, as shown in Figure 4. Plastic COP containers provide two distinct benefits over glass containers of the same size. The first is due to the visco-elastic properties of COP. Forces applied to the vial below its yield point will allow it to return to its original shape once the force is removed. Vials being deformed with forces beyond the yield point of COP will tolerate permanent deformation without a catastrophic failure or shattering as with glass. A permanent dimensional deformation with COP vials can be screened from the lines with camera systems checking that the dimensions are within tolerance.

2. Barrier Coating Performance Against Vial Deformation

A series of compression forces studies were performed on vials and syringes for both top-down (Figure 5) and side-wall forces. In these

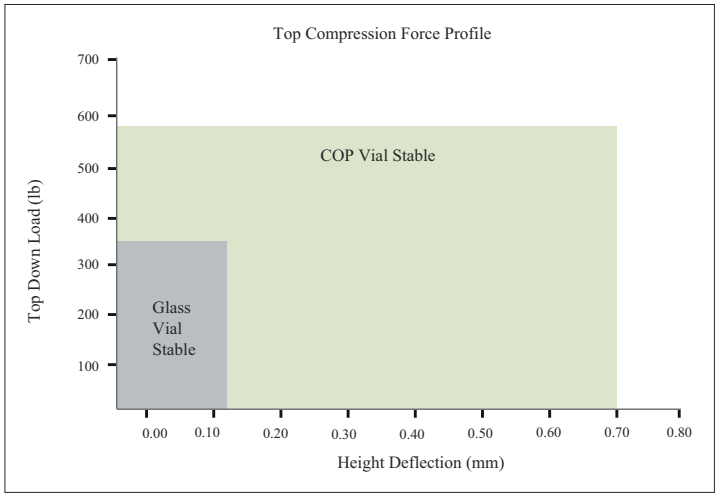

Figure 4: Deformation of glass vial *versus* COP vial.

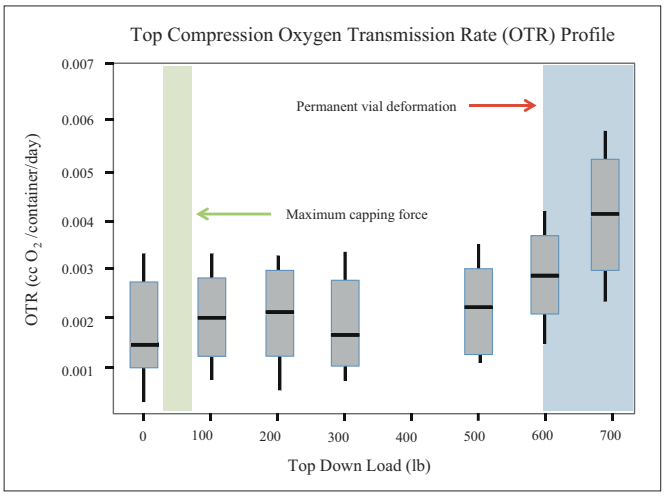

Figure 5: Oxygen transmission rate of glass coated 5 ml vials after increasing top down compression loads.

studies, increasing forces were applied to the containers and released until a permanent deformation of the container was observed. Both OTR and particulate counts were measured at each applied load prior to the permanent deformation at the yield point. It was observed that the coatings were intact (i.e. no increase in OTR or increase in particulates in the container versus control) up to the yield point of the container.

The plasma deposition process produces flexible ultra-thin layers of pure silicon oxide that are several hundred nanometres thick. The extremely thin nature of the coatings enables their ability to tolerate strain that can lead to breakage as seen with conventional glass parenteral containers.

THERMAL STABILTY PERFORMANCE EVALUATION

Parenteral containers and the barrier coating system are required to survive an extreme of temperature excursions, from the storing of drugs at cryogenic temperatures to the ability to withstand a steam sterilization cycle, all the while maintaining a barrier coating system that will maintain its optimal performance characteristics.

1. Temperature Excursion Stability

Primary parenteral packaging can be exposed to a variety of thermal stresses during processing, including extremes of temperature from -70°C (e.g. frozen storage and lyophilization) to 121°C (e.g. terminal sterilisation). Over these temperature excursions, the barrier coating system integrity must not be compromised. The following temperature exposure investigation was conducted on barrier-coated vials and an uncoated control.

A. Environmental exposures:

1. Cryogenic Temperatures: Barrier-coated vials were filled with 5ml of WFI, sealed, and exposed to a number of freeze thaw cycles, from -70°C to room temperature (by freezing in a -70°C freezer and then allowed to sit at room temperature until the contents reached 20°C).
2. Steam Sterilisation Temperatures: Barrier-coated vials were filled with 5ml of WFI, sealed, and terminally sterilized by steam at 121°C for thirty minutes, allowed to cool to room temperature, and sterilized for a second time under the same conditions.

B. Evaluation conducted on both environmental exposures to the vials coated with the barrier coating system:

1. Vials with the barrier coating system were evaluated for OTR.
2. Solution was evaluated for particulates.
3. Solution was evaluated for dissolved Si.

C. Results of the temperature extremes investigations for both exposures:

1. No change in OTR from the control vials.
2. No increase in particulates from control vials.
3. Insignificant increase in the amount of dissolved Si from the control vials.

The integrity of the barrier coating system post-exposure to cryogenic temperatures is seen in Figure 6 below. Ruthenium-based solution is used to stain plastics, but will not stain glass that is used to construct the barrier coating system.

"PLASTIC CONTAINERS WITH THE BARRIER COATING SYSTEM OUTPERFORM BOTH PLASTIC AND TRADITIONAL GLASS CONTAINERS IN TERMS OF THE SELECTED CHALLENGE CHEMICAL INTERACTIONS"

The clear vial shows no evidence of staining to the inside of the plastic vial because the barrier coating system has remained intact/uncompromised, compared with the uncoated control vial (as seen in Figure 6).

Figure 6: Clear vial indicates uncompromised barrier coating system after cryogenic shock followed by a Ru stain.

SUMMARY

The results from performance stability studies demonstrate that SiO_2 Medical Products' barrier coating system applied to plastic primary containers is robust under chemical, thermal, and mechanical conditions representing the extremes of pharmaceutical and biotech drug formulations and processing. These studies confirm that the plastic container and the barrier coating system maintain mechanical integrity during processing and normal use and that the coating system remains intact when experiencing forces incurred during production, handling, and use.

The results from chemical studies indicate that plastic containers with the barrier coating system outperform both plastic and traditional glass containers in terms of the selected challenge chemical interactions.

ABOUT SIO_2:

SiO_2 Medical Products is a privately held company founded and supported by CV Holdings, LLC, an organisation with 90 years of worldwide experience in development and manufacturing of diagnostic and food packaging. SiO's pilot R&D and manufacturing facilities are professionally staffed with fully equipped analytical and mechanical laboratories. In Q1 2014, SiO will open its additional newly constructed 160,000 sq ft headquarters in Auburn, AL, US, where the state-of-the-art facility will feature three 10,500 sq ft ISO Class 7 clean rooms 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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2) *Swift R, "Glass Containers for Parenteral Products." Chapter 11 in Pharmaceutical Dosage Forms: Parenteral Medications, 3rd Ed (2010), Vol 1. (Informa Healthcare).*

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Director of R&D, Dr Weikart is responsible for development of plasma coating processes to support product development, and coordinates development activities of the in-house technical staff and external consultants. Dr Weikart has a PhD in Chemical Engineering from the University of Missouri. Prior to joining SiO_2, he was R&D Manager for the energy and materials business at the Dow Chemical Company, where he served for 11 years.

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

Peter Sagona:
SiO Vice-President and Secretary, Mr Sagona is responsible for programme and IP strategy. Prior to joining SiO_2, Mr Sagona spent 11 years with CV Holdings, and seven years at SmithKline Beecham managing automation development projects. Mr Sagona received a MS in Engineering Management from Drexel University, PA, US.

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Intelligent Hospital Systems™

PHARMACY IV AUTOMATION: A MATURE, PROVEN TECHNOLOGY

Here, Niels Erik Hansen, PhD, President & Chief Executive Officer, Intelligent Hospital Systems, asks why manual compounding of IV formulations is still the norm in so many hospital pharmacies, arguing that automated compounding is far preferable, and is now readily available as a viable and proved alternative.

As automation technologies enhance a growing number of hospital services – including imaging, surgery, radiotherapy and rehabilitation, among others – the hospital pharmacy remains largely un-automated. Despite its central role in patient care, technicians in most hospital pharmacies still compound medications manually, in much the same way as it has been done for generations.

Such a long history, combined with refinements in aseptic techniques and training, means manual IV compounding remains the accepted standard of care. But how much longer should it be? Recent outbreaks of illness and adverse reactions linked to compounded medications, as well as numerous pharmacy product recalls, make the shortcomings of manual compounding increasingly hard to ignore.

Although pharmacy technicians are trained in the physical process of compounding, few understand the physics behind the process. And, being human, even the most experienced technicians make mistakes; some studies have documented observed manual error rates of up to 10% in hospital pharmacies. Being able to repeat a compounding technique is not the same as ensuring accurate repeatability.

Ongoing reliance on manual techniques would be understandable if there were no alternative. But automated IV compounding systems have existed for more than a decade. Moreover, the technology is proven to enhance the safety of compounded medications, reduce pharmacy costs and increase productivity. So why aren't more hospitals using it?

While pharmacists have generally welcomed technological innovation, many within the industry feel automated IV compounding technology is not yet sufficiently developed for widespread implementation. It's an unfortunate perception, and inaccurate.

At its most basic, the automation of medication compounding is simply the application of proven robotic technologies to well-understood processes and known physical parameters. Available IV compounding technology can not only duplicate the manual process, but do so with substantially more accuracy, efficiency and repeatability.

Automation is the use of machines, control systems and technology to increase productivity and the quality of goods beyond what is possible through human labour. The development of such technologies goes back more than three-quarters of a century – the first industrial robot was built in 1937 – and has undergone continuous enhancement and refinement ever since.

Today robotic automation is used to manufacture numerous products including cars, appliances, food, computers and mobile devices. Robots are particularly useful where a high degree of accuracy is required. For example, silicon chip manufacturing often requires tolerances measured in microns, orders of magnitude smaller than the tenth-of-a-millimeter measurements necessary in pharmacy compounding.

But in order to automate any manufacturing process successfully, it is essential to understand the process fully – inputs, weights

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and measures, individual production steps, and desired outputs. In other words, to automate medication compounding, you have to know how medication is compounded. Fortunately, the process and physics of medication compounding are well documented.

In more than a decade of research, a team of engineers worked to measure and quantify virtually every aspect of IV compounding. Their analysis included such variables as admixture fluid weight, surface tension, specific gravity and viscosity, differences in the diameter of 'standard' needle bore holes, the amount of force necessary for needles to puncture a vial stopper, and much more. The resulting IV automation technology, called RIVA, can account for the various physical properties of inputs and also compensate for variation.

For those who might look to output quality as evidence of production efficacy, pharmacy automation has proven a resounding success. Since RIVA was commercialised in 2008, systems have been installed at more than 30 sites worldwide and have cumulatively produced over two million IV doses safely and accurately. Further, installed units have performed approximately 150,000 routine growth media contamination tests with zero failures. These numbers far exceed typical quality control validation measures for almost every type of manufacturing. The bottom line is that pharmacy IV automation is a mature, well-established technology, with a solid record of quality control and output that is proven to be superior to manual processes. As numerous hospital operations and healthcare procedures are improved with automation, it is past time for automated compounding to become the standard of care in pharmacies. The benefits – reduced cost, increased efficiency and, most important, greatly enhanced medication and patient safety – make IV automation imperative.

"TECHNICIANS IN MOST HOSPITAL PHARMACIES STILL COMPOUND MANUALLY, IN MUCH THE SAME WAY AS IT HAS BEEN DONE FOR GENERATIONS"

ABOUT THE AUTHOR:

Dr Niels Erik Hansen is President and CEO of Intelligent Hospital Systems, Winnipeg, Canada. He holds a PhD in control engineering and an MS in mechanical engineering from Technical University of Denmark, and has more than 30 years' experience in technology engineering and production with emphasis in motion control, fluid management and environmental engineering.

ABOUT INTELLIGENT HOSPITAL SYSTEMS:

Intelligent Hospital Systems is a medical device company focused on the design and development of automated solutions for the hospital environment.

Its product, RIVA, is the most comprehensive solution for automated preparation of IV medications. Developed from research conducted by a team at the St Boniface Research Centre (Winnipeg, Canada) in the mid-1990s, RIVA is used by hospital pharmacies to automatically and accurately prepare IV syringes and IV bags. By automating the admixture preparation, RIVA addresses the issues of safety for the patient and the pharmacy technician, efficiency and effectiveness in the pharmacy and the challenges of a changing regulatory environment.

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TODAY'S TOOLMAKER: FROM MOULD MANUFACTURER TO FULL-SERVICE SOLUTION PROVIDER

Here, in the context of the pharmaceutical and delivery device industries' demand for increasingly complex tooling, Jan-Willem den Hollander, Business Development Manager, IGS GeboJagema, relates how the company has evolved from mould maker to a full-service tooling solutions provider.

The development costs of a new drug can increase to more than €1 billion (£830,000) and can take 10-15 years' development time. Modern global pharmaceutical companies audit high-tech toolmakers with their own sourcing teams and value their capabilities on project management, design for manufacturing and mould validation.

In last decade, IGS GeboJagema experienced that the required part-for-manufacturing know-how is not always available at the pharmaceutical companies and often external medical device development companies are involved in the engineering of this new drug delivery platform. This is where the need for a professional tooling partner for pilot-, preproduction-, and multi cavity-moulds is born.

Toolmakers that supply the healthcare industry and are involved in large-scale tooling programmes such as the delivery of multiple 32-cavity hot-runner moulds need to have more skills than just innovative mould engineering and accurate mould manufacturing capabilities. They have to add value with senior project management, DOE and DFMEA's, captive validation capabilities for factory acceptance tests, skilled process engineers and appropriate metrology equipment. Besides these technical skills, toolmakers supplying the healthcare industry need to have a solid financial backbone to be able to support the moulds during the full lifetime of the medical device

In the 1990s, IGS GeboJagema recognised the need to change from an ordinary mould-maker to a full-service solution provider and invested in tool manufacturing efficiency programmes, such as robotised, automated equipment for high-speed milling and spark eroding, and enhanced the engineering team to almost 25 professionals, including five project managers.

Each project manager is dedicated to a medical device project. Some projects even have a back-up project manager, to safeguard the continuity of the project. So from start to finish the project manager is the contact person during the entire project for the customer, whether it is about mould design, Gantt charts, DFMEA studies or metal steel safe re-cuts.

IGS GeboJagema also installed a new validation centre (Figure 1) with more than 10 injection moulding machines in separate validation cells to guarantee the full secrecy of the customers' developments. The Factory Acceptance Test of the moulds at IGS can be done either on IGS's own injection moulding machine or on a customer's machine, which can be temporarily installed in one of the available validation cells.

IGS GeboJagema is fully equipped with hot-runner controllers, chillers, coolers, resin drying and master batch colouring equipment. The well-trained process engineers are more than operators, but are always striving to develop the most efficient and optimum processes (Figure 2). They exactly know how to run a factory acceptance test, including dry-cycle tests, process

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Figure 1: IGS GeboJagem Validation Centre.

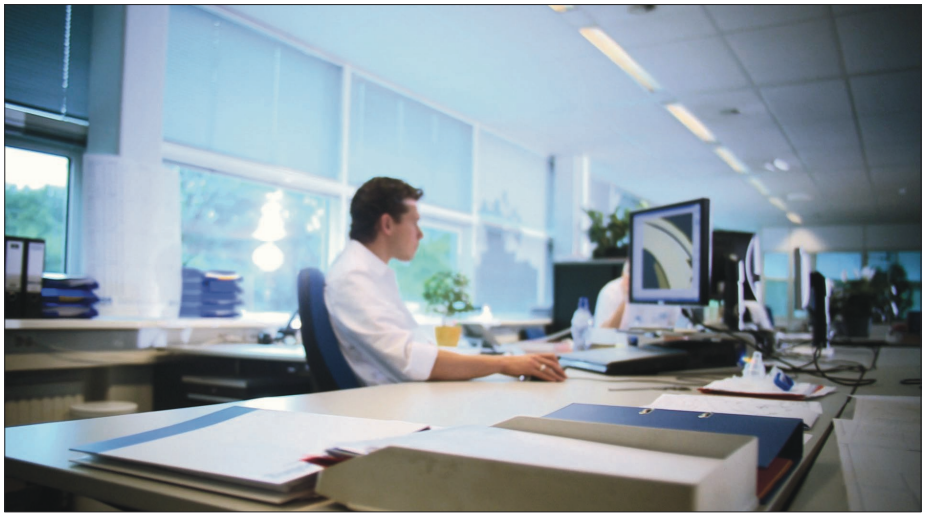

Figure 2: Engineering Department.

development, FOT programs, balance of fill analyses, DOE analysis and four-hour FAT runs and prepare a number of shots for a full first article inspection report. They will ensure moulds are production-ready, within the demanded Ppk values and dimensional tolerance. IGS GeboJagema transformed from a regular toolmaker to a full-service solution provider and became the professional partner the modern pharmaceutical companies are looking for today.

This is why IGS GeboJagema is involved in medical device programmes and is able to support large-scale tooling projects.

ACCURATE INSULIN DOSING DEMANDS BETTER TOOLING

Increasingly accurate insulin dosing systems will increase the need for more complex and accurate tooling. Not only the dosing volume itself but also important is the speed of a viscous drug that goes through a needle and enters into the human body. This last item specifically is something where insulin device developers can diversify themselves from other insulin pen providers.

Today the device developers will use their engineering capabilities in full and will design the most difficult axle drive sleeves, lead screws and other complicated parts. It then becomes the challenge of a toolmaker to transfer these extreme difficult features into cores and cavities for a multi impression mould. To achieve the best result toolmakers will have to invest heavily in specially equipped, multi-tasking machining.

The Okuma MULTUS B300II was installed at IGS GeboJagema in Q4 2013 (Figure 3). This multi-tasking CNC machine performs process-intensive machining for shorter deliveries, and is the ultimate fusion of turn-mill operations, with lathe, vertical or horizontal machining centre and material handling operations consolidated into one 8-10 inch chuck class machine. With fewer setups, work in process is drastically reduced and machine utilisation is greatly increased.

This investment fully equips and readies IGS GeboJagema to manufacture the most extreme spindles and axles that are already included in today's most sophisticated insulin pen designs.

ABOUT IGS GEBOJAGEMA:

IGS GeboJagema is a toolmaker, based in the Netherlands, with >100+ employees. The company has been manufacturing high-precision injection moulds for more than 65 years, and is known for its proven track-record in full-service solutions in the design, manufacturing and full validation of high-precision multi cavity moulds used in the healthcare industry. IGS moulds are used to produce injection moulded parts for auto-injectors, insulin pens, metered-dose inhalers, dry-powder inhalers and other medical devices.

Figure 3: The Okuma MULTUS B300II, installed at IGS GeboJagema in Q4 2013.

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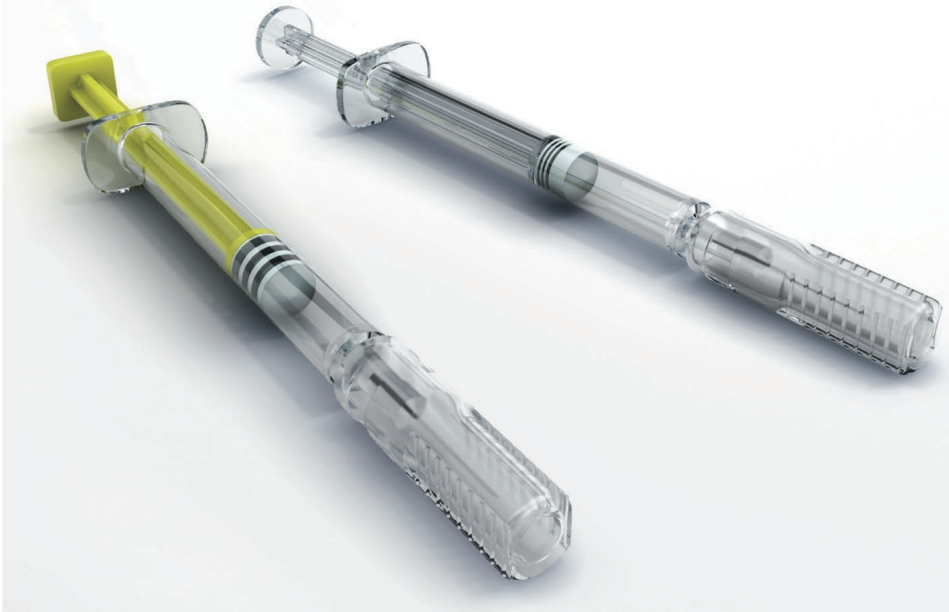

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ENHANCING PREFILLABLE SYRINGE COMPONENT QUALITY … BY DESIGN

In this article, Tibor Hlobik, Director, Global Prefillable Syringe Platform, West Pharmaceutical Services, Inc, decribes how the application of Quality-by-Design principles in the development and manufacture of prefillable syringe components is linked with improving drug safety and efficacy.

In recent years, there has been a shift in the pharmaceutical industry toward a Quality by Design (QbD) philosophy. To maximise a drug product's safety and efficacy, pharmaceutical companies and their drug packaging and delivery partners are building new quality principles into the entire manufacturing process, from design and development to commercialisation and administration. This scientific, risk-based QbD approach is fast becoming an essential strategy for bringing high-quality therapeutics to market quickly and efficiently.

"UNDERSTANDING HOW DRUG CONTAINER CLOSURE SYSTEMS AND THEIR VARIOUS COMPONENTS IMPACT A DRUG'S SAFETY AND EFFICACY IS FUNDAMENTAL TO THE QBD APPROACH"

One area where pharmaceutical packaging and device delivery companies are successfully applying QbD principles is the manufacturing of high-quality components for prefillable syringes. The quality, safety and efficacy of a drug product can be linked to the suitability of its container closure system (Figure 1). Understanding how drug container closure systems and their various components impact a drug's safety and efficacy is fundamental to the QbD approach.

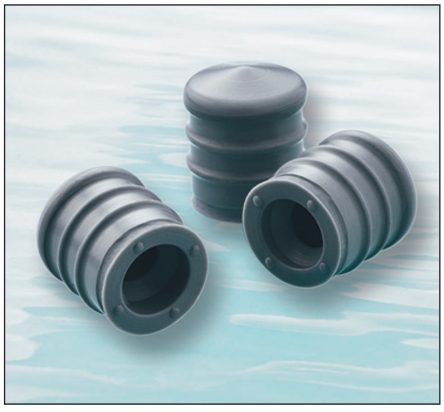

Figure 1: The quality, safety and efficacy of a drug product can be linked to the suitability of its container closure system.

Market trends toward home-use and patient self-administration of drugs used to treat chronic conditions (e.g. multiple sclerosis and rheumatoid arthritis) have made prefilled syringe systems an ideal choice for single-dose drugs (Figure 2). Prefilled syringe systems for pharmaceuticals and biopharmaceuticals offer convenient, fixed dosing and are adaptable to automated injection devices.

For patients, use of a prefilled syringe system has the potential to minimise microbial contamination and reduce medication dosing errors. The syringe systems offer ease of use and enhanced convenience for those who require frequent dosing, and when combined with an auto-injector system, can provide a more portable drug delivery system.

Pharmaceutical and biopharmaceutical manufacturers who select a prefillable syringe system for their drug product may be able to reduce therapy and injection costs, as well as signifi-

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Figure 2: Trends toward home-use and self-administration for chronic conditions have made prefilled syringe systems an ideal choice for single-dose drugs.

cantly reduce overfill when compared with single-dose vials. The system may also optimise the number of doses from the existing drug supply, while offering a delivery option that will help to differentiate the system in a crowded market and potentially increase patient preference.

Strategies employed in early phases of drug development that consider delivery devices such as prefillable syringes and their components can mitigate risk to quality, and position the product to meet needs of the ongoing drug product lifecycle. The return on investment can be realised once a drug product is commercialised and has gained patient loyalty through ease of use, therapeutic benefit and high confidence in the delivery device. While it is not easy to meet these challenges, a drug product manufacturer can benefit from early investment in the right drug delivery system and high-quality components.

MITIGATING RISK IN PREFILLABLE SYRINGE COMPONENTS

Prefillable syringes are an ideal choice for single-dose drugs, especially those used to treat chronic conditions such as multiple sclerosis, rheumatoid arthritis and other autoimmune diseases. Often medications used to treat these conditions can be self-administered by patients. Prefillable syringes offer convenient, fixed dosing, are easy to use and can be combined with an auto-injector system. In addition, prefillable syringes have the potential to minimise microbial contamination and reduce medication dosing errors.

With prefillable syringe systems becoming more widely used, it is essential that the components used to contain and deliver the drug be of the highest quality in order to minimise impact on the drug product. A critical component in a prefillable syringe system is an elastomeric plunger – also known as a piston or stopper – which expels the contents of the barrel to deliver the drug to the patient. The plunger serves as the primary seal for container closure integrity and helps maintain the purity of the drug throughout its shelf life. It is important for drug packaging and delivery manufacturers to ensure plungers are compatible with the drug product and will not impact the integrity of the drug product.

Plungers are typically made from butyl rubber and coated with a fluoropolymer film, such as FluroTec® film, that helps increase lubricity and serves as a barrier between the drug and the elastomer to reduce risk from negative interaction. The phenomenon of chemicals migrating from the elastomers into the drug product is known as leaching, but the reverse process of the drug product adsorbing or absorbing onto the plunger can also occur. The impact of extractables and leachables, and adsorption/absorption can be significantly reduced with a barrier film.

To streamline the manufacturing process and handling of prefillable syringe components, the pharmaceutical industry has moved toward ready-to-use (RU) plungers. RU plungers are washed and sterilised prior to delivery to the drug manufacturer with specifications for particulates and endotoxins, reducing the risk of microbiological contamination to the drug product during final packaging. There are several methods for sterilisation of plungers and an increase in extractable breakdown products has been observed under gamma radiation; therefore, autoclave steam sterilisation of these components is a preferred, low-risk choice.

"THE PLUNGERS THAT FIT 1ML LONG STAKED NEEDLE SYRINGES WERE ORIGINALLY DEVELOPED FOR A MANUAL INJECTION ACTION. AS INDUSTRY REQUIREMENTS FOR HIGHER QUALITY AND PATIENT NEEDS FOR SELF-INJECTION WITH AUTO-INJECTORS HAVE EVOLVED, THE DEMAND FOR PLUNGERS WITH IMPROVED FUNCTIONALITY HAS GROWN"

APPLYING QBD TO PREFILLABLE SYRINGES

When designing and developing a component using QbD principles, manufacturers must define desired product performance and identify critical quality attributes (CQAs). The component and process are then designed to meet those product attributes, which leads to understanding the impact of material attributes and process parameters on the CQAs and identification and control of sources of variability. As a result of this knowledge, a company can continually monitor, update and improve its manufacturing process to assure consistent product quality.

Since prefilled syringes are considered a combination product, consisting of a drug and a device, two US federal quality regulations apply: cGMP Finished Pharmaceuticals part 21 CFR 210-211 and QSR Regulation for Devices 21 CFR 820. To meet these regulations, pharmaceutical manufacturers must comply with several areas including management responsibility, purchasing controls, corrective and preventive action, design controls and a design history file. As part of the industrialisation of plungers using the QbD approach, these aspects were considered and elements incorporated into the manufacturing process and product.

Most subcutaneous drug product injections use a staked needle in a 1mL long prefilled syringe format that can retain a fill volume ≤1.0mL. The plungers that fit 1 mL long staked needle syringes were originally developed for a manual injection action. As industry requirements for higher quality and patient needs for self-injection with auto-injectors have evolved, the demand for plungers with improved functionality has grown.

To meet growing demand for high-quality components, it is important that drug manufacturers look for prefillable syringe components that have the following attributes:

- *Dose Accuracy and Injection Time Reliability* – Variations in the quality of the glass barrel/ plunger interface may cause inconsistent break-loose and glide forces. This can be compensated for by the force applied to the plunger by the patient or caregiver during manual injection. However, when an auto-injector is used this variability may cause incomplete injections or stall the plunger's movement, resulting in variable delivered dose volumes.
- *Low Levels of Particulates and Visual Defects* – The US FDA is continually spurring the pharmaceutical industry to reduce patient risk and improve safety and compliance. As part of this process, continuous improvements are needed for loose and embedded particulates, including visible and sub-visible, to minimise drug interactions and patient harm.

> "PREFILLABLE SYRINGE COMPONENTS POSE A POTENTIAL RISK TO A DRUG'S EFFICACY, BUT IF DEVELOPED AND MANUFACTURED WITH CONSISTENT QBD PRINCIPLES IN MIND, THEY CAN PLAY A CRITICAL ROLE IN ENSURING A DRUG PRODUCT'S INTEGRITY AND EFFICACY"

By designing with these attributes in mind, prefillable syringe components can help maximize a drug product's efficacy and safety profile while enhancing product manufacturability. QBD philosophy and principles can help to optimise break-loose and glide force and significantly reduce plunger variation from part-to-part. Following a QbD approach throughout the product design and development process can help manufacturers ensure that components are developed based on science and data-driven decisions and meet critical specification for defects, visible and sub-visible particulate and extractables consistently.

THE WEST SOLUTION: NOVAPURE® HIGH-QUALITY COMPONENTS

Using QbD principles, West developed NovaPure components for prefillable syringe systems to provide high reliability for break-loose and glide force, dimensional accuracy and consistency, sub-visible and visible particulate control, and low parts per million (ppm) defect attributes.

The optimised functional and dimensional performance for NovaPure plungers provides predictable injection times and statistical consistency when used in conjunction with 1mL long staked-needle syringes and an auto-injector system.

The 1mL long NovaPure plunger followed a development framework, which used a Quality Target Product Profile (QTPP) to establish CQAs for control of break-loose and glide forces. As the product – which included risk-based design inputs, Finite Element Analysis (FEA) modelling, data generation on multiple concepts, and final product performance verification with glass barrels from multiple suppliers of a 1mL long staked-needle syringe – was developed, the QTPP served as a guideline to assure that targeted specification values for break-loose and glide force were met.

In order to achieve a high-quality product, QbD components are washed and steam sterilised for optimised material compatibility and the knowledge gained throughout the process used on an ongoing basis to maintain continuous improvement by the manufacturer. Selecting a manufacturing partner like West early in the development process can help pharmaceutical companies choose a high-quality component for use in prefillable syringe systems that will meet demands for high quality, improved total cost, and increased safety and security for the drug product.

CONCLUSION

With so many different elements involved in bringing a drug product to market, it is increasingly important to incorporate QbD principles into the manufacturing of both the drug product and its container closure system. Quality should be built into all of these components with a thorough understanding of the process by which it is developed and manufactured and knowledge of the risks involved.

The selection and quality of components used in prefillable syringes are important parameters in pharmaceutical development and throughout the drug product lifecycle – from the design and manufacturing process, to transport and storage, through to administration. Prefillable syringe components pose a potential risk to a drug's efficacy, but if developed and manufactured with consistent QbD principles in mind, they can play a critical role in ensuring a drug product's integrity and efficacy.

Additionally, the use of high-quality components, such as NovaPure plungers, in prefillable syringe systems can help facilitate efficient manufacturing processes and support a reliable supply of drug products. The knowledge gained throughout the QbD process can be used on an ongoing basis to maintain continuous improvement by the manufacturer and meet demands for high quality, improved total cost, and increased safety and security for the drug product. The return on investment can be realised once a drug product is commercialised and has gained patient loyalty through ease of use, therapeutic benefit and high confidence in the delivery device.

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