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Dec	Connecting Drug Delivery
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Feb	Prefilled Syringes & Injection Devices
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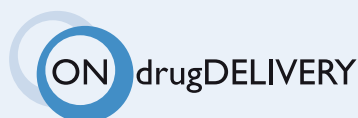
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Cover image, "LED UV curing of adhesive on glass syringe with stainless steel needle" from ATS Automation's article "LED-Generated UV for Adhesive Curing in Medical Devices" (see this issue, Page 40).
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SUCCESS FACTORS FOR THE YPSOMATE FAMILY OF AUTOINJECTORS

In this article, Orfeo Niedermann, Business Development Director at Ypsomed, looks at the key factors behind the growth and continued success of the YpsoMate family of two-step autoinjectors. He also introduces YpsoMate Design, which enables freeform outer shell design around the proven YpsoMate mechanism and manufacturing lines.

SIGNIFICANT DEMAND

With the large number of new biologics and biosimilar product launches, the demand for devices for the subcutaneous self-injection of biopharmaceuticals continues to grow and develop. Above all, the growing demand of autoinjectors for antibody-based therapies impresses the most.

Some of the autoinjectors are used to cover the increased overall demand for biosimilars of blockbuster biologics, but most are needed for new injectable drugs, such as liquid-stable, once-weekly glucagon like peptide-1 analogues (GLP-1s) treating diabetes, and for treating autoimmune diseases, such as rheumatoid arthritis, psoriasis and multiple sclerosis. There are also many innovative biologics in pharma pipelines for treating a range of conditions including more specific arthritis indications, psoriasis, IBD/Crohn's disease, dermatitis, asthma, migraine, orphan therapies, haemophilia and cancers.

After the launch of the first disposable autoinjectors in 2006, for the administration of therapeutic proteins, it was believed that 1 mL was the maximum injectable volume that could be tolerated by a patient within the typical 10 second injection time. Over the last five years, however, this myth has been dispelled and the demand for therapies based on standardised 2.25 mL prefillable syringes compatible with autoinjectors has grown significantly.

YPSOMATE – THE TWO-STEP AUTOINJECTOR

YpsoMate serves patients with an easy and convenient two-step automatic injection. The patient pulls off the cap to remove the needle shield from the prefilled syringe and then pushes the autoinjector onto the skin to trigger the injection. The operation does not involve any additional button-activated steps.



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“After the launch of the first disposable autoinjectors in 2006, for the administration of therapeutic proteins, it was believed that 1 mL was the maximum injectable volume that could be tolerated by a patient within the typical 10 second injection time. Over the last five years, however, this myth has been dispelled and the demand for therapies based on standardised 2.25 mL prefillable syringes compatible with autoinjectors has grown significantly.”

“For more viscous drugs, Ypsomed has developed the YpsoMate 2.25 Pro – which uses the same proven handling concept – and features a proprietary constant force drive system.”

YpsoMate signals the start as well as the completion of the injection through clearly audible clicks. In parallel, the patient can observe the injection progress in the large viewing window. The needle remains hidden at all times and is shielded after use to prevent needle stick injuries. All these features are built into a compact housing that fits nicely into the palm of the hand and, due to its unique square shape, the YpsoMate autoinjector does not roll off tables or other flat surfaces.

Low Risk, Short Time-to-Market

Ypsomed decouples the development of new platform products from the customer project and thereby moves the timeline and risks associated with platform development and installation of manufacturing infrastructure in-house.

Each customer-specific commercial variant is derived from an existing platform product based on proven technology. The custom product platform strategy continues to attract new customers and many established customers are running a number of projects at Ypsomed. Being able to work on multiple projects fosters a close working relationship, increases synergies and significantly reduces overall development timelines and project management activities for each programme.

Pharma partners continue to



Figure 1: The family of YpsoMate autoinjectors with the YpsoMate for 1 mL long syringes (left), YpsoMate 2.25 for 2.25ml syringes (centre) and YpsoMate 2.25 Pro (right) for elevated viscosities.

be attracted by the fast and low-risk supply of innovative injection systems manufactured on automated equipment in Switzerland and Ypsomed’s new manufacturing site in northern Germany.

YpsoMate Family of Autoinjectors

Based on the preferred two-step use concept, Ypsomed has developed and industrialised a family of YpsoMate autoinjectors (see Figure 1) to support different drug needs. The YpsoMate 2.25 holds a 2.25 mL syringe and offers injection volumes up to 2 mL. For more viscous drugs, Ypsomed has developed the YpsoMate 2.25 Pro – which uses the same proven handling concept – and features a proprietary constant force drive system.

Reliability and Differentiation

A self-injection device should provide product differentiation through improved human factors and increased safety compared with vial-syringe and prefilled syringe product presentations. Moreover, pharma companies strive to differentiate their own self-injection device from devices used by

“Ypsomed has invested in automated manufacturing capacity for YpsoMate and YpsoMate 2.25. This allows customers to access and source the device at a fraction of the overall upfront cost compared with investing in bespoke manufacturing infrastructure.”

competitors. Meeting these objectives can be challenging for pharma companies and device manufacturers.

A modern and safe self-injection device needs to be customised to fit the primary needs of the patient, the formulation characteristics such as drug volume and viscosity, the needle insertion depth and injection time as required for certain therapies. YpsoMate is compatible with all major 1 mL long and 2.25 mL syringes made of glass or copolymer and can be customised within defined specification ranges for all relevant parameters and to new colours and shapes within defined design limits.

If specific patient groups or demand for differentiation in a specific market calls for a completely new outer shape Ypsomed offers YpsoMate Design (Figure 2).

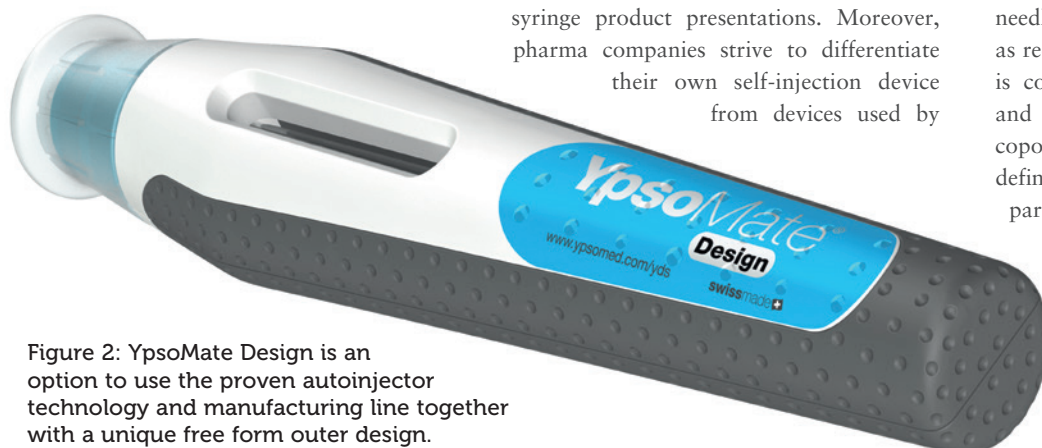


Figure 2: YpsoMate Design is an option to use the proven autoinjector technology and manufacturing line together with a unique free form outer design.

The mechanism relies on the proven YpsoMate technology, and external design shells allow more design freedom to generate a unique and ergonomically optimised shape. In addition to the possibility of designing free-form surfaces, it is also possible to use different surface materials to improve grip and to emphasise how to hold and use the device.

AUTOMATED MANUFACTURING AT MULTIPLE FACILITIES

Consistent High Quality & Efficient Scale-Up

To keep timelines short and project upfront investment low, Ypsomed has invested in automated manufacturing capacity for YpsoMate and YpsoMate 2.25 (Figure 3). This allows customers to access and source the device at a fraction of the overall upfront cost compared with investing in bespoke manufacturing infrastructure. Furthermore, Ypsomed’s manufacturing infrastructure allows customers to increase their reserved capacity incrementally after launch when they have better control of the drug / device forecast.

Ypsomed increases the manufacturing capacity for YpsoMate autoinjectors continuously ahead of market demand based on customer forecasts. Today, Ypsomed has three automated lines installed and qualified that assemble the YpsoMate and YpsoMate 2.25 devices, with additional lines on order. With multiple lines situated in Switzerland and Germany, Ypsomed provides risk mitigation measures for its customers.



Figure 3: Fully automated assembly with validated process and IPC for YpsoMate and YpsoMate 2.25 (YpsoMate 2.25 pictured).

Flexibility & Support for Final Assembly

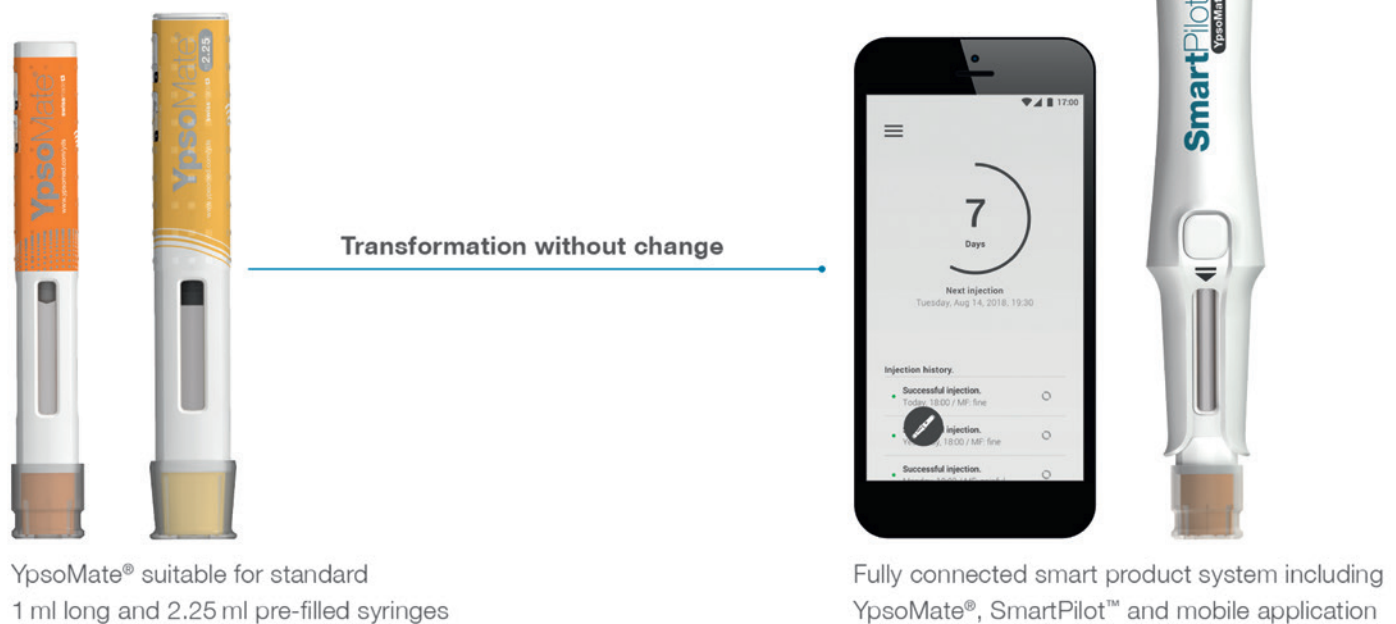
For the drug and device end-assembly process, Ypsomed supports its pharma customers in selecting the best possible setup for their production and supply chain strategy. For pharma companies that want to assemble in-house, Ypsomed recommends a select number of renowned assembly equipment manufacturers that offer existing YpsoMate machine concepts for manual, semi-automatic and fully automated end-assembly covering different capacity needs.

Alternatively, the key global filling and packaging contract manufacturing organisations have installed equipment to assemble the YpsoMate autoinjector family. These end-assembly options provide customers with the freedom to implement

the best final assembly set-up including backups and capacity increase options.

UPGRADE OPTION ADDS CONNECTIVITY

Connected drug delivery systems will become instrumental in improving medication adherence and supporting the effective self-management of chronic diseases. SmartPilot for YpsoMate (Figure 4) is a reusable connected add-on module with built-in sensor technology and wireless communication capabilities for the YpsoMate two-step autoinjector.



YpsoMate® suitable for standard 1 ml long and 2.25 ml pre-filled syringes

Fully connected smart product system including YpsoMate®, SmartPilot™ and mobile application

Figure 4: SmartPilot for YpsoMate is a reusable smart add-on that flexibly transforms YpsoMate into a fully connected system with advanced sensor capabilities to track device usage and guide patients.

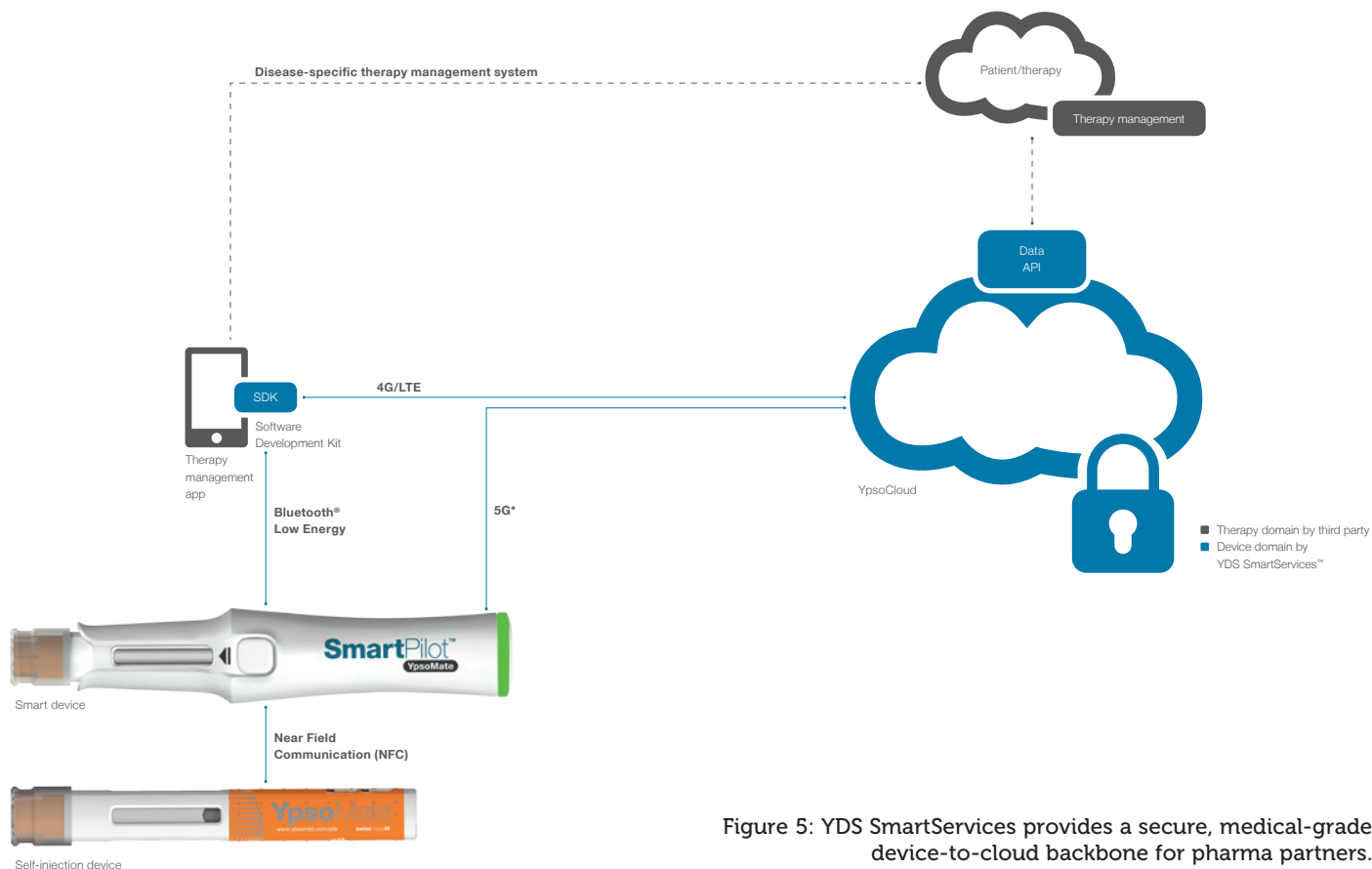


Figure 5: YDS SmartServices provides a secure, medical-grade device-to-cloud backbone for pharma partners.

“With SmartPilot and YDS SmartServices, Ypsomed has built a device and full device management solution that allows pharma customers to develop therapies and services rapidly that address non-adherence in clinical trials and commercially.”

With the help of the SmartPilot monitoring device, Ypsomed transforms every existing standard shape Ypsomate platform variant into a fully connected smart product system. SmartPilot comes with two sets of functionalities. One monitors device usage and makes available the therapy-

relevant injection data to providers, caregivers and healthcare stakeholders using Bluetooth connectivity. The other guides patients step-by-step through the self-injection process including, for example, authentication of the self-injection device, or advice on the following use step.



Figure 6: Ypsomed's newest manufacturing site in northern Germany meets future demand and provides risk mitigation for Ypsomate and other Ypsomed platform products.

The adoption of connected devices requires the implementation of scalable device-to-cloud communication before building a therapy solution. Ypsomed offers YDS SmartServices (Figure 5) that reflect a medical-grade device-to-cloud IoT backbone. This device management solution securely and seamlessly provides relevant injection data to therapy solution providers, CROs, and other third-parties.

With SmartPilot and YDS SmartServices, Ypsomed has built a device and a full device management solution that allows pharma customers to develop therapies and services rapidly that address non-adherence in clinical trials and commercially.

OUTLOOK

Ypsomate has been approved in combination with five drugs to date, including Mylan's biosimilar Huloio® (adalimumab), Teva's Copaxone® (glatiramer acetate) and Amag's Vyleesi® (bremelanotide). A number of further launches are imminent, including the first Ypsomate 2.25 customised devices.

The capacity growth for Ypsomate autoinjectors is supported by the new Ypsomed manufacturing facility in Germany (Figure 6), which came on stream in Q3 2019.

Originator drug molecules dominate the

YpsoMate customer portfolio reinforcing the technology's competitive edge for patients and pharma customers alike. The Ypsomed platform portfolio continues to grow as we move into the second decade of the custom product journey, with the development of the new prefilled, connected, large-volume patch injector YpsoDose, in addition to the SmartPilot connected add-on for YpsoMate 1.0 mL and YpsoMate 2.25 devices.

Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant injection data and processing them to facilitate the self-management of chronic diseases.

ABOUT THE COMPANY

Ypsomed is an independent developer and manufacturer of both innovative mechanical and connected autoinjector and pen injector systems for self-administration. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable

pens, ready-to-use prefilled wearable bolus injectors, and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems portfolio.

As a pioneer with more than 35 years of experience and IP from the development and manufacturing of innovative injection and infusion systems, Ypsomed is developing a range of smart devices and services, supported by unique in-house capabilities in electronics, software and connectivity.

Its platform products and services are developed and made in Switzerland and

Germany with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control guidelines and cGMP, with operational QA/QC experts on-site at each location.

Ypsomed's manufacturing facilities are US FDA registered, regularly inspected by both pharma customers and regulatory agencies and supply devices for global markets including US, Europe, Japan, China and India.

ABOUT THE AUTHOR

Orfeo Niedermann is Business Development Director with Ypsomed Delivery Systems. His responsibilities at Ypsomed include business development activities in the US, Europe, Japan and China as well as product strategy for Ypsomed's range of YpsoMate autoinjector devices. He has spoken at numerous international conferences and authored or co-authored a number of articles. Mr Niedermann studied mechanical engineering at the Swiss Federal Institute of Technology in Zurich, Switzerland (MSc, ETH) and management in Bern (MBA, BFH). Before joining Ypsomed in 2005 he held various positions, from engineering, project management and sales to R&D management, in the packaging machinery industry.

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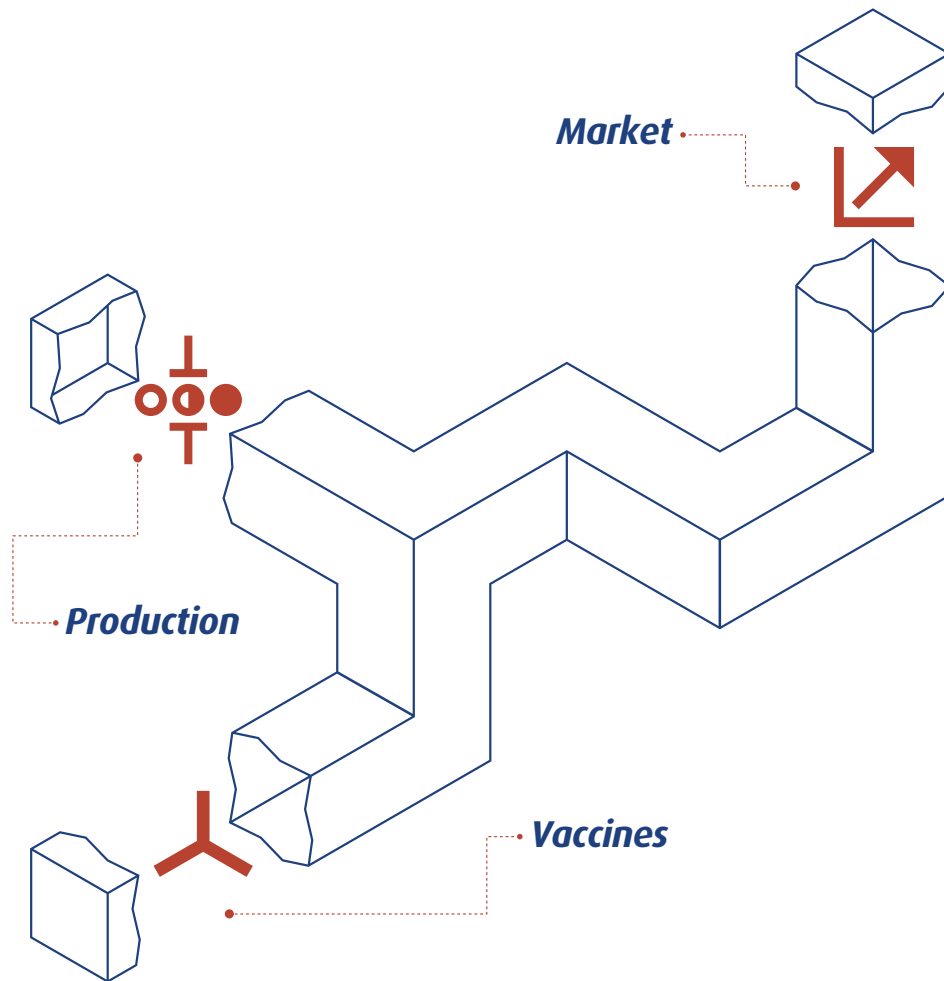
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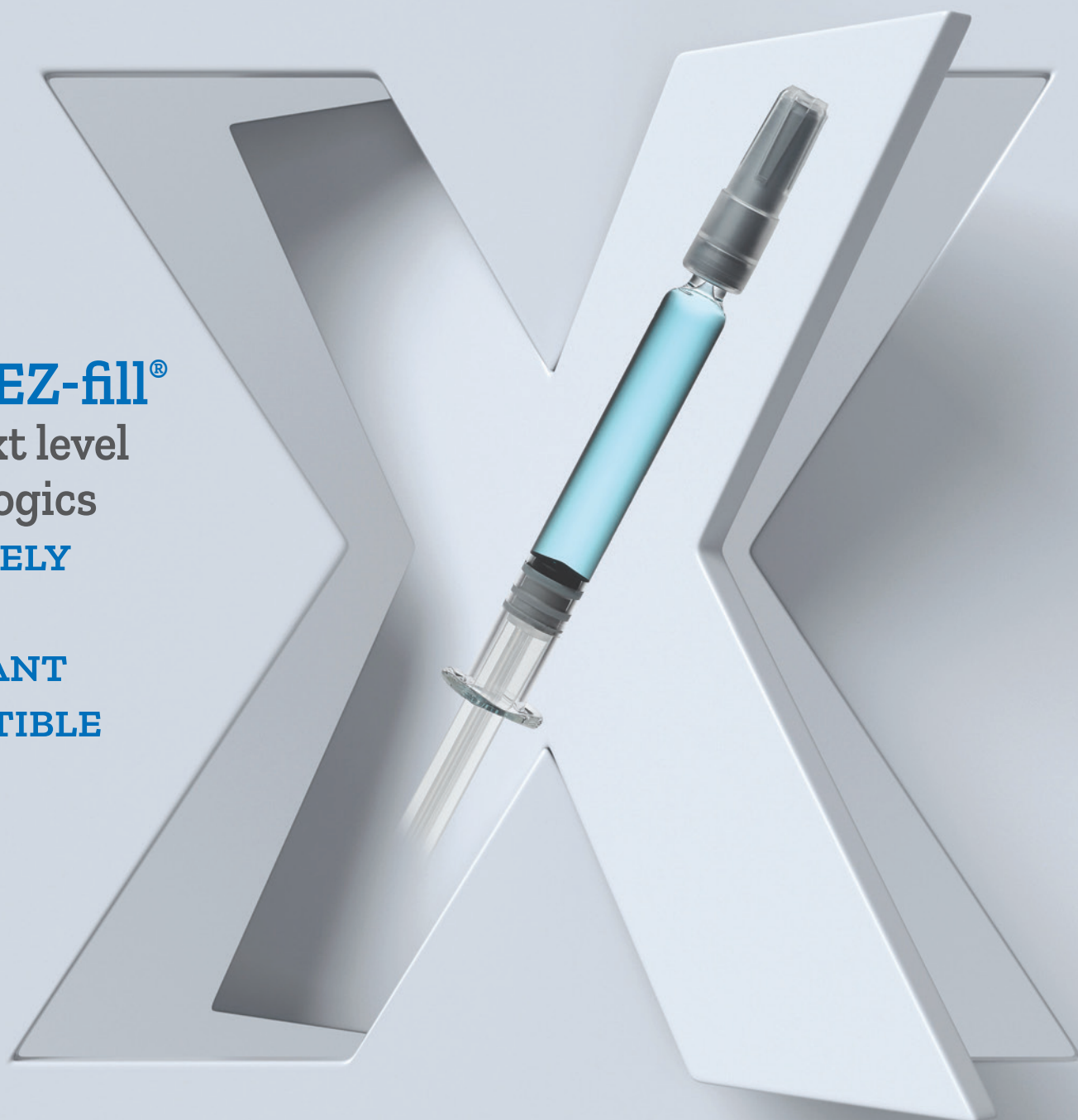
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THE INTERFACE BETWEEN PREFILLED SYRINGE AND AUTOINJECTOR – A DEVELOPMENT FRAMEWORK

In this article, Jeffrey Philippon, PhD, Drug Delivery Test and Evaluation Specialist, and Tom Kemp, PhD, Drug Delivery Design and Optimisation Specialist, both of PA Consulting, outline the challenges for autoinjector developers at the interface between the device and the prefilled syringe – and describe a framework to formalise analysis of the interface.

The prefilled syringe (PFS) has widely published benefits over the traditional syringe and vial,¹ leading to an increasing share of the drug delivery market in recent years.² The addition of an autoinjector to deliver a PFS can enhance safety and the patient experience,³ opening up new opportunities for home- and self-administration.⁴

The typical starting point for development of an autoinjector solution, whether a novel development or application of a market-ready device, is an existing PFS used in clinical trials – but this leaves little opportunity for syringe selection or modification. Many of the technical challenges facing device developers stem from dysfunction at the interface between the device and the primary container and nowhere is this more evident than at the interface between PFS and autoinjector: formed glass barrel meets precision-moulded parts, stopper glide force meets dynamic device spring-load, and syringe robustness meets plunger impact load.

This article outlines the key features of the interface between device and syringe, addressing the functional dependencies and the challenges that can arise. A framework is then described to formalise the analysis of these features through the introduction of an interface specification that brings together overlapping requirements of the two subsystems to ensure compatibility and drive the development of test methods that directly address critical interdependencies.

“Formed glass barrel meets precision-moulded parts, stopper glide force meets dynamic device spring-load, and syringe robustness meets plunger impact load.”

Finally, we extend the interface concept beyond purely functional considerations to include organisational challenges – dysfunction at the interfaces within and between organisations involved in selection and development of autoinjectors can mirror challenges within the device. The benefits of getting it right are far-reaching and include rapid and effective evaluation of new PFS-autoinjector pairings, improved device performance and reliability, and accelerated development timelines.

CRITICAL DIMENSIONS AT THE GEOMETRIC INTERFACE

The most obvious point of contact at the interface is the axial mounting of the PFS within the device. Early autoinjectors mounted the PFS at the flange, which has the natural perpendicular geometry to resolve the axial load during syringe emptying. Unfortunately, the geometry that makes it so apparently suitable for mounting also makes it a key weak point that is vulnerable to fracture under load. Unacceptably high rates of breakage on firing were attributed to stresses on the

“The choice of mounting location and geometry defines many aspects of the final assembled device, including critical requirements such as injection depth.”



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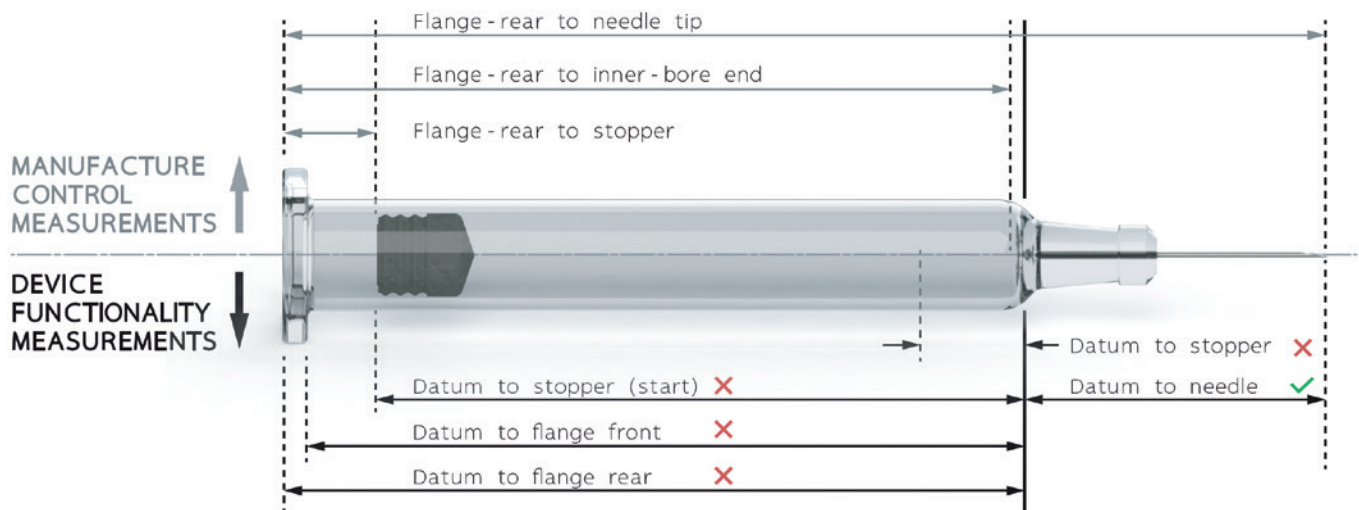


Figure 1: Diagram showing dimensions for manufacturing control and those critical to device functionality. A red cross indicates dimension typically not provided; a green tick indicates dimension typically provided. The details can vary from one manufacturer to another. The datum is the point on the syringe shoulder in contact with the device.

flange, leading to recalls in extreme cases.⁵ Something had to change.

Most autoinjectors currently on the market mount the PFS at the shoulder, where the needle meets the glass body, which is the only other suitable surface. This change was adopted to reduce stress on the flange.⁶ However, the impacts of that decision went far beyond the initial drivers that motivated it.

The choice of mounting location and geometry defines many aspects of the final assembled device, including critical requirements such as injection depth. The syringe shoulder is created by forming semi-molten glass over a tungsten pin, in a process that inevitably results in a variable geometry, although this can be

“In the new world of biologics, with higher spring loads required to accommodate increased volumes and viscosities, we as an industry must remain vigilant.”

mitigated by post-forming inspection. To make matters worse, although all manufacturers comply with the ISO-specified dimensions, varying processes can still result in different nominal geometries.

Needle placement during manufacture and stoppering during fill and finish are usually referenced to the flange, resulting in unpredictable offsets that appear as variability in critical dimensions such

as the shoulder-to-needle-tip distance. Figure 1 shows the critical measurements from the points of view of manufacturing and device functionality.

The story of in-use syringe breakages may have further twists in store. In the new world of biologics, with higher spring loads required to accommodate increased volumes and viscosities, we as an industry must remain vigilant and ensure the limits to syringe robustness are well understood.

FORCE BALANCE AT THE INTERFACE

In addition to the geometric interface, the balance of forces between PFS and autoinjector is also critical to device performance (Figure 2). The spring rate and precompression must be sufficient to overcome the stopper break-loose force to initiate syringe emptying, exceed the glide force to prevent stalling and achieve the required injection time. At the upper limit, spring load is limited by available space and the maximum impact force to avoid damage to the syringe and material creep in moulded parts. Although long springs with a low spring rate can seem like an ideal solution, with almost constant spring load, equilibrium spring length is limited by the challenge posed by compressing very long springs as part of an automated assembly process.

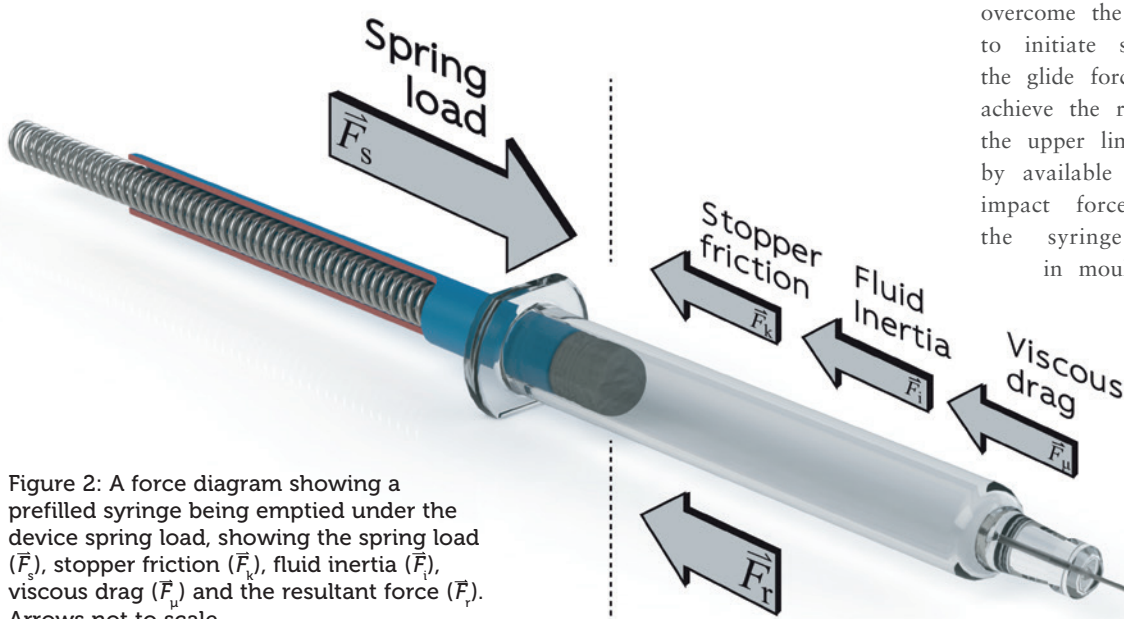


Figure 2: A force diagram showing a prefilled syringe being emptied under the device spring load, showing the spring load (\vec{F}_s), stopper friction (\vec{F}_k), fluid inertia (\vec{F}_i), viscous drag (\vec{F}_v) and the resultant force (\vec{F}_r). Arrows not to scale.

The standard force characteristics measured by manufacturers and users of PFSs in characterisation and quality control studies include the break-loose force and glide force at constant velocity. Glide force is generally reported as a mean value at a given velocity, whereas design for a specified injection time must take account of the dynamic force profile of the combined drive system and load. Consider that the spring load is constantly decreasing as the spring expands, while the stopper friction varies with both velocity and lubrication. Siliconisation reduces stopper friction but lubricant mobility during stopper travel can add further variability.⁷

A critical characteristic that can be extremely challenging to quantify is the threshold force for impact breakage. On release, the plunger accelerates towards the stopper under the applied spring load, generating a large transient force on impact. Designers attempt to minimise the initial gap between the plunger and stopper but the gap must be sufficient to avoid contact before firing, accounting for dimensional tolerances. Impact forces can be modelled or measured relatively easily but the corresponding threshold for syringe breakage is more of a challenge.

Simply replicating the conditions inside an autoinjector is not expected to yield observed breakages for any reasonable test sample size. A nonparametric tolerance limit can be placed on breakage rate based on observed incidence of non-breakages but demonstrating an acceptably low breakage rate would again require unrealistic sample sizes.

For example, demonstrating a breakage rate below one part-per-million with 95% confidence would require observation of 2,995,731 firings with no breakages. Alternatively, a parametric approach can be used, measuring the force at which breakage does occur by using much higher loads than those applied during device firing. In principle, the distribution of breakage forces can be compared with the measured device impact force distribution, with the overlap integral between the two representing the expected breakage rate and the difference between the tolerance limits on the two distributions representing a conservative safety margin.

There are limitations to this approach: a test apparatus that can reliably achieve syringe breakage cannot be fully representative of device spring load,

“A critical task when integrating a PFS with an autoinjector is a detailed characterisation of the primary container, matching up measured characteristics of the syringe with their counterparts in the device.”

materials or mechanical construction. The choices of spring rate and precompression influence the observed breakage force, necessitating a stepped approach with multiple impacts at increasing forces to produce a conservative estimate of the threshold breakage force. Statistical analysis of the results must be undertaken with care; breakage processes tend to be non-normal, with long high tails that can lead to misinterpretation of results.

Cap removal force is an important characteristic of autoinjectors and, for drugs indicated for acute conditions, can be an essential performance requirement. Although a modest additional friction component is added by the device, cap removal force is dominated by the force to remove the needle shield. Such high forces are required to accommodate the variable seating geometry, while maintaining container closure integrity. The standard claimed upper limit on needle shield removal force is 35 N, constraining the design window for cap removal force and leading to usability problems.³ Although most fall well below this limit, forces over 25 N are not uncommon, particularly at low temperature. Many syringe manufacturers are now filing IP for needle shield removal tools for manual administration^{8,9} and some device developers are adding mechanisms to assist with cap removal.¹⁰

A FRAMEWORK FOR ADDRESSING OVERLAPPING REQUIREMENTS AT THE INTERFACE

A critical task when integrating a PFS with an autoinjector is a detailed characterisation of the primary container, matching up measured characteristics of the syringe with their counterparts in the device. A useful framework for this is the concept of an interface specification, with requirements defined in terms of functionality and referenced to both the design input requirements of the device and a specification for the PFS.

A clearly defined interface specification can be used to define a matched set of

characterisation tests to assess compatibility between autoinjector and PFS. The development of the specification and the associated tests is a crucial learning step that should be integral to the device development process. It further comes into its own when the inevitable question is asked: “Can the device deliver a different PFS?” Whether it is a new drug product, a new syringe or both, the interface specification provides a clear process and unambiguous answers to critical questions of compatibility.

In an ideal world, the syringe requirements would simply be taken from the manufacturer drawings and other specifications. However, life is rarely so simple. Dimensions specified by manufacturers relate to the manufacturing process rather than to optimal seating within an autoinjector, having been developed for manual administration. The mass-produced glass prefillable syringe has existed for 65 years¹¹ and is highly optimised as a low-cost, sterile, high-barrier primary container and drug delivery system, manufactured in enormous volumes.

THE INTERFACE WITHIN AND BETWEEN ORGANISATIONS

Beyond purely functional considerations, challenges extend to the organisational interface between primary container and medical device teams. Pharmaceutical companies have long had dedicated teams focused on evaluation and selection of primary containers, including syringes, which play critical roles protecting the drug product, maintaining sterility and achieving the required shelf-life. More recently, dedicated medical device teams have appeared, focused on evaluation and selection of devices such as autoinjectors.

The relatively recent appearance and generally low profile of medical device teams can lead to a disconnect between them and the wider organisation, with limited communication and a lack of joined-up decision making. This mirrors the siloed

mentality that has traditionally existed between the chemistry, manufacturing and control (CMC) and research and development (R&D) divisions.

Overcoming this divide has the potential to pay significant dividends through sharing of expertise, strategic decision making and early consideration of opportunities for drug delivery devices when selecting a primary container for clinical trials. Typically, primary container selection is locked down long before any consideration is given to medical device options and there is a natural reluctance to change the container selection when proceeding to device selection or development.

The concept of the organisational interface can be extended to address the interface between the business models of syringe manufacturers and pharma companies. Syringe procurement by pharma companies considers a wide range of characteristics but historically there has been no reason to include the external dimensions in this assessment – and the manufacturing process for production of glass syringes reflects this. Some manufacturers are willing to provide glass syringes with tighter dimensional tolerances through post-selection using automated vision systems but this approach has not been widely adopted due to increased costs. With rapid growth in the autoinjector market, optimisation through better alignment across the supply chain has the potential to benefit all parties.

For many reasons, syringe manufacturers have been slow to adopt polymer syringes: the excellent barrier properties of glass; sensible risk aversion, a “go with what you know” attitude; and some inevitable inertia. Japan is a notable exception, having fully transitioned to moulded polymer syringes, cartridges and vials, partly due to the risk of glass breakage during earthquakes.

Polymer syringes would certainly address concerns around dimensional tolerances and the Japanese example demonstrates the effective and scalable nature of this solution. Market shifts point to a steady increase in the use of polymer syringes and that is one way to address complexities at the interface with drug delivery devices.

CONCLUSION

Dysfunction at the interface between prefilled syringe and autoinjector? With a clear view of the critical inter-dependencies and a well-characterised syringe, it need not

come to that. We have a vision of prefilled syringe and autoinjector working together in harmony and, with good communication within and between partner organisations, we as an industry can make it happen.

ABOUT THE COMPANY

PA Consulting is an innovation and transformation consultancy with more than 2,800 specialists working in a number of key industries globally. It has over 40 years' experience in the design, development, characterisation and evaluation of drug delivery devices. PA has a dedicated parenteral drug delivery team, covering everything from prefilled syringes and reconstitution kits to autoinjectors, pen injectors and large-volume devices. Services include complete device development, device selection and customisation, device strategy, primary container characterisation, development of custom test equipment, human factors studies, design verification programmes and transfer to manufacturing.

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30 YEARS IN THE MAKING – AN INSIDE PERSPECTIVE ON THE EMERGENCE OF AUTOINJECTORS

This year, one of the pioneering companies behind the development of the autoinjector, SHL Group, is celebrating its 30th anniversary – a journey of rapid development that reflects the growing demand for advanced drug delivery systems in the healthcare market. In this article, Michael McGowan, Director of Market Intelligence at SHL Medical, gives a perspective on the emergence of the autoinjector as a key component of the drug delivery industry.

The prevalence of self-injection in the home setting has developed considerably in recent years and the advent of digitally enhanced, connected devices will certainly take the industry in new directions that were unimaginable until recently. However, looking back over the past 30 years, to the end of the 1980s, the prefilled syringe was still in its relative infancy and the first reusable insulin pen devices were only just emerging on to the market. As a primary drug container, the prefilled syringe was used principally to deliver calcium and sodium heparins as well as a broad range of vaccines. The global prefilled syringe market size was at that time under 200 million units per year and the dominant barrel sizes were 0.5 mL and 1 mL standard.

However, the advent of low-molecular-weight heparins around the late 1980s

and early 1990s resulted in a marked acceleration of the prefilled syringe market. This led to the introduction of what is now commonly referred to as the 1 mL long barrel dimension. Heparins still represent around 50% of the prefilled syringe market, which, according to IQVIA, now exceeds 2.2 billion units.

EARLY AUTOINJECTOR PROJECTS ACCELERATE THE LEARNING CURVE

It was also around this time that one of the world's leading pharmaceutical companies started to investigate the use of a prefilled syringe in conjunction with a self-injection device for a new anti-migraine drug that was in development. Because of the unpredictable nature of migraine attacks and the improved outcomes experienced after a rapid administration of the injectable form of the drug, it was recognised that self-administration would be advantageous for the migraine patient. However, it was also understood that the potentially debilitating effects of a migraine attack could significantly reduce a person's ability to think clearly and to follow a multi-step injection preparation procedure.

One of the early presentations of this anti-migraine drug consisted of

“It was already recognised back in the early 1990s that combining a prefilled syringe with a mechanical autoinjector would present a number of important challenges to ensure the safe and effective delivery of the drug.”



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a standalone prefilled syringe that had to be manually inserted into a reusable injector device. This relatively complex procedure was still less than ideal for users who were suffering from a migraine. Subsequent improvements during the early and mid-1990s saw the introduction of a new generation of self-injection devices that was much easier for patients to use.

It was already recognised back in the early 1990s that combining a prefilled syringe with a mechanical autoinjector would present a number of important challenges to ensure the safe and effective delivery of the drug. At the outset, a glass prefilled syringe was designed for manual use where the user could quite easily adapt their technique to manage natural variances in the characteristics of the prefilled syringe. Examples of these include the variable force required to remove the elastomer needle shield or the changing pressure required to fully depress the plunger rod to inject the drug. For a prefilled syringe to work properly with a mechanical autoinjector, syringe manufacturers would need to closely manage critical process parameters, such as the siliconisation of the barrel and the plunger stopper.

It was also clear that the syringe's dimensional tolerances, as well as the variance in the strength of the glass finger flange, would present further challenges for the use of the syringe in the autoinjector. The stress introduced into the glass barrel during the manufacturing process could lead to breakage when subjected to the high-force delivered by the mechanical spring of the autoinjector. Once again, it was vital to understand and manage the manufacturing process of the prefilled syringe in combination with the design of the autoinjector for the two to function well together. For example, the prefilled syringe used in the anti-migraine autoinjector project referred to earlier, was adapted to have a small, round and unclipped flange – the purpose of which was to generate less structural stress in the barrel and to distribute more evenly the force generated by the autoinjector spring. The small round flange syringe was developed but its introduction inadvertently introduced a new manufacturing challenge as the standard finger flange was used to transport the syringe during the production and processing steps.

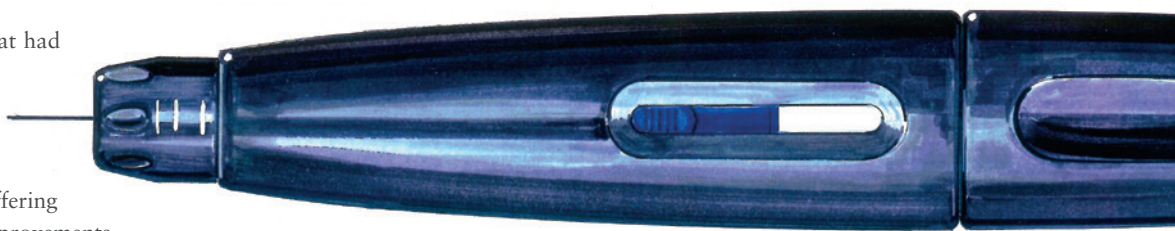


Figure 1: SHL's first injector product was launched with an ED drug in 1996.

“As a leader in the industry, SHL has been at the forefront of autoinjector development, supporting customers with solutions best suited to their requirements for either automatic or manual needle insertion.”

Thinking back on my experience as a business development manager with the prefilled syringe manufacturer at the time, I am convinced that the experience of working in collaboration with a leading pharmaceutical company on the anti-migraine autoinjector project helped them to improve considerably their understanding of their own products and manufacturing processes. To this day, the rigorous investigation of the dimensional and functional variances of the prefilled syringe remains an important part of any autoinjector development project. It is paramount to identify and understand the potential challenges these variations will have on autoinjector design. The prefilled syringe has progressed tremendously over the intervening two decades and many options, both glass and polymer, are now available to optimise the syringe and device combination.

INTEREST IN AUTOINJECTORS GROWS BUT COMMERCIAL SUCCESS REMAINS ELUSIVE

The interest of the pharmaceutical industry in the self-administration of drugs did not waver during the 1990s when a number of projects were started, but then abandoned, for a variety of reasons. Mainly, the technical challenge of producing a reliable device that could work in conjunction with the prefilled syringe was not easy to

achieve cost-effectively. Thus, the number of self-administration products on the market remained few.

However, in 1996, SHL's first commercialised self-injection device was launched on the market with a drug prescribed for erectile dysfunction (Figure 1). The strong customer-centric approach of the drug manufacturer combined with the entrepreneurial skills of SHL helped drive this high-profile project through to commercialisation. Working together with the pharma partner, the device was designed by SHL to be easy to use, non-medical in appearance, and less intimidating before and after use. The entire project was completed from start to finish in around nine months.

THE ERA OF BIOLOGICS – A WINDOW OF OPPORTUNITY FOR AUTOINJECTORS

Although many events contributed to the development of the autoinjector market, it was the advent of biologics at the end of the 1990s and throughout the 2000s that really accelerated the pharmaceutical industry's interest in self-injection systems. At the same time, awareness of injection safety as a result of the Occupational Safety and Health Administration (OSHA) guidelines was also increasing. The new generation of drugs coming to the market were approved for long-term treatment of chronic diseases, and self-injection devices integrating safety features from needlestick injury, would become an integral part of creating market differentiation.

Some of the first biologics that were introduced were targeting rheumatoid arthritis patients who suffered from quite specific dexterity difficulties. The discussions between the biopharmaceutical companies and the device suppliers were therefore initiated quite naturally at an early stage in the drug development process. The end user needs were relatively well defined, but the technical challenge of meeting these needs in a self-injection device built around a prefilled syringe remained significant. For example, the interaction of the biologic drug

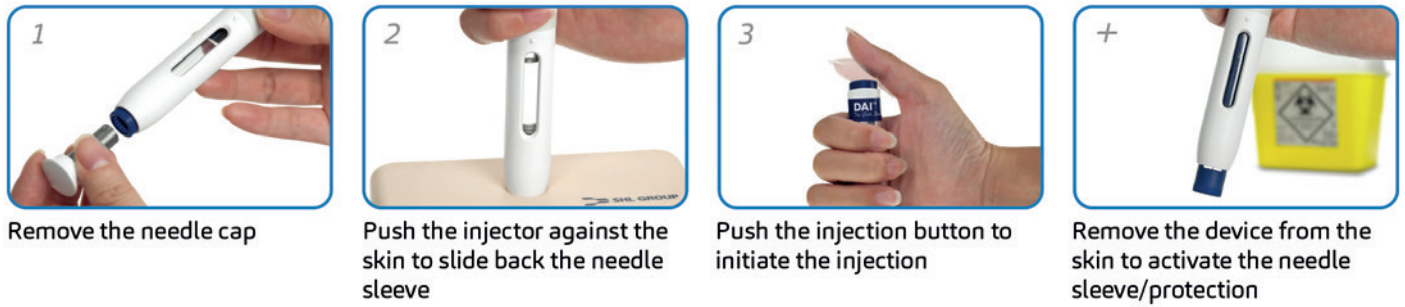


Figure 2: Injection sequence of a three-step autoinjector.

with the syringe materials and the silicone lubricants presented difficulties that have required prefilled syringe manufacturers to develop new product offerings to address the specific needs of biologic compounds.

THE EVOLUTION AND REFINEMENT OF THE AUTOINJECTOR

Biologics, on the whole, are available only in an injectable form and often command a relatively high selling price. It is important therefore that the self-injection device functions reliably so that users are able to use the device successfully without the supervision of a healthcare professional. The first autoinjector devices introduced to the market typically required three or four steps that were usually sequence-dependent (Figure 2).

As experience with autoinjectors grew and further insight was gained into the preferences of end users, their designs became simpler, with fewer steps to complete the injection. For example, SHL's DAI®, a three-step, button-activated autoinjector first introduced in 2006, has continued to evolve over the years to give rise to a number of different designs and new product families. More recent development projects have shifted to two-step solutions where the users simply uncap and inject to complete the administration of the drug.

DAI® is an example of automatic needle insertion where the needle is inserted into the skin by the force of the spring, while Molly® utilises a manual insertion method where the needle is pushed into the skin by the action of the user pushing down on the injector. There is still much discussion on the merits of automatic needle insertion versus a manual needle insertion and, in SHL's experience, both options remain valuable and are accepted by patients for different reasons, such as device size, sound,

insertion control and more. As a leader in the industry, SHL has been at the forefront of autoinjector development, supporting our customers with solutions best suited to their requirements for either automatic or manual needle insertion.

BIOLOGICS AND THE ERA OF BIOSIMILARS

Over the past 10-15 years, the number of approved and commercialised combination products in prefilled syringe-based autoinjectors has increased substantially. Over 30 drugs have been commercialised in SHL Group devices alone, reflecting the growth and dynamism of the market. The therapy areas in which autoinjectors are used have broadened over the period to include many auto-immune/inflammatory diseases and conditions such as multiple sclerosis, migraine, Type 2 diabetes,

anaemia and hypercholesterolaemia, to name a few.

Based on experience in developing and commercialising projects, SHL understands that each device project is unique and that, in many ways, each development is a bespoke collaboration between the device supplier and drug company. However, many elements of a project are quite common and a recent "Voice of Customer" survey conducted by SHL Group highlighted the interest from the pharmaceutical industry for platform products that can be customised to a given drug or customer need. This concept is not new. For example, SHL's preconfigured device technology, Molly®, has been successfully adapted and customised across a number of projects for a number of years already.

One of the drivers of interest in preconfigured products is certainly coming from the growth in the number of



Figure 3: With 30 years in the industry, SHL offers range of autoinjectors for prefilled syringes and cartridges.

“As digital healthcare becomes a reality, self-injection devices with integrated connectivity will become an important element of the digital ecosystem.”

biosimilars entering the market. As the first wave of biologics comes off patent, biosimilars are looking to gain market share based mainly on their cost-effectiveness. The biosimilars companies, therefore, need a device with a proven track-record of reliability, end user acceptance and a short but cost-effective development timeline. The need for customisation remains a relevant

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element of the development process, the extent of which will depend on the customers' needs, timelines and commercial strategy.

CONCLUSION

As medical research progresses and our understanding of some of today's major healthcare challenges increases, the development of complex biologics will continue. Likewise, novel delivery devices will be needed to deliver these compounds. The mechanical autoinjector market is likely to branch off into many different routes to accommodate the specific properties of compounds that will emerge from pharmaceutical research.

For a number of years already, there has been a trend towards less frequent injections – weekly, monthly or even quarterly injections will become the norm. Increasing drug viscosity and larger injection volumes may also result from current research, as formulation scientists find ways to get new compounds into an injectable format. Electromechanical autoinjectors, liquid/dry mixing autoinjectors, on-body injectors and

cartridge-based autoinjectors will all probably find their space and place in the market alongside the traditional, prefilled syringe-based mechanical devices (Figure 3).

As digital healthcare becomes a reality, self-injection devices with integrated connectivity will become an important element of the digital ecosystem. Evolving from simple Bluetooth-enabled devices that connect to self-management applications, the smart autoinjector of the future will be able to provide wide-ranging data to key stakeholders on the injection, handling errors, adherence, prescription renewal, reimbursement, clinical trial reporting, complaint management and more. The possibilities are endless and the implications are far-reaching.

The unique position of drug delivery devices within this future digital health ecosystem will certainly result in a new phase of growth for the industry. As SHL Group celebrates its 30th anniversary, the company is preparing for the next phase of its expansion through investment in state-of-the-art production facilities in Liufu, Taiwan, the establishment of a new global headquarters in Zug, Switzerland, and through its active partnerships in the digital healthcare sector.





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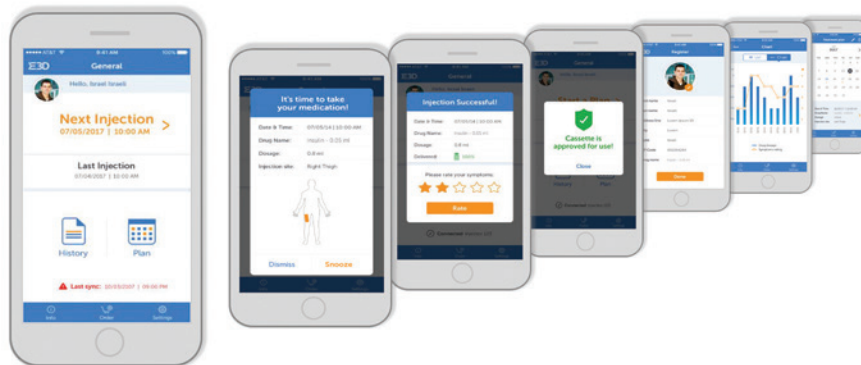
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FUNCTION-BASED PRIMARY PACKAGING DESIGN FOR INJECTING VISCOUS NON-NEWTONIAN FORMULATIONS

In this article, Marta Vilaplana, Senior Device Development Engineer; Alex Vasiev, PhD, Senior Device Development Engineer; and Susie White, Device Development Engineer; all of Oval Medical Technologies, explore the challenges of delivering high-viscosity, non-Newtonian fluids emphasising the importance of robust tools to characterise specific device and formulation parameters in light of increasing regulatory scrutiny.

Recent years have seen a rise in high-viscosity formulations within parenteral drug delivery. This change can be attributed to the increasing development of biologics – which offer greater specificity but tend to have high molecular weights – and the increasing popularity of long-acting injectables (LAIs).

Formulating LAIs involves creating a physical barrier around the active pharmaceutical ingredient which slows its release. This can be achieved by dissolving it in highly viscous, slow-absorbing oil or containing it within hydrogels or microcarriers – methods which often result in a product with unusual or challenging flow characteristics. The release of therapeutics at a controlled rate over a period of weeks or months benefits both patients and

“As the biologics and LAIs markets grow, there is greater scrutiny of the interaction between biologic/drug products and primary drug containers.”

“The release of therapeutics at a controlled rate over a period of weeks or months benefits both patients and healthcare providers.”

healthcare providers. LAIs reduce dosing frequency, which improves convenience for patients and reduces healthcare costs.

LAIs exhibit some or all the following characteristics that make them very difficult to deliver:

- High viscosity
- Drug in suspension
- Non-Newtonian behaviour (e.g. shear thinning)
- Propensity to clog due to large particulate sizes
- Propensity to settle during storage
- High sensitivity to environmental conditions
- Need for depot formation to control pharmacokinetics

Consequently, there are several factors that designers need to consider when



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designing an autoinjector and selecting a primary drug container for these formulations.

STANDARD PRIMARY PACKAGING AND AUTOINJECTOR DESIGN APPROACH

As the biologics and LAIs markets grow, there is greater scrutiny of the interaction between biologic/drug products and primary drug containers, including stability during shelf life and particulate burden, among other critical quality attributes.

The design of an autoinjector is also largely determined by the selection of the primary drug container – a decision which occurs early in the drug development process. Traditional primary packaging formats may not be ideal for the application and may put the future device at a relative disadvantage.

Considerations for Glass Containers

In previous years, recalls have increased due to quality issues in primary glass containers leading to breakage or delamination. As more attention is paid to the integration of primary drug containers with autoinjectors to form combination products, finding solutions to these problems has taken on an increased urgency – to protect patients and ensure the integrity and proper delivery of medication.

The US FDA rates the level of concern of a given primary pack, based on route of administration and drug type (Table 1). Packaging for injection is ranked as the highest concern category based on risks associated with route of administration and packaging-drug reactivity.¹ This gives more emphasis to the importance of the design considerations relating to primary drug containers. Additionally, its “Immunogenicity Assessment for Therapeutic Protein Products” called attention to issues commonly associated with container closure systems, including:

- Denaturation and aggregation of proteins at glass and air interfaces
- Delamination and particulate formation in certain formulations
- Protein aggregation associated with silicone-lubricated containers
- Leachables from container components.

Glass primary packaging is an ideal choice when the focus is a well-known regulatory pathway, well-defined stability

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions*	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral Powders	Oral Tablets and Oral (Hard and Soft Gelatine) Capsules

* For the Purpose of this table, the term suspension is used to mean a mixture of two immiscible phases (e.g. solid in liquid or liquid in liquid). As such it encompasses a wide variety of dosage forms such as creams, ointments, gels and emulsions, as well as suspensions in the pharmaceutical sense.

Table 1: Illustration of degree of concern regarding the route of administration with the likelihood of packaging component-dosage form interactions.²

“Traditional filling methods limit the needle and mechanism options available to the designer.”

characteristics and low cost. Two common glass primary drug containers are glass cartridges (e.g. lidocaine and insulin) and staked-needle prefilled syringes (e.g. heparin and adalimumab). However, glass is brittle, with its failure defined by the weakest link or most critical defect present on the surface.

Critical defects arising through abrasion during manufacture reduce the pressure resistance of a glass primary container and ultimately limit the pressures that a high-viscosity autoinjector can generate. This is especially true if a pressure spike occurs as the autoinjector impacts the container at the start of delivery. Specialised processes and coatings for glass containers are now offered by some producers, who claim a threefold improvement in breakage resistance.² However, these processes inevitably offset some of the low-cost advantage attributed to glass.

Traditional filling methods limit the needle and mechanism options available to the designer. Filling a highly viscous fluid into staked-needle syringes can introduce voids, which then foam and expand when

a vacuum is applied during stoppering. The bubble introduced during back filling also poses an issue for biologics, which tend to agglomerate at the gas-liquid interface. Tip filling, common to dental cartridges, virtually eliminates voids and bubbles but is limited by the accuracy of the filling equipment and the design of the primary drug container.

Glass Interaction with the Autoinjector

Both glass cartridges and syringes have limited features for accurate location within an autoinjector. Glass syringes are generally held by their shoulder or a flange formed at the back of the container, the shapes of which are not well defined due to the limitations of the glass-forming process. In an autoinjector, this leads to tolerancing issues and high variability of inserted needle depth. These can also introduce stress concentrations that weaken the component. Glass cartridges typically rely on their neck for axial position. This applies load to a point where residual stresses from manufacturing operations can increase the risk of failure.



Figure 1: Oval’s COC primary drug container technology optimised for high-pressure, high-viscosity delivery.

A NEW APPROACH TO DRUG PRIMARY PACKAGING AND AUTOINJECTOR DESIGN

An Alternative to Glass

Oval Medical Technologies has developed a cyclic-olefin copolymer (COC) primary drug container for high-viscosity drugs (Figure 1), which resolves many of the aforementioned issues with glass primary packaging and autoinjector design. This primary drug container can tolerate significantly higher pressure and, unlike glass, it does not experience catastrophic failure. It also incorporates robust positioning and bubble-reducing features, offering flexibility for tip or back fill. Table 2 compares Oval’s high-pressure COC primary container with typical glass primary packaging commonly used in autoinjectors.

Several technologies are now available to modify the drug contact material where COC is not appropriate, including vapour deposition of glass-like coatings.^{3,4}

Function-Based Approach to Primary Drug Container Design

Oval’s primary drug container designs are the result of years of development, and a thorough understanding of all the functions, considerations and requirements that the primary drug container

“Developing robust tools and methods to characterise specific parameters that are the focus of regulatory concern is key.”

must incorporate to safely store and deliver drug products with potentially challenging characteristics.

We characterise the requirements shown in Figure 2 in the context of the drug product properties and user needs. This process involves multiple tools and resources, some of which are well known within the industry (mathematical modelling), whilst others have been fully developed by Oval (Injection Characterisation System). Using these tools to investigate variables in the context of specific primary drug container functions allows them to be translated into tangible design features, such as the geometry and materials.

This article provides context to the choice of tools used at Oval to characterise the myriad variables that play a role in understanding formulation delivery (Table 3).

	Oval High Pressure COC Primary Drug Container	Glass cartridge	Prefilled glass syringe
Locating features for handling and positioning in device	Custom locating features and tight tolerances	Shoulder or neck of the vial, crimp	Flange of the syringe
Fill options	Customisable Tip or Back fill (with low bubble volume)	Tip or Back fill	Back fill
Lubrication	None required	Baked on silicone and stopper lubrication (various)	Spray-on silicone lubrication and stopper lubrication (various)
Needle	Dry needle	Dry needle	Staked needle
Oxygen permeation resistance ⁵	Poor (Excellent with co-injected barrier layer)	Excellent	Excellent
Vapour permeation resistance	Good ⁶ (Excellent with co-injected barrier layer)	Excellent ⁵	Excellent ⁵
Maximum operational pressure limit	100-150 bar	~20-60 bar ⁷	<75 bar ⁸
Impact resistance ⁵	Excellent	Poor ⁵	Poor ⁵
Failure mode	Plastic deformation	Brittle fracture	Brittle fracture

Table 2: A comparison of Oval’s high-pressure COC primary drug container with typical glass primary packaging commonly used in autoinjectors.

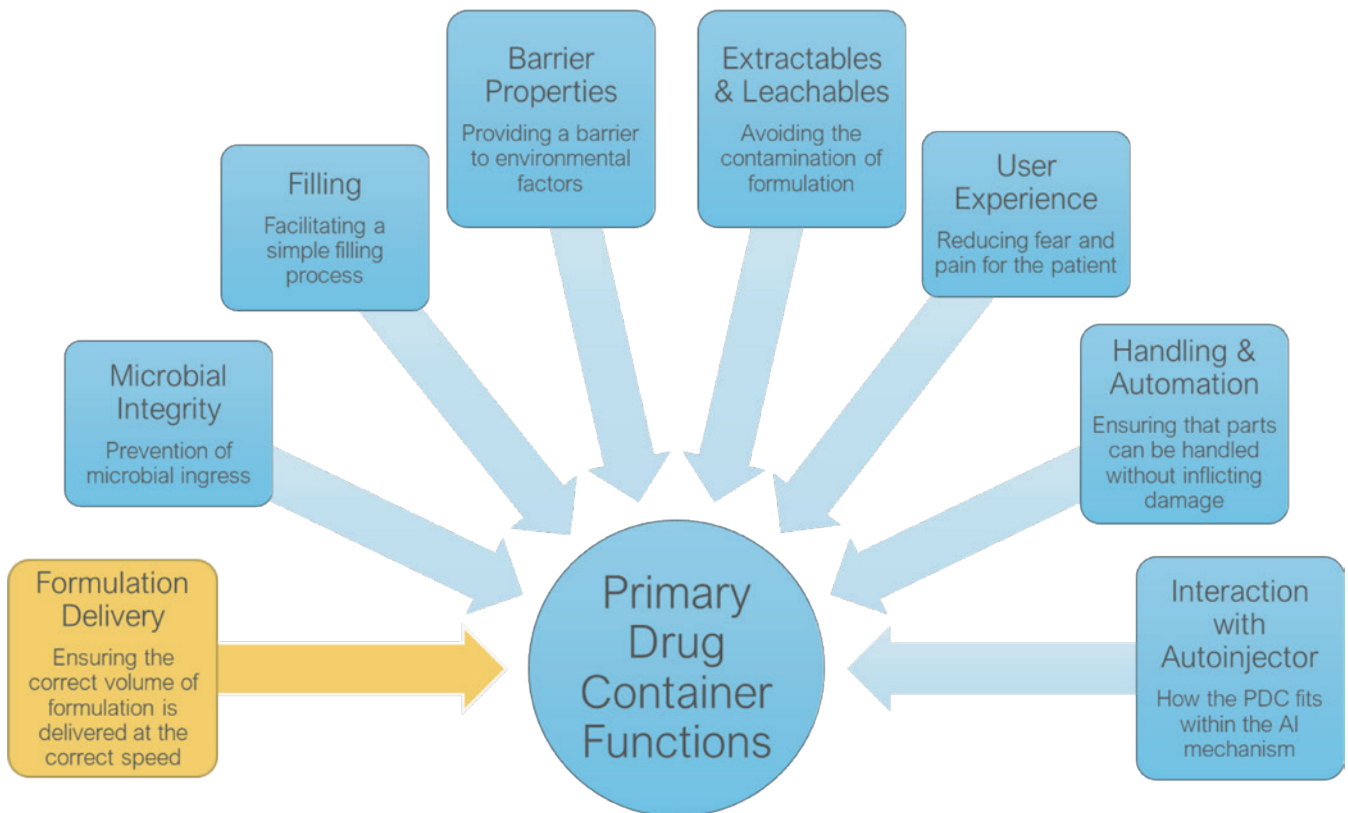


Figure 2: An illustration of key attributes that shape and define the specifications of each primary drug container function.

Primary Drug Container Function	Tools & Resources	Variables	Outputs
Formulation Delivery	<ul style="list-style-type: none"> Mathematical models Monte Carlo simulations Proprietary Injection Characterisation System (ICS) Rheology 	<ul style="list-style-type: none"> Delivery force Delivery speed Needle geometry Shear rate Temperature Volume Formulation viscosity Formulation 	<ul style="list-style-type: none"> Spring rate / geometry Optimum delivery force Safe system pressure Primary Drug Container material selection Optimum needle geometry Predicted/real delivery time & rate Formulation

Table 3: Oval’s approach to understanding formulation delivery involves the use of various tools to characterise variables and identify outputs that help define primary drug container design.

UNDERSTANDING FORMULATION DELIVERY

Understanding the physical characteristics of a drug formulation early in the product development process is of the utmost importance. It increases the likelihood of achieving the required specification and reduces the risk of unforeseen technical challenges later in development.

Formulation viscosity is often determined with a viscometer or rheometer – but these measurements have limitations. Care must be taken to ensure that the shear rate at which testing is performed is representative of that seen during injection. For spring-powered high-viscosity autoinjectors, this varies during the stroke and is likely to be between 2,000 and 100,000 s⁻¹. Whilst

certain rheometers can achieve these shear rates, they are outside the scope of much viscosity testing. Exposing these fluids to the environment can also lead to a loss of solvent and impact the measured value.

Formulations can behave differently within an autoinjector than might be predicted from rheometer data alone. Unforeseen difficulties in delivery may only become apparent when injecting with a needle and syringe (e.g. settling of a suspension).

Large particle sizes and aggregation can cause serious problems such as clogged needles or irregular flow. Separation of suspensions from a carrier fluid can cause non-homogenous delivery, variability in delivered dose and altered pharmacokinetic profile.

Describing Non-Newtonian Fluids

Many high-viscosity formulations exhibit shear-dependant behaviour defined by various models including power law, Carreau and others. Power law fluids, which are the focus of this article, demonstrate a time-independent log-log relationship between shear stress and viscosity described by:

$$\mu_{eff} = \mu_0 \left(-\frac{du}{dr} \right)^{n-1}$$

Where du/dr is the flow velocity gradient, μ_0 is the flow consistency index which describes the low-shear viscosity and n is the flow behaviour index. Unlike Newtonian fluids which form a parabolic flow profile in a needle (Figure 3), the flow profile of power law fluids is defined by the expression for flow velocity u at a given radial location r :

$$u(r) = \frac{n}{n+1} \left(\frac{dp}{dl} \frac{1}{2\mu_0} \right)^{1/n} \left(R^{\frac{n+1}{n}} - r^{\frac{n+1}{n}} \right)$$

Where R is the maximum internal radius and dp/dl is the pressure gradient along the length of the needle. This creates a unique volumetric flow rate Q at a given pressure (applied force F and container internal bore D):

$$Q = \frac{\pi d^3}{8 \left(\frac{1}{n} + 3 \right)} \left(\frac{Fd}{\pi D^2 l \mu_0} \right)^{\frac{1}{n}}$$

Where d is needle internal diameter, and l is the needle length.

Injection Characterisation System

Oval's proprietary Injection Characterisation System (ICS) overcomes issues associated with traditional rheological formulation characterisation by performing it *in situ*. The set-up of the ICS is like that of an autoinjector, with the addition of a range of instrumentation to provide feedback on the injection process.

It consists of a syringe attached to a needle via a pressure transducer to monitor internal pressure within the syringe. Behind the syringe is a plunger rod connected to a linear encoder, tracking the rate of delivery. This is powered by a spring which acts on a load cell to monitor the force needed for delivery. Combining the outputs of these sensors provides a huge range of information about the formulation.

Apparent formulation viscosity is determined for a wide range of tests (varying needle gauge and length, spring force, etc.) and environmental conditions. Changes in the formulation arising from recipe changes, processing and ageing can also be detected, giving an indication of the impact of batch-to-batch variation or comparing different candidate formulations for injectability.

Closely approximating the delivery system at an early development stage helps detect and mitigate unforeseen risks.

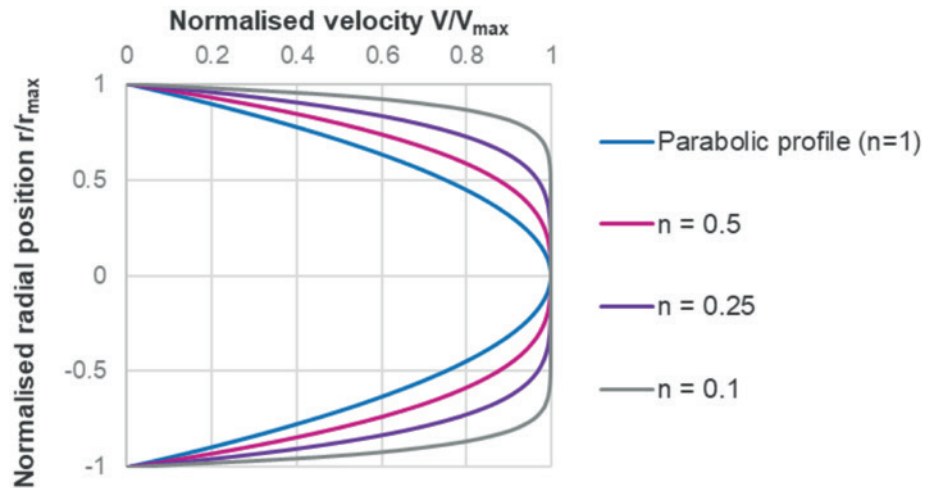


Figure 3: Illustration of a power law fluid velocity profile in a needle depending on the flow behaviour index n .

Using Drug Characterisation to Define Mathematical Models

The force of springs traditionally used in autoinjectors varies depending on the level of spring compression. The spring force at a certain spring length F is defined by:

$$F = F_0 - kx$$

Where F_0 is the initial force, k is the spring rate constant and x is the displacement of the spring in axial expansion. Substituting the spring force relation into the previously defined flow rate equation and integrating over the delivery stroke provides a relation for injection time:

$$\text{Injection Time (t)} = \frac{d^3}{Ck \left(1 - \frac{1}{n} \right)} \left[F_0^{1-\frac{1}{n}} - (F_0 - Lk)^{1-\frac{1}{n}} \right]$$

$$\text{Where, } C = \frac{d^3}{2D^2 \left(\frac{1}{n} + 3 \right)} \left(\frac{d}{\pi D^2 l \mu_0} \right)^{1/n}$$

Where L is the delivery stroke (mm).

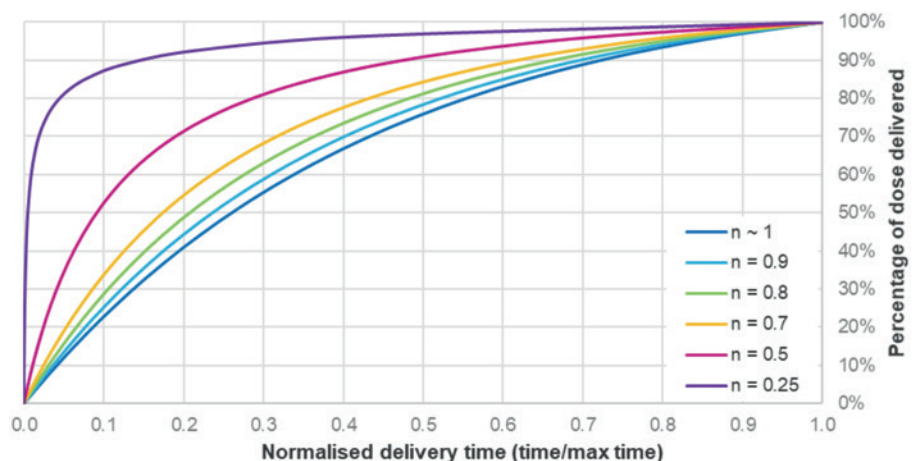


Figure 4: Illustration of power law constants' effect on delivery profile. Assumptions: $\mu_0 = 1000 \text{ mPa s}^n$, $D = 8.65 \text{ mm}$, $l = 20 \text{ mm}$, $d = 0.34 \text{ mm}$, $F_0 = 45 \text{ N}$, $k = 1.5 \text{ N/mm}$, $F_{\text{min}} = 5 \text{ N}$.

This allows injection time for a power law fluid to be calculated from the starting force and the delivery stroke (Figure 4).

Application to Monte Carlo Simulations

With injection time represented by a simple mathematical relation, a Monte Carlo simulation of delivery times can be performed (Figure 5). Each input variable is described by an appropriate statistical distribution generated from supplier specifications, predicted process capability or characterisation of device components. Through random sampling from the input variables, the simulation generates predicted delivery time for millions of simulated devices.

This process allows the impact of needle and spring combinations to be evaluated early in the development process. Verification of the model is done using physical testing of the formulation in the appropriate context (lab-based injection rigs or prototype devices). Power law formulations characterised in the ICS show a high degree of correlation

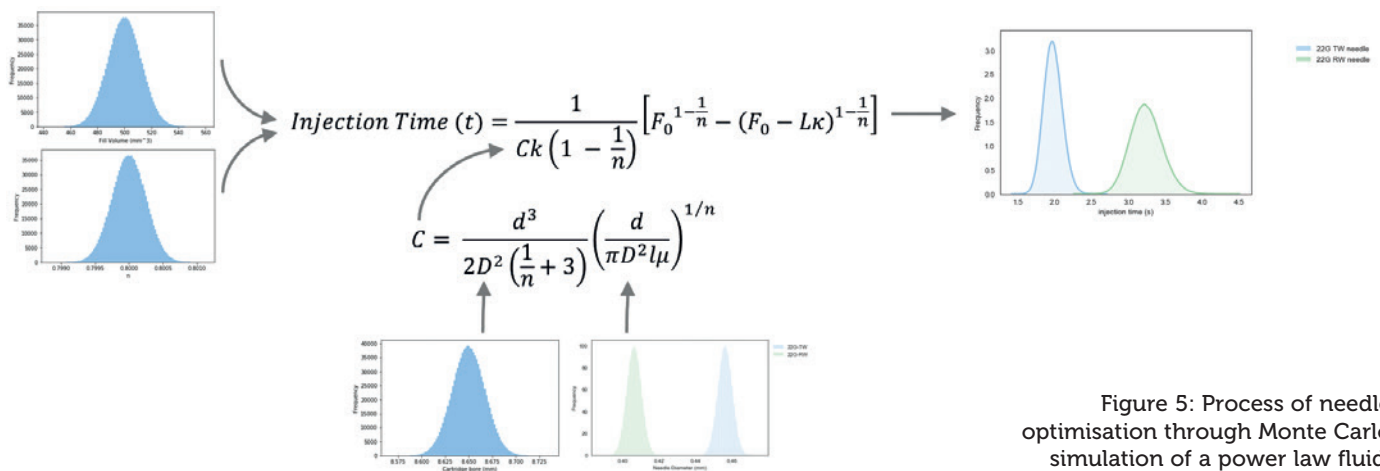


Figure 5: Process of needle optimisation through Monte Carlo simulation of a power law fluid.

between real and simulated deliveries. Due to confidentiality and the unique behaviour of the formulations, these results cannot be shown.

A ROUTE FORWARD

The increase in regulatory scrutiny on primary packaging requires a more proactive role on the part of pharmaceutical/biologic companies to address the various concerns and considerations associated with standard approaches. Developing robust tools and methods to characterise specific parameters that are the focus of regulatory concern is key.

Establishing partnerships with primary packaging manufacturers early in product development may help create unique solutions to the challenges of LAIs, biologics

and injectable drug packaging that are otherwise detected too late in the process.

ABOUT THE COMPANY

Oval Medical Technologies is a drug delivery company whose patient-centric autoinjector platforms enable pharmaceutical companies to deliver a wide range of drug formulations for both subcutaneous and intramuscular injection. Oval's flexible, robust drug delivery platforms can be tailored precisely, providing unprecedented scope for pharmaceutical companies to address the needs of current patient populations and develop and market new products. With its patented integrated primary drug

container technology at their core, Oval's devices are safe, reliable and easy to use in their target patient populations. The company is certified to ISO 13485 (2016).

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ABOUT THE AUTHORS

Marta Vilaplana is a Product Design Engineer with >10 years of experience within the medical device industry. Throughout her career, Ms Vilaplana has focused in the engineering of mechanical systems, integration of product and industrial design and the development of solutions for various delivery systems for the medical sector. She joined Oval's team in 2018. Ms Vilaplana graduated from the University of Barcelona (Spain) with a BEng(Hons) in Industrial & Product Design Engineering.

Alex Vasiev, is an engineer with extensive experience in medical device R&D who joined Oval as a Senior Device Design Engineer in 2019. His primary focus has been the interface of materials, microstructures and mechanisms with biological systems. Dr Vasiev has worked in the development of microcarriers, hydrogels, microfluidics and several high-viscosity autoinjectors. He graduated with an MEng in Mechanical Engineering with Aeronautics, and a PhD in Biomedical Engineering from the University of Glasgow (Scotland, UK).

Susanna White has worked as a Device Development Engineer at Oval Medical Technologies for the past seven years, where she is involved in the design and test programmes for the company's innovative polymeric primary drug container (PDC). Much of her work has focused on the study of highly viscous and non-Newtonian drug formulations, using numerical modelling techniques in combination with experimental investigation in order to achieve the most appropriate delivery system for challenging formulations. Ms White graduated from the University of Cambridge (UK) with a Master's Degree in Engineering for the Life Sciences.

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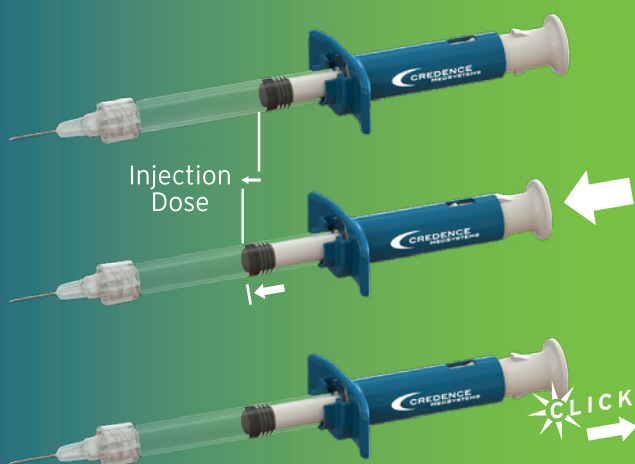
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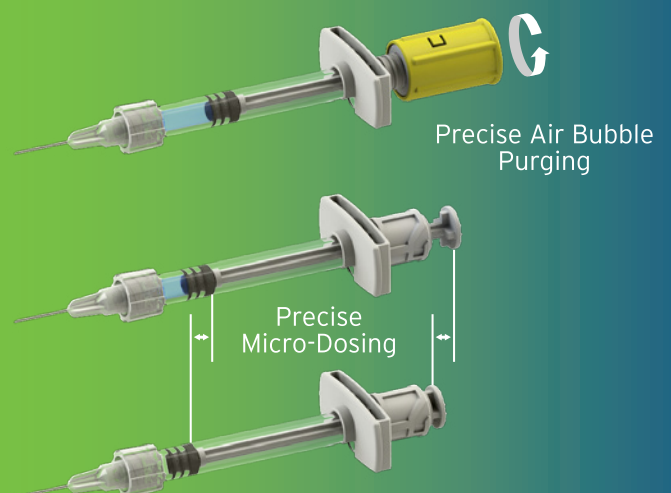
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8 MM NEEDLE – IMPROVING SUBCUTANEOUS CHRONIC DRUG DELIVERY

In this piece, Aurelie Pager, Clinical & Human Factors Program Leader, BD Medical – Pharmaceutical Systems, describes how reducing needle length can improve the risk profile of subcutaneous injections and can make injecting viscous formulations easier and quicker, and highlights BD’s development programme for an innovative shorter needle with ultra-thin walls for prefilled syringes.

CHRONIC DISEASE, UNMET MARKET NEEDS

Chronic diseases are on the rise worldwide^{1,2} and require regular administration of drug therapies to relieve the patients from their symptoms. Biologics, and more specifically monoclonal antibodies (mAbs), are becoming dominant in the biopharmaceutical pipeline thanks to their success in treating chronic conditions, and biologics are expected to account for ~50% of top-100 drug sales by 2024.³ The parenteral route is commonly used, with >80% of chronic biologics delivered subcutaneously using prefilled syringes.^{4,5}

Great progress and efforts have been made in offering drug delivery systems for chronic diseases over the past decades. However, several market unmet needs persist⁶ and should be considered when developing new manual drug delivery solutions. They include the need to:

- reduce the injection/needle-related anxiety and pain perception
- reduce the risk of accidental intramuscular (IM) injection
- maintain acceptable injection force and time for high-volume and high-viscosity drugs.

To improve patient quality of life and potentially treatment adherence, reducing injection frequency can be one of the strategies adopted by pharma companies. A way to achieve this could be to increase drug dosage⁷⁻⁹ either by increasing the concentration of the drug and/or by delivering a larger volume. Both options may lead to specific challenges.

Increasing the concentration of a biologic solution consequently increases its viscosity. Viscous and large-volume solutions take more force and/or require more time to perform the injection, which can impact end-user (healthcare providers, caregivers and self-injecting patients) acceptability.

Needle innovations, including the use of a shorter 8 mm needle, offer drugs, to enable the delivery of larger, more viscous drugs, without compromising end-user experience.¹⁶

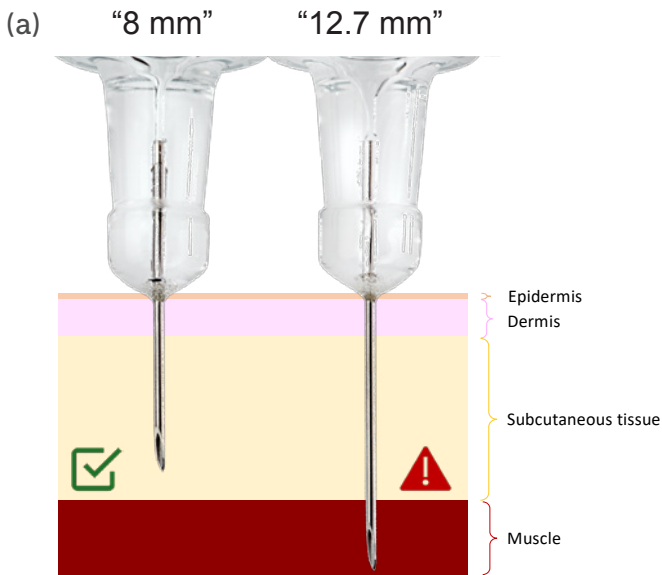
“Needle innovations, including the use of a shorter 8 mm needle, offer solutions to enable the delivery of larger, more viscous drugs, without compromising end-user experience.”



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Representation to scale based on average adult male thigh skin layers thicknesses.

Figure 1: (a) Short needle (8mm) reduces IM injection risk without increasing ID injection risk. (b) IM and ID injection risk percentages per needle length, age, needle insertion angle (no skin pinch) and injection sites. Risks were calculated with an internal mathematical model¹⁸ based on human skin layers thicknesses (388 adults and 49 children 7-13 years).¹⁰⁻¹¹

(b)

		Adults (>18y)				Legend: <5% 5-30% 30-70% >70%
		90° angle (no skin pinch)		45° angle (no skin pinch)		
Injection sites	Risk	12.7mm	8mm	12.7mm	8mm	
Thigh	IM risk	62.4%	25.3%	33.8%	8.3%	
	ID risk	0.0%	0.0%	0.0%	0.0%	
Abdomen	IM risk	37.1%	8.4%	13.2%	1.6%	
	ID risk	0.0%	0.0%	0.0%	0.0%	
Arm	IM risk	54.8%	17.2%	24.8%	4.2%	
	ID risk	0.0%	0.0%	0.0%	0.0%	
Buttock	IM risk	26.0%	4.2%	7.2%	0.6%	
	ID risk	0.0%	0.0%	0.0%	0.0%	

		Children (7-13y)			
		90° angle (no skin pinch)		45° angle (no skin pinch)	
Injection sites	Risk	12.7mm	8mm	12.7mm	8mm
Thigh	IM risk	96.1%	63.8%	75.9%	24.7%
	ID risk	0.0%	0.0%	0.0%	0.0%
Abdomen	IM risk	91.7%	59.2%	70.0%	26.8%
	ID risk	0.0%	0.0%	0.0%	0.0%
Arm	IM risk	99.6%	86.3%	93.1%	48.3%
	ID risk	0.0%	0.0%	0.0%	0.0%
Buttock	IM risk	89.4%	47.8%	60.5%	15.5%
	ID risk	0.0%	0.0%	0.0%	0.0%

IM RISK, INJECTION-RELATED ANXIETY & PAIN PERCEPTION

Standard needles for chronic disease treatment and parenteral administration are historically 12.7 mm (half an inch) long. Regarding the thickness of the different skin layers¹⁰, a 12.7 mm needle may reach the IM layer during a subcutaneous (SC) injection. This risk is increased in the absence of skin pinch (usually recommended with this needle length) or when done incorrectly and especially for populations with thin SC fat, such as people with low body mass index (BMI), children, and those with certain diseases.

Reducing the needle length to 8 mm would reduce the risk of accidental IM injection in most cases (Figure 1a) without increasing the risk of accidental intradermal

(ID) injection (which may lead to unwanted immune responses¹²).

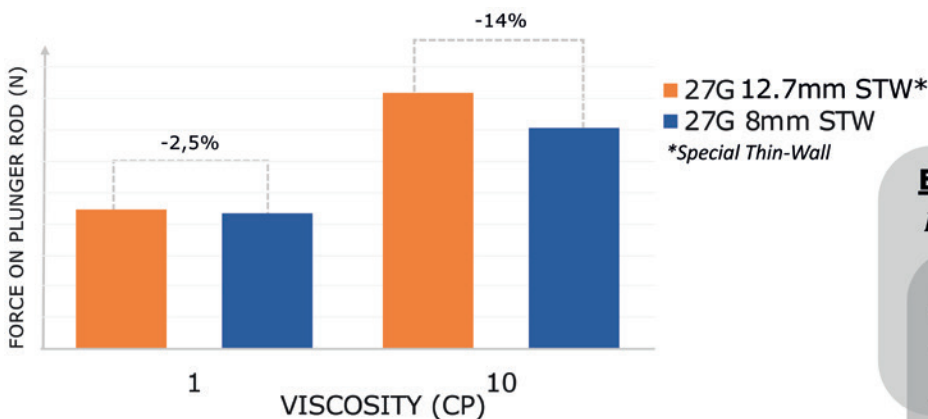
One therapeutic area that uses short needles for SC administration is endocrinology, mainly in the treatment of diabetes. Optimising insulin administration for patients while minimising the risk of IM administration, which can have severe health consequences, has been a key driver for new delivery solutions. Shorter needles are now commonly used by diabetics and enable efficient delivery of insulin into the SC space as recommended by the Forum for Injection Technique and Therapy: Expert Recommendations (FITTER).¹³

Concentrated biologics such as mAbs and other common therapeutics for other chronic conditions have their own pharmacokinetics/pharmacodynamics and physiological interactions, meaning the

consequences of IM and ID injections should be carefully evaluated on a case-by-case basis when selecting the most appropriate drug delivery system.

Adopting a shorter 8 mm needle length reduces the risk of IM injection without increasing the risk of ID injection in both adults and children^{10,11} (see Figure 1b). On average, when using 8 mm needles, the risk of IM injection without skin pinch and at a 90° angle was reduced by 72% in adults and 32% in children (aged 7-13 years). The risk of IM injection in the thigh or abdomen – commonly used self-injection sites – was reduced by 59% and 77%, respectively, in adult patients; and by 34% and 35%, respectively, in children.

In addition to the benefit of reducing IM injection risk, shorter needles have a direct impact on injection-related anxiety and pain perception in patients using pens



Injection forces simulated with a mathematical model for injections. The model relies on Bernoulli and Poiseuille equations for fluid and pressure drop simulation respectively (see upper grey frame on right). Values were obtained with assumptions relative to manual SC injection (see lower grey frame on right) for two different needle configurations and fluid viscosities.¹⁵

Figure 2: Injection force required to push on plunger rod is reduced with 8 mm needle.

Equation:

$$F_{ejection} = F_{gliding} + F_{fluid}$$

Hypothesis:

- Injection time: 15sec
- Injection volume: 2mL
- PFS format: 2.25mL

with exposed needles¹⁴. Moreover, needle length is one of the factors contributing to injection performance and flow.

INJECTION PERFORMANCE

When working with highly concentrated biologics, the viscosity and volume are key factors that directly impact several injection parameters such as the force and the duration of injection.

During manual injection, a higher drug viscosity would require a higher injection force to deliver the solution in the same amount of time. Mathematical simulations¹⁵ of injection forces were performed with both 12.7 mm and 8 mm needles, using different fluid viscosities at a given injection time of 15 seconds. The results showed that with low viscosity (1 cP), injection force remained essentially the same regardless of needle configuration. However, with higher viscosity (10 cP), the short 8 mm needle configuration led to a reduction of ~14% in injection force (Figure 2).

A human factors validation study investigated the impact of injection force reduction by measuring end-user acceptance of simulated injections performed with 12.7 mm and 8 mm

“40% of end-users found the injection force acceptable when using an 8 mm needle versus 15% when using a 12.7 mm needle.”

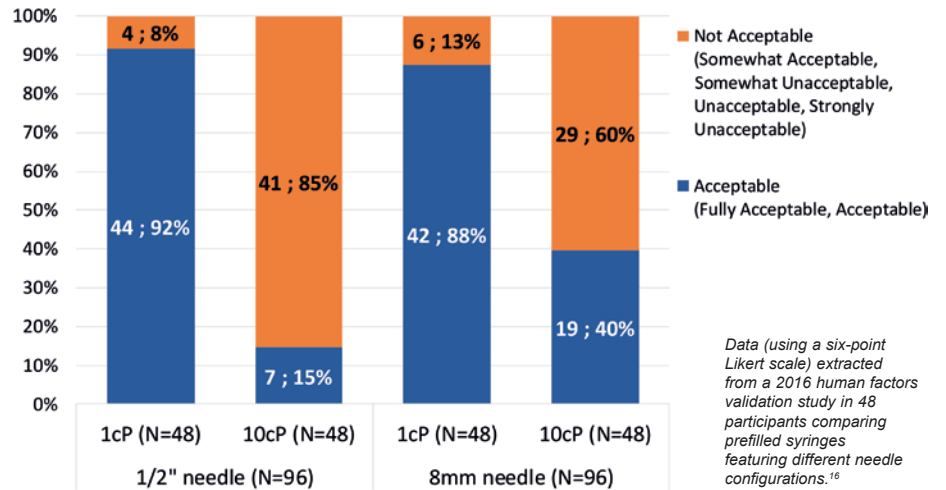


Figure 3: End-user injection force acceptance is enhanced with 8mm needle.

needles at different viscosities.¹⁶ Results showed that end-users positively felt the injection force reduction with the shorter 8 mm needle compared with the 12.7 mm needle for the 10 cp solution. That is to say, 40% of end-users found the injection force acceptable when using an 8 mm needle versus 15% when using a 12.7 mm needle (Figure 3).

To address the specific needs of pharma companies developing viscous/ high volume (2.25 mL) biologics, BD has launched and industrialised a short 8 mm needle solution, based on its state-of-the-art BD Neopak™ glass prefilled syringe (Figure 4).

INNOVATIVE NEEDLE TECHNOLOGIES PUSH VISCOSITY BOUNDARIES

BD has a strong track-record in needle innovation, answering to specific and evolving needs of pharma companies and end-users. In the last decade BD worked to reduce needle insertion pain, with the launch of BD Physiolis™ 29G Thin Wall needle¹⁷, and to increase injection flow rate with BD Hyflow™ 27G special Thin Wall needle.

With manual delivery needle standards, pharma companies developing viscous drugs for chronic use may need to compromise on patient injection experience. One way to improve the performance of viscous drug delivery without increasing injection force is to increase the inner diameter of the needle.

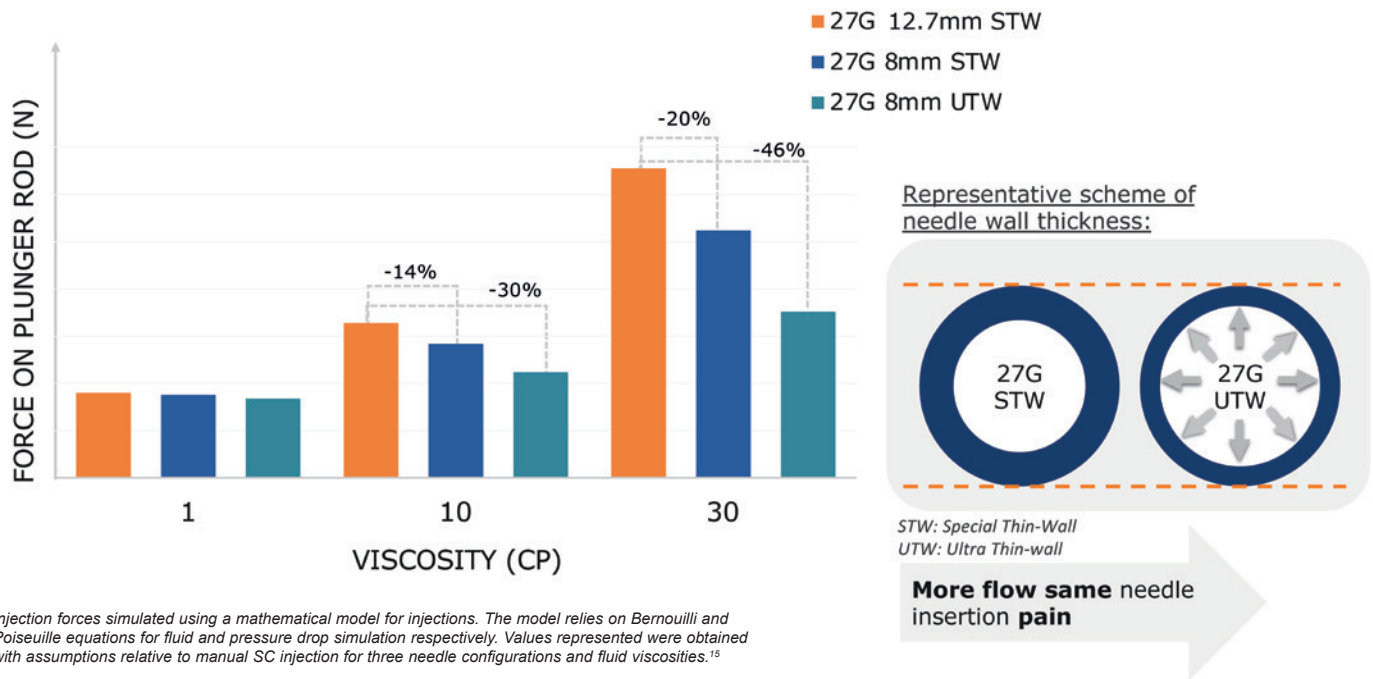
To address this, BD is developing a prefilled syringe solution combining shorter needle length (8 mm) with ultra-thin wall (UTW) needle technology. This technology increases the inner diameter of the needle by reducing the thickness of the needle wall without having to increase the external diameter (see Figure 5). The outer diameter of a needle is known to be an important feature as it influences needle insertion pain perception and the level of injection-related anxiety experienced by patients.^{14,17}

While at low viscosity (1 cP), injection force remains similar for all types of needle, mathematical simulations show that using an UTW needle can reduce injection force by 46% for highly viscous solutions 30 cP (Figure 5).

“This innovation combining short 8 mm with ultra-thin wall technology therefore reduces the injection force, especially for viscous solutions, without compromising on needle insertion pain and pain-perception.”



Figure 4: BD Neopak™ 2.25 mL glass prefilled syringes with 12.7 mm and 8 mm needles.



Injection forces simulated using a mathematical model for injections. The model relies on Bernoulli and Poiseuille equations for fluid and pressure drop simulation respectively. Values represented were obtained with assumptions relative to manual SC injection for three needle configurations and fluid viscosities.¹⁵

Figure 5: Combination of short 8 mm and thinner needle wall technology contributes to reduced injection force.

This innovation combining short 8 mm with UTW technology therefore reduces the injection force, especially for viscous solutions, without compromising on needle insertion pain and pain-perception.

INTEGRATED SYSTEM SOLUTIONS

With the aim of improving the self-injection experience for chronic disease patients in the home setting, pharma companies often develop self-injection devices combining a primary container (e.g. PFS) with needle-stick safety guard or autoinjector solutions (i.e. integrated systems). System integration challenges might arise due to the number of functional interfaces and especially when the different components are purchased from multiple vendors, as they must operate perfectly together once assembled.

To design a robust, high-quality device that will deliver the drug to patients safely and effectively with reproducible performance across millions of units, manufacturers need to ensure excellent compatibility between biologics, primary container and secondary device.

Developing and launching a drug-device combination product is a long and expensive journey for pharma companies and their partners. In order to ensure that pharma companies succeed in this process, BD, with its long history and experience in combination products, is well positioned to support the development of more robust, better-designed systems. BD is able to manage all the requirements through the cascading

process from delivery system requirement definitions, sub-system requirements, component requirements, manufacturing process requirements during the definition and development phases. It covers all design control aspects including usability (human factors) engineering, preclinical and clinical evaluation.

Ideally positioned with its exhaustive portfolio of drug delivery solutions for the chronic market, BD offers seamless integration of short 8 mm needle BD Neopak™ 2.25 mL syringes with BD injection devices including the BD Intevia™ 2.25 mL large-volume autoinjector.

CONCLUSION

Shorter 8 mm needle solutions demonstrated several benefits versus the current 12.7 mm standard needle. Notably, occurrences of unwanted IM injections are reduced and better performance parameters such as injection force reduction for viscous solutions can be positively perceived by end-users. Furthermore, patients experienced reduction in both anxiety and pain perception when using shorter needles, improving their overall injection experience.

BD's application of UTW technology to a shorter 8 mm needle should improve the end-user injection experience, taking it to the next level, by presenting the chronic disease market with a meaningful, viable solution that addresses the challenges related to high volume/highly viscous drugs that it faces.

Identifying enhanced needle solutions and offering integrated system solutions to serve chronic market unmet needs is a great step towards improved injection experience and quality of life for patients suffering from chronic diseases. BD adopts a patient centric design approach and develops drug delivery solutions tailored to home care, with the vision to improve patient adherence to chronic disease treatments.

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ABOUT THE AUTHOR

Aurelie Pager is Clinical and Human Factors Program Leader at BD Medical – Pharmaceutical Systems. She contributes to new drug delivery device development by managing clinical and human factors studies from concept phase until product launch. Ms Pager holds a Master of Science in preclinical research field and a university degree in the field of clinical research. She had been working for several years in preclinical research before joining BD.

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LED-GENERATED UV FOR ADHESIVE CURING IN MEDICAL DEVICES

As demand for syringes continues to grow, in terms of volume and also in terms of the range of applications, evolving the manufacturing processes can be just as important as the development of new treatment and the development of new medical devices. Here, Roland Lindner, Systems Engineer; Matthias Schulze, Applications & Systems Engineering Manager; and Bill Jaworski, Director Life Sciences Business Development; all of ATS Automation – sortimat Assembly Technology, discuss how the needs around adhesive use in the manufacture of medical devices such as glass syringes have evolved and how ATS sortimat has developed a new process to meet the industry's demands.

Syringes first emerged many years ago, in the times of medieval Arabia and the Byzantine Empire, roughly around 1000 AD. The devices continued to evolve but it was not until 1843 that British surgical instrument maker, Daniel Ferguson, received a patent for his “elegant little syringe” with a hand-made hollow needle that was screwed into a glass body of the device.¹



Figure 1: UV-cured adhesive bonding needle to syringe.

With continued developments in materials and production technology, glass syringes are now mass-produced medical devices. In 2016, the glass syringe market grew to more than US\$6 billion (£3.8 billion) and continues to grow at an annual rate of 8.4%.² Much of the current demand can be attributed to the rise in chronic diseases, an aging global population, an increasing number of treatments requiring injectable delivery, and an increase in use of prefilled syringes with self-injection devices. The sterile, prefilled disposable syringe with a fixed cannula for direct injection or for use with autoinjectors has become an industry standard.

CURRENT ADHESIVES & MEDICAL DEVICE JOINING PROCESSES

Ultraviolet light (UV)-cured adhesives are used in almost all medical devices where various components are bonded and joined. These relatively fast curing adhesives use UV wavelength light, and thus do not require the use of solvents for curing. Since the adhesives are able to tolerate steam sterilisation conditions, they are very applicable for sterile and consumable medical devices including tube sets, pen needles, autoinjectors and glass



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syringes (for the bond between the syringe hub and needle shaft).

These adhesives were initially developed to be cured with UV light produced by mercury vapour lamps (Figure 1). An alternative light source, light-emitting diode (LED) technology, has also continued to evolve. With better availability and more attractive costs, many medical device manufacturers are asking whether UV LED lamps could, or indeed should, be used in place of mercury vapour lamps.

COMPARING MERCURY VAPOUR & LED

Mercury vapour lamps are the current industry accepted standard for the generation of light for bonding stainless steel needles onto glass syringes. They generate a spectrum of light, including frequencies in the ultraviolet range, when the mercury vapour inside the lamp body is excited by a massive electron flow. Though these light sources tend to be more efficient than standard incandescent lamps, they do have various disadvantages including but not limited to short lamp life, high maintenance requirements, heat generation, energy consumption, and health and safety concerns related to the use of mercury and creation of ozone.

LEDs are solid-state devices that convert electrical energy directly into light. The past 40 years have seen significant evolution of LED technology, increasing the performance life and decreasing operating costs. Light source prices can vary but the pricing of LED lamps in general has dropped as the application and use of LED lamps have grown. Compared with mercury vapour lamps, LEDs have a long performance life resulting in lower maintenance costs and reduced service frequency. They also have a lower energy consumption and produce less heat. Overall, there is a lower total cost of ownership.

Another benefit is that solid-state LED lamps require no start-up or cool down period. It is generally accepted that they generate their desired spectrum and reach a steady state performance within milliseconds. Comparatively, mercury vapour lamps require a warm-up period to hit their steady-state performance characteristics. Though both light sources will exhibit performance decay during their lifetime, an LED light source tends to decay at a slower rate than its mercury vapour counterpart. Table 1 provides a summary comparison of the two UV light sources.

	Mercury-Vapour UV Lamp	LED UV Lamp
Technology maturity	Mature	Established technology but emerging application
Power consumption	High	Low
Heat generated	High	Low
Lamp life	Low	+10x
Performance decay (stability)	Faster	Slower
Maintenance burden	High	Lower
Warm up / time to steady-state	Not instantaneous	Virtually instantaneous

Table 1: Comparison of mercury vapour lamp and LED for UV light generation.

THE DEMISE OF MERCURY VAPOUR LAMPS

The 2013 *Minamata Convention on Mercury* was established to protect human health and the environment by reducing the release of mercury. This treaty has the goal of eliminating the manufacture, import and export of products containing mercury by 2020. This means that adhesives requiring UV curing will no longer be able to rely on mercury vapour lamps. Bottom line? Regardless of preference, alternative UV-generating light sources must be developed, proven to be equivalent to the current curing method, and adopted.

LED CURING DEVELOPMENT

In the 1980s Henkel (Düsseldorf, Germany) developed its Loctite AA3345[®] adhesive, which was primarily designed for bonding glass to metal. It is a UV-cured adhesive that has been widely adopted by medical device manufacturers globally. Loctite AA3345[®] is compliant with ISO 10993, which evaluates the biocompatibility of medical devices and furthermore is used in many medical devices that have been approved by the US FDA. As a result of the anticipated prohibition of mercury vapour lamps as a UV curing source, Henkel has been exploring alternative light sources in order to avoid the timely exercise of developing a new adhesive formula.

sortimat[®] Assembly Technology, a division of ATS[®], has a long-standing relationship with Henkel having designed and built many glass syringe assembly machines that use Loctite AA3345[®]. In close partnership, ATS sortimat and Henkel have worked together to establish a process using

“In close partnership, ATS sortimat and Henkel have worked together to establish a process using LED lamps that will allow the curing of Loctite AA3345[®] without a change in the adhesive’s formulation.”

LED lamps that will allow the curing of Loctite AA3345[®] without a change in the adhesive’s formulation.

In order to establish equivalency in adhesive performance between mercury vapour lamp curing and UV LED curing, ATS sortimat developed a design of experiment (DOE), which included a detailed experiment plan and an assembly system to be used as the test platform for the acquisition of data. The goal was not only to demonstrate adhesive performance but also to arrive at a stable process and technology solution that could be used in automation for our clients (Figure 2). This effort has been going on for several years with a committed team at ATS sortimat, and the results are now the subject of a pending patent application filed by ATS.

THE AUTOMATION TECHNOLOGY

The Discovery[™] Line conveyance system has been ATS sortimat’s proven platform for glass syringe assembly lines with an installation base throughout Europe and North America and many years of successful operation. It was no surprise that this

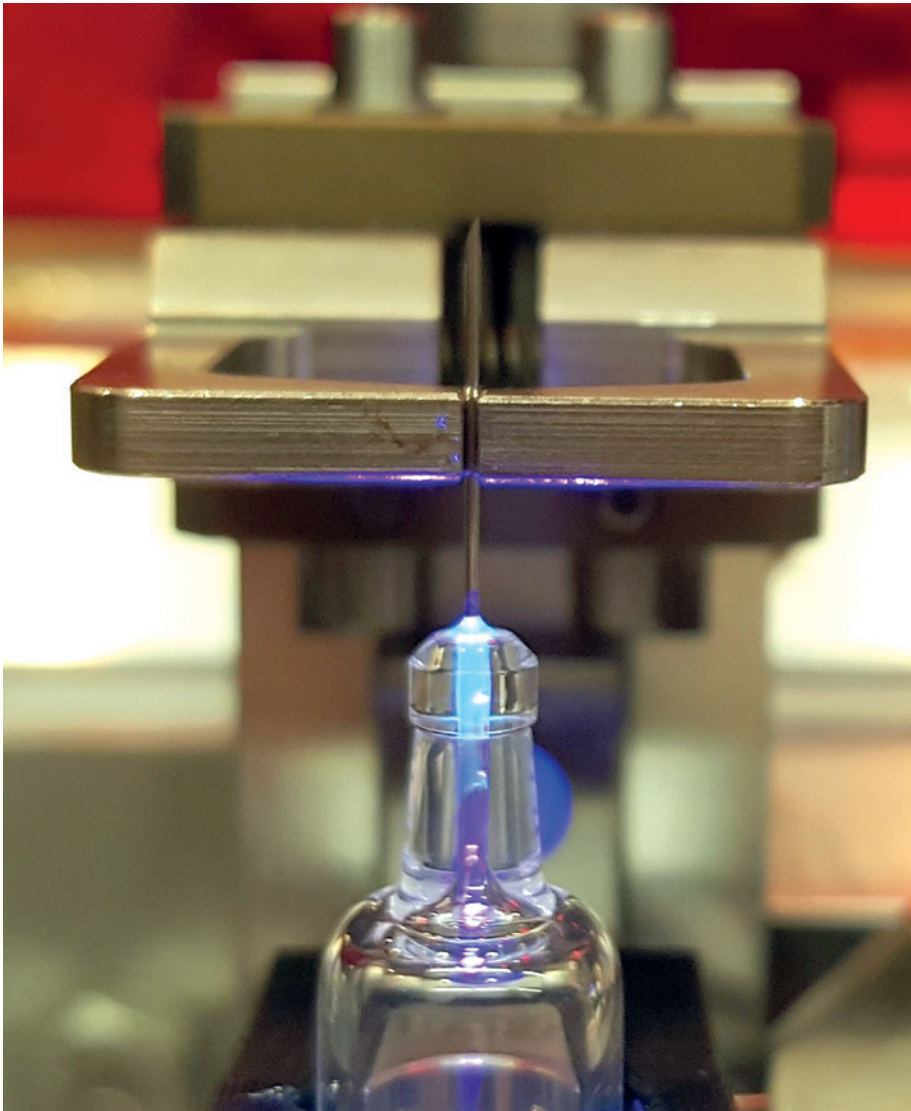


Figure 2: LED UV curing of adhesive on glass syringe with stainless steel needle.

was assumed to be the ideal platform for the adhesive study. However, during the initial phase of the project, it was quickly discovered that a more flexible platform would be required for the new LED curing technology in anticipation of variations in processing and curing times. Because of this, the machine platform for the tests was changed to the ATS SuperTrak® chassis.

The ATS SuperTrak® conveyance system is a high-speed, flexible system that can operate in an asynchronous manner to accommodate the varying processing speeds of different assembly steps. This platform is well-suited for the development of the LED curing process and technology with the added benefit of higher output rates for glass syringe production. With the ATS SuperTrak® platform, production rates of 500 parts per minute are achievable for glass syringe production.

ATS sortimat's experience with the assembly of glass syringes and needles also

provided insights to the types of in-process verification, process checks and other non-machine related tests that would be useful for manufacturers. In combination with the assembly technology, these process step checks will build confidence that the LED cured process is repeatable, stable and equivalent to mercury vapour cured process.

During the course of this process and technology development, there was extensive collaboration between ATS sortimat and Henkel to analyse the various trial results and ensure thorough understanding of the adhesive properties during LED curing.

Additionally many of the experiments were conducted or results were verified through a technical research institute (DIK Prüfgesellschaft mbH) that brought additional expertise and impartial verification to the effort.

Testing included pull force after sterilisation, surface inspection, and

monomeric residue (an indicator of extractables). Preliminary results are promising with pull-force results greater than 100 N on a 25-gauge needle in a glass barrel, and a completely dry surface after curing.

EXPERIENCE AND EXPERTISE TO ENABLE SYSTEM SUCCESS

ATS sortimat has designed and delivered many purpose-built syringe assembly systems, addressing unique customer needs and requirements, and adapting technology approaches as necessary to accommodate advancements in science, processes, and products. The exploration of LED UV curing as an alternative to mercury vapour UV light curing is just the most recent undertaking for ATS in response to a regulatory challenge in the medical device industry.

With ATS sortimat's most recent developments utilising Loctite AA3345® adhesive and collaboration with Henkel, glass syringe manufacturers can be confident in an alternative UV curing mechanism, LED generated UV light. LEDs can improve maintenance burden, provide in-process feedback and will meet the requirement to reduce reliance on the chemical element mercury.

The process development work in this space has provided ATS sortimat with a vast knowledge bank around the UV light adhesive-curing process including, but not limited to, an understanding of dispensing characteristics, dispensing volumes, curing rates and in-process verification feedback. This has provided ATS sortimat with more refined expertise to support our clients and their own specific process for glass syringe and needle assemble or in other medical devices that require UV cured adhesives.

ABOUT THE COMPANY

Automation Tooling Systems (ATS®) is an automation solutions provider to the life sciences, chemicals, consumer products, electronics, food, beverage, transportation, energy, and oil and gas industries. Its offering includes custom automation, repeat automation, automation products and value-added services, including pre automation and after-sales services, to address the sophisticated manufacturing automation systems and service needs of multinational customers. ATS provides life science customers with low-risk, turnkey, compliant, manufacturing systems for medical devices, pharmaceuticals and diagnostic companies.

ATS understands that quality of product, assurance of supply and sustainable manufacturing is of particular interest

to drug delivery companies. Clients trust ATS with the development of systems for autoinjectors, transdermal devices, syringes,

inhalers, electronic meters and devices, IV catheters, tube sets, specialised infusion kits, high accuracy dispense and placement, filling and packing.

ATS employs approximately 4,400 people at 23 manufacturing facilities and more than 50 offices in North America, Europe, Southeast Asia and China. ATS Automation Tooling Systems, Inc, is publicly owned, and its shares are traded on the Toronto Stock Exchange (TSX: ATA).

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ABOUT THE AUTHORS

Roland Lindner, is a Systems Engineer within the Applications Department of ATS Automation – sortimat Assembly Technology. He began his career with sortimat in 2000 as a Design Engineer and was the lead on many high-profile programmes. As a Systems Engineer for the past four years, he has been responsible for technical process development in the automation of medical product manufacturing. This requires developing a deep understanding of life science customers, their products, the assembly process and complex automation and then finding novel means to help our customers be successful. This has more recently included refining and enhancing ATS sortimat’s approach to the application and curing of adhesives.

Matthias Schulze, Manager, Applications & Systems Engineering at ATS Automation – sortimat Assembly Technology, started his career as a Mechanical Engineer and afterwards became a Lead Engineer for different projects, and a site supervisor in Europe. He joined sortimat in 2016 as an Applications Engineer and took over the role as Manager, Applications & Systems Engineering, in 2018.

William (Bill) Jaworski has held a variety of strategic roles at the intersection of healthcare and technology. This included roles such as Product Manager, Segment Marketing Manager, Global Marketing Director with GE Healthcare to current role as Business Development Director at ATS - Life Science.



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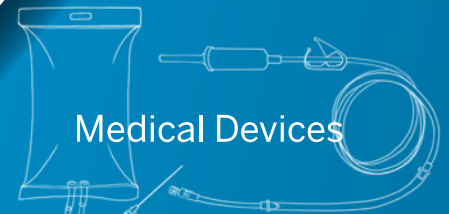
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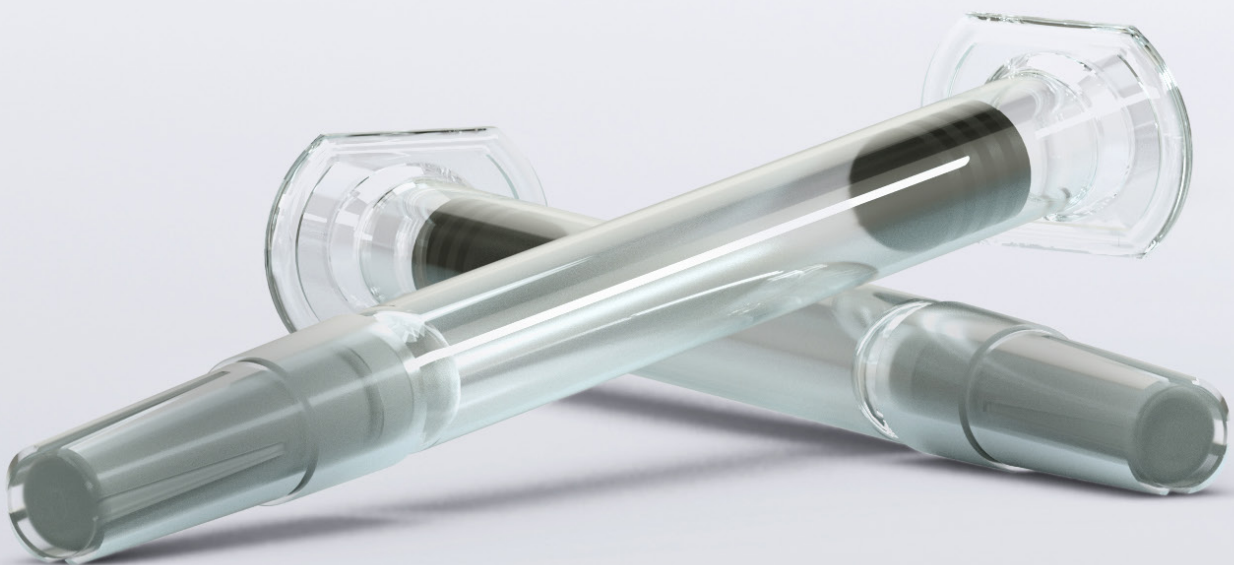
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F2V: A STERILE, CUSTOMISABLE LIQUID FILL-FINISH PLATFORM FOR THE TOTAL LIFECYCLE

In this article, Simon Strothers, Director of Business Development, 3P innovation, presents an integrated fill-finish platform, F2V, designed to represent a commercial filling system as a bench-top solution. The article also includes a recent case study where the F2V was used by Consort Medical to help develop and industrialise a flagship delivery device. Finally, a summary is provided of the key factors that should be considered to help ensure success in new drug and device development and industrialisation.

Current market trends indicate that next-generation biopharmaceuticals will have a major impact on the way drugs are formulated and the devices that deliver them. The pharmaceutical industry is also increasingly seeing a rise in the development of personalised medicines, which are tailor-made solutions designed specifically to meet the needs of a particular patient. These drug products require low-volume manufacture and a high degree of flexibility. Regulatory pressures to improve the patient experience are also driving new combination products and associated device developments. Many companies involved in this area are small start-ups, university spin-offs and

“Equipment innovation and sterile facilities are required that can fill a much wider variety of container formats in smaller volumes.”

venture capital-backed businesses usually with some novel intellectual property.

Production of parenteral products, especially primary drug filling and finishing, demands sterile production environments with aseptic manufacturing systems and know-how. Regulators are demanding that parenteral manufacturers “automate more” during preclinical and early clinical phases to reduce human

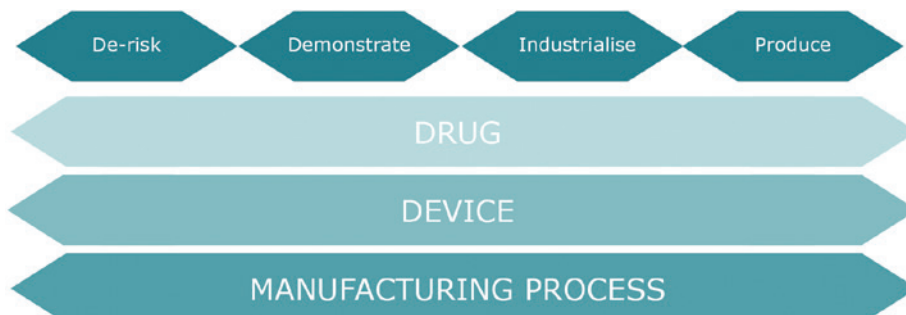


Figure 1: A simple framework to consider when planning and resourcing for a new drug or device development project.



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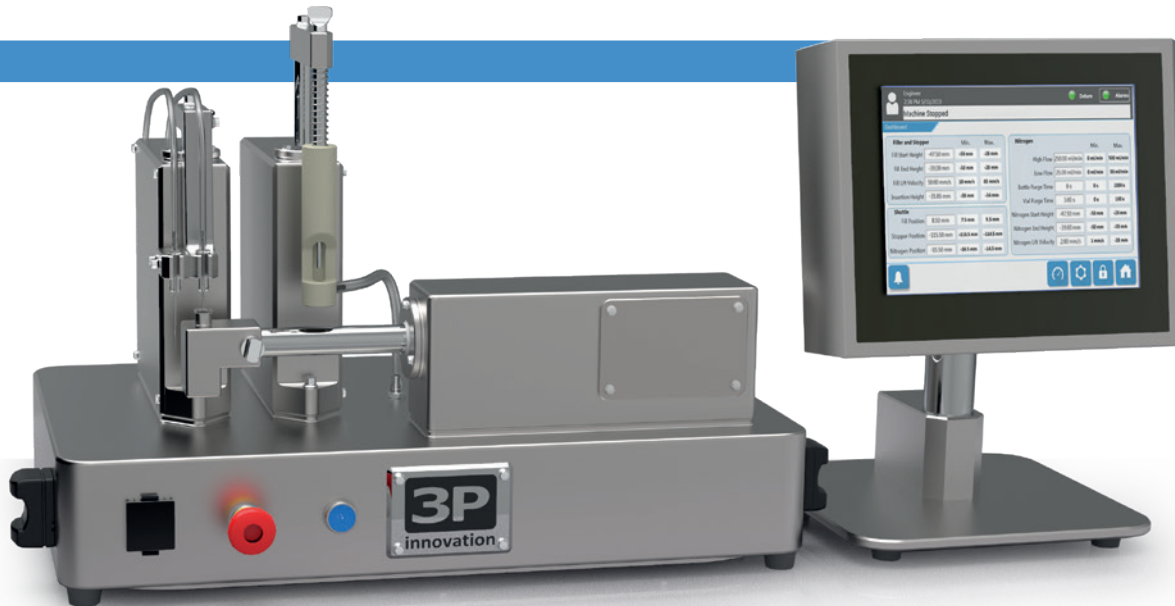


Figure 2: F2V sterile fill/finish, configured for syringe filling with nitrogen purge and vacuum stoppering.

operator influences on the process to improve product quality and safety.

The combined effect of the above is having a significant impact on existing supply chains and manufacturing models. Equipment innovation and sterile facilities are required that can fill a much wider variety of container formats in smaller volumes. There are new challenges for liquid filling; higher accuracies, highly viscous products and multi-product devices demanding more advanced pump technologies and inspection methods.

PLANNING FOR SUCCESS

Built on previous project experience we propose a simple framework to consider when planning and resourcing for a new drug or device development project (see Figure 1). The four headings represent the key activities that should be considered when developing a new combination product. Drug, Device and Manufacturing Process are the three main work-streams that typically demand different resources and skills sets and which should be considered in parallel to ensure the interdependencies are explored, defined and considered from the start.

F2V – LIQUID FILL-FINISH PLATFORM

With the objective of helping customers to address all of the key activities and workstreams highlighted in Figure 1, 3P has developed F2V, an isolator-ready, flexible, customisable platform for both filling and finishing of a wide variety of containers and devices including syringes, cartridges, vials, bottles and customised drug containers.

Whereas most lab-scale systems offer individual process stations only, F2V (shown in Figure 2) provides a GMP-compliant, all-in-one integrated system for nitrogen purging, liquid filling, vacuum stoppering and other processes on the same

machine. This increased level of automation improves productivity, product quality and patient safety, whilst still providing the flexibility you would expect from a bench-top, low-volume system. Operators are not required to transfer containers between the critical fill and stoppering processes, thereby simplifying the process and reducing risk.

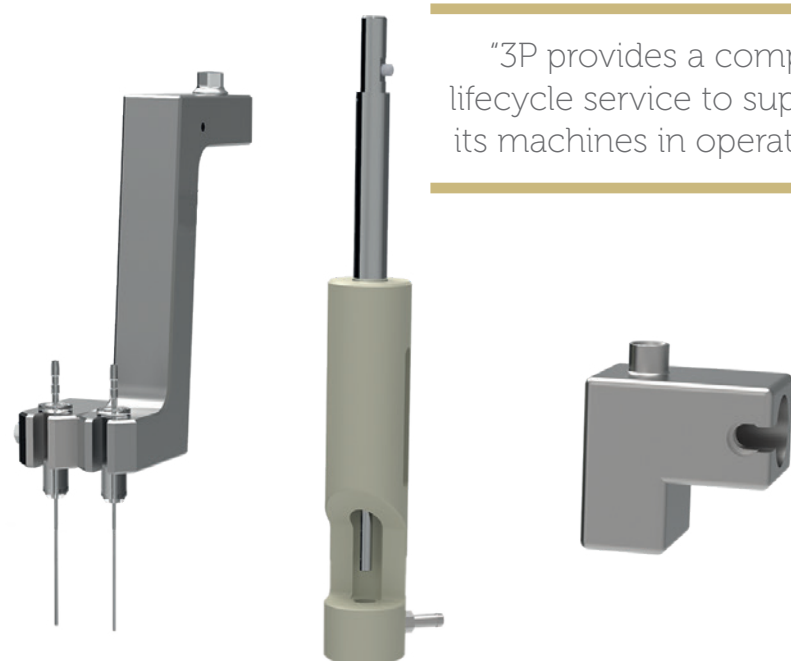
With ongoing support from the 3P team, the F2V platform is fully customisable and comprises a series of fully programmable, servo-controlled modules for bottom-up filling, nitrogen purging, vacuum stoppering and stopper pick-and-place. A separate bench-top Rotary Crimper is also available and enables customers to complete the finishing process for cartridges and vials. An easy-to-use, touch-screen display enables easy adjustment of speeds and strokes to suit individual container types and dimensions.

Recipes can be created and recorded to suit different container types and sizes.

Once recorded, the associated parameters will be stored against the named recipe. Operators can then reselect a recipe at a later date to retrieve the exact same settings and conditions for production. This option speeds up changeovers between batches and supports development activities such as design of experiment (DoE) and sensitivity analysis.

Containers are loaded manually into a transfer puck. Pucks are custom-designed, specific to a particular container type. The puck is connected by to a servo motor-controlled arm which gently moves the container between the filling and finishing stations. A gentle motion profile prevents spillage or unwanted movement of liquid up the sides of the container, which may affect stoppering and the sterile barrier.

The transfer puck forms part of the F2V change tooling set (Figure 3) and can be rapidly changed over to take different



“3P provides a complete lifecycle service to support its machines in operation.”

Figure 3: F2V change tooling set can be rapidly changed over to take different container sizes and types.

container sizes and types. For example, following filling of a batch of cartridges, F2V can be quickly changed over to fill a batch of vials. As required, this could be with a different pump technology, a different liquid and a different dose weight.

Complete Lifecycle Service

3P provides a complete lifecycle service to support its machines in operation. During the container development phase, new change parts can be 3D-printed by our engineers to enable initial test fills and supply of samples. As a design becomes firm, 3P will support with manufacture and supply of GMP-compliant change parts, suitable for clinical and production manufacturing.

A major benefit of F2V is therefore its ability to accommodate late-stage changes in device and container design. F2V is intentionally designed as a flexible and versatile production platform rather than a single, fixed machine. An F2V system can be configured to suit specific processes which may be applicable to individual containers or a range of container types. Figure 4 shows how a new system is configured by choosing the required processes combined with a choice of pump type.

It is also possible to supply multiple pump types for a given process. For example, we can supply rotary piston pumps, more suitable for higher-accuracy or higher-viscosity drug products as well as peristaltic pumps, ideal for single-use, biopharmaceutical filling.

F2V STATIONS AND THEIR APPLICATIONS

Different F2V stations perform specific functions supporting the development and manufacture of various container types (see Figure 5).

Liquid Filling and Nitrogen Purge

The liquid filling module (Figure 6a) integrates with any pump format as required to suit the application, including peristaltic, and rotary piston pumps. A wide choice of nozzle types and sizes is available to suit the dose volume, liquid and container type. Programmable bottom-up filling enables fine adjustment of needle position, speed of lift and fill rate, avoiding splashing, frothing or contamination of the stoppering zone. A nitrogen purge option is available which uses the same programmable controls as for liquid filling.

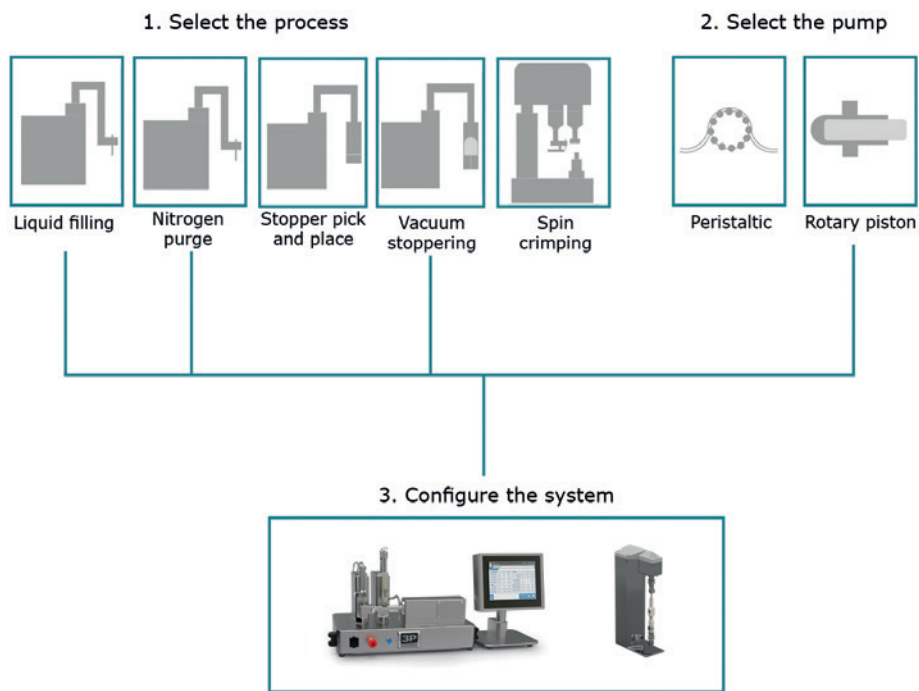
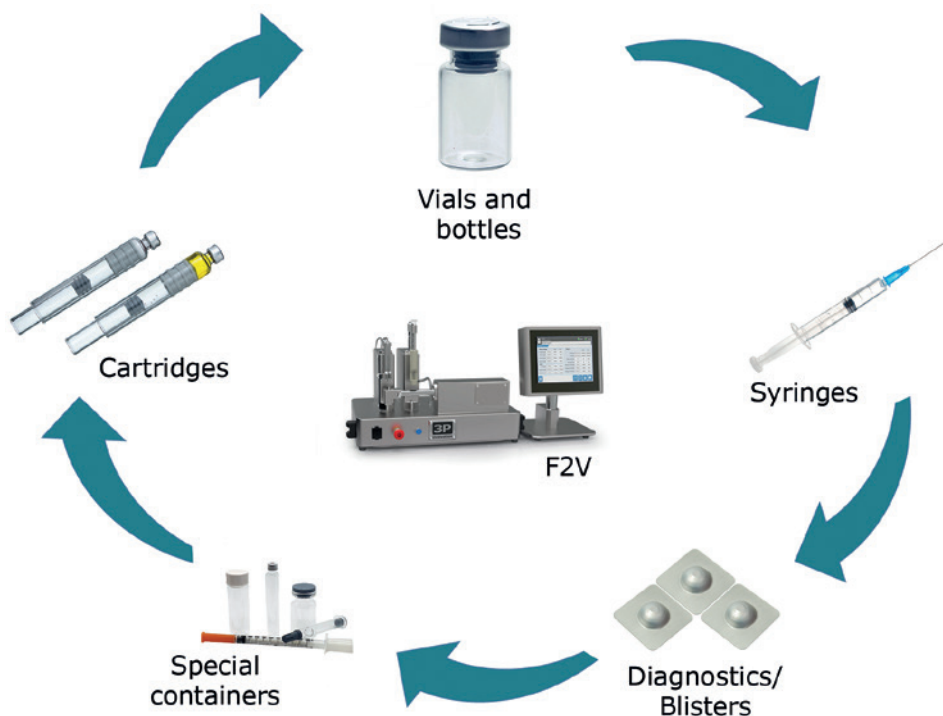


Figure 4: A new system is configured by choosing the required processes and pump type.



	Bottom-Up Liquid Filling	Nitrogen Purge	Vacuum stoppering	Stopper pick-and-place	Spin crimping
Syringes	✓	✓	✓		
Cartridges	✓	✓	✓		✓
Vials	✓	✓		✓	✓
Bottles	✓	✓		✓	
Specials	✓	✓	✓	✓	✓

Figure 5: The functions and container types that different F2V stations support.

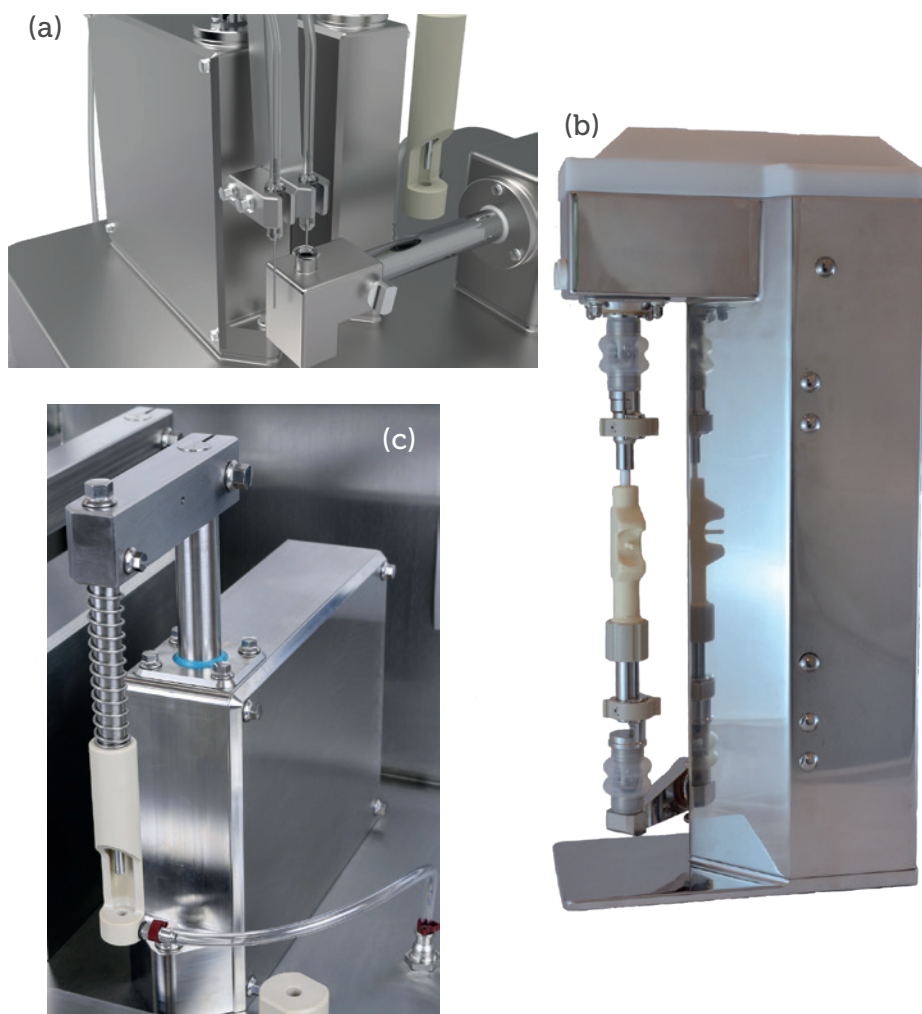


Figure 6: Liquid filling module (a), isolator ready rotary pump (b), vacuum stoppering station (c).

Pump Innovation

The novel rotary pump module (Figure 6b) from 3P's pump partner, Bio Solutions Gate (BSG, Francheville, France), compliments the F2V system, providing the same degree of flexibility and reconfiguration in one integrated system. Isolator-ready, the compact, bench-top system uses high-quality ceramic pumps from Neoceram (Strépy-Bracquegnies, Belgium), providing very high accuracy and repeatability, ultra-low particle

release, no interaction with the drug product and long life-time capability. Connected to the F2V system, the BSG pump can fill liquids from 0.03-175 mL (depending on selected ceramic pump) with an accuracy up to $\pm 0.1\%$. Toolless assembly is enabled by BSG's fast-locking concept. An alternative dosing unit is also available, dedicated to micro-dosing and capable of fill volumes from 0.01-8.5 mL, also with an accuracy up to $\pm 0.1\%$.

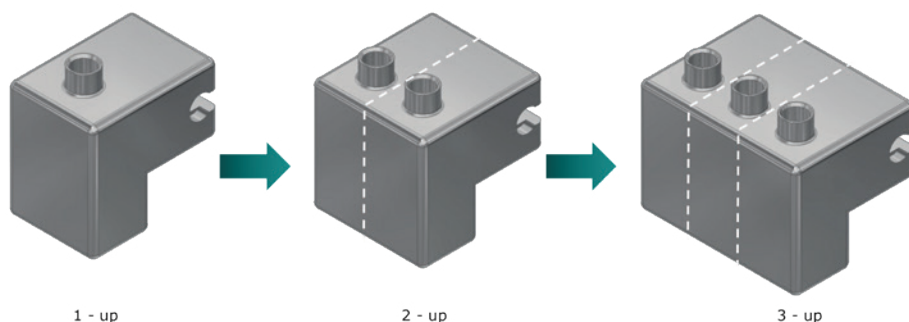


Figure 7: Scale up and out – container puck can be designed to hold one, two or three containers at a time.

Vacuum Stoppering

Suitable for closing cartridges, syringes and other special containers, the vacuum stoppering station (Figure 6c) integrates with a standard vacuum pump. Vacuum levels can easily be adjusted and a sensor ensures target vacuum has been achieved prior to motorised insertion of the stopper. The stopper insertion depth is finely adjustable via the touch-screen human-machine interface (HMI).

Stoppers are loaded manually into a device-specific housing. This housing forms part of the F2V change tooling set. All change tooling can be removed quickly and easily, without the need for tools or equipment and can be disassembled, cleaned and sterilised using conventional sterilisation equipment.

Stopper Pick and Place

The stopper pick-and-place station uses vacuum to pick and transfer stoppers and caps to close vials, bottles and other special containers. Stoppers and caps are loaded manually, followed by automated picking and placement onto the container.

Scale Up and Scale Out

The F2V platform is designed to enable fast, easy scale-up through simple change parts and, if necessary, adding additional pumps to the system. Figure 7 shows how the container puck can be designed to hold one, two or three containers at a time. Filling needles and change tooling for the vacuum stoppering station are similarly configured to process one, two or three products at a time.

When higher volumes are required, 3P supports with the design and supply of faster machines or, as indicated previously, through scale-out by implementing multiple F2V machines, which may be sufficient to generate significant volumes for late-stage clinical and even commercial volumes depending on the product and the market demand.

F2V – Rotary Crimper

The spin crimper is supplied as a separate module to enable segregation from the filling and finishing processes. This is typical best practice to minimise risk due to generation of particulates. The module is designed for aseptic processing, suitable for use in sterile isolators and for fully automated and manual sterilisation processes such as hydrogen peroxide vapour (HPV) sterilisation.

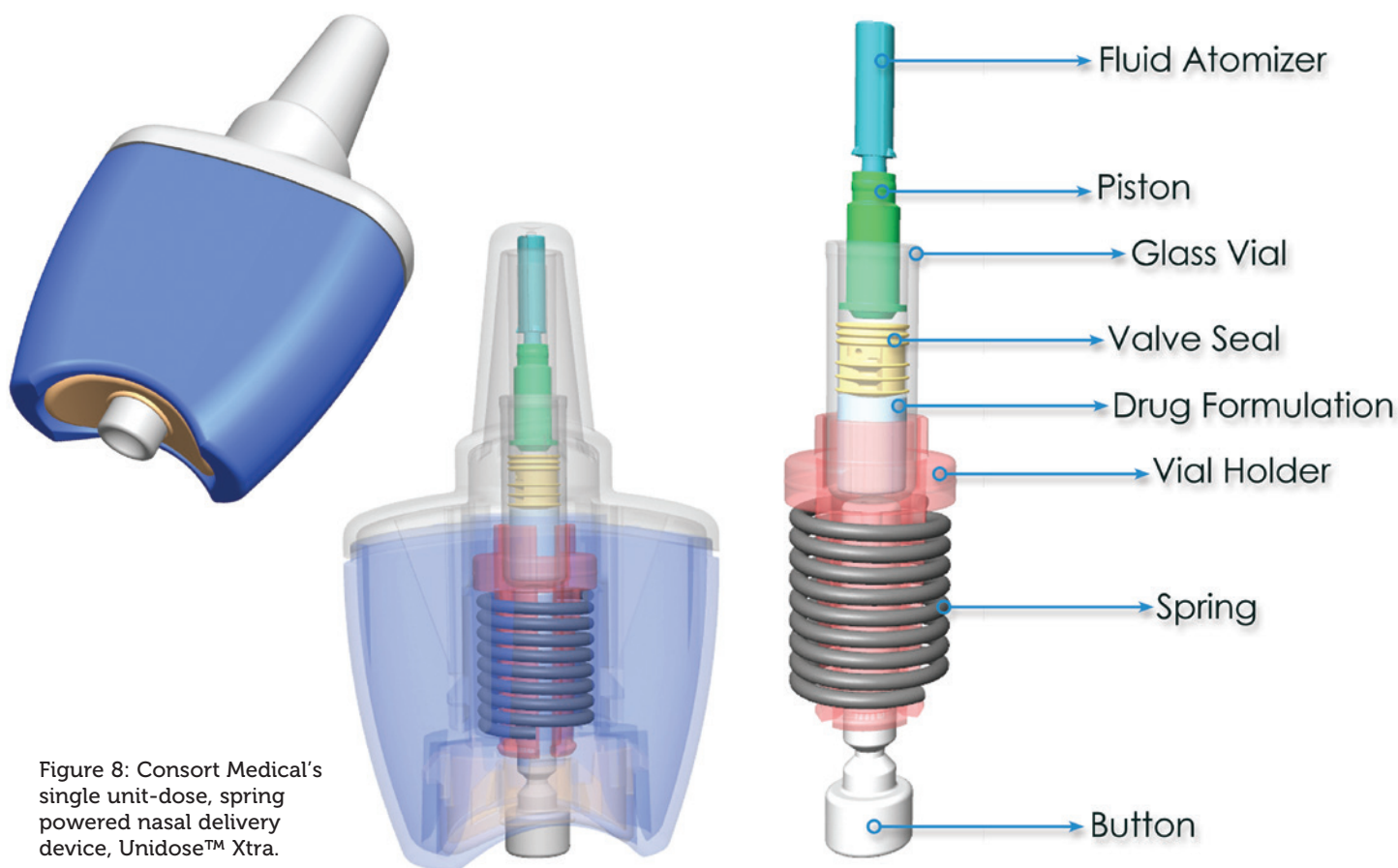


Figure 8: Consort Medical's single unit-dose, spring powered nasal delivery device, Unidose™ Xtra.

A CASE STUDY – LAB-SCALE LIQUID FILLING USING F2V

The following case study provides an example application of F2V for a drug delivery device client. Although it focuses on a nasal device, the equipment used, processes developed, lessons learnt and feedback from the client, Consort Medical's Aesica Pharmaceuticals division (Queenborough, UK), are all directly relevant to parenteral delivery device filling applications where there are numerous crossovers and similarities.

Consort Medical has developed the innovative Unidose™ Xtra nasal spray device (Figure 8) to provide unique performance advantages through a novel, patented device actuation and drug delivery solution. The device was discussed in detail in an interview with ONdrugDelivery earlier this year (see "Interview: Paul Allsop, Miles Kottman, Hannah Priestly and Jon Reed, Consort Medical". *ONdrugDelivery Magazine, Issue 96 (Apr 2019), pp 36-40*). Unidose™ Xtra is compact, simple and intuitive to use, with a low actuation force and a reliable drug delivery that is independent of the force or speed being provided by the end user.

Consort Medical provides its pharma partners with API and finished

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"3P listened to our needs and responded with flexible, precise and user-friendly machines that have been invaluable in helping us to understand and develop our device more effectively. Our operators have all commented on just how easy and intuitive it is to use. Thank you 3P for your close co-operation and for a quick turnaround."

Dave Bland, Development Director, Consort Medical

dosage formulation development and manufacturing service for the device, and as part of this service had a requirement to establish a highly flexible but scalable liquid filling and stoppering system capable of precisely filling a wide range of different liquids and viscosities. In addition, the system needed to be designed for GMP manufacture and capable of nitrogen flushing the drug container for oxygen-free filling and stoppering of their cartridge.

In response to the above, and conscious of the increasing pressures from regulatory bodies such as the US FDA to automate more to improve the safety of drug manufacturing for both end product and operators, Consort selected 3P's F2V as a versatile, lab-scale liquid filling and vacuum stoppering system.

The core filling and stoppering processes are automated and inherently scalable,

avoiding the need to revalidate the process when faster production speeds and higher throughput is required.

The machine has helped Consort Medical by providing:

- A cost-effective means to develop and derisk new devices and combination products at an early stage in their project.
- Valuable insight and clear understanding of manufacturing process and capability – providing data essential to ensure a robust manufacturing process that will stand up to scrutiny and validation.
- Top quality equipment with which to demonstrate manufacturing know-how and scale-up route to their end customers.
- The means for quick and easy manufacture of pre-clinical and GMP volumes of product to support clinical trials, performance testing, human factors studies, stability trials etc.

CONCLUSION

In addition to the equipment it supplies to its partners, 3P's reputation is built on providing first-class service and support. The combination of these elements – equipment with service and support – is one of the key factors for project success. Box 1 (next page) provides a summary of other key factors to include, together with pitfalls to avoid, to ensure successful project outcomes. Developing and refining device design has been made easier by F2V. This invention allows for the end-product to be tested sooner to measure feasibility quicker. In addition, the individual unit operations are representative of production, meaning that validation does not need to be repeated when a scaled-up solution is required. The F2V is flexible, scalable, easy to use and clean, and can be integrated with other modules for higher-volume semi-automated and fully automated production. The result is a faster product launch and faster return on investment.

ABOUT THE AUTHOR

Simon Strothers joined as a Director of 3P innovation in 2013 and is responsible for Business Development and Marketing. His background is in mechanical engineering. He qualified with a Bachelor's degree in Mechanical Engineering at the University of Manchester (UK) and has a Masters Degree in Business Management from Warwick University (UK). Mr Strothers' career started with Lucas Aerospace, where he worked as Design Engineer, Systems Engineer and Programme Manager, responsible for flight control and engine actuation systems for aircraft. He then worked as a management consultant for four years, driving business improvement projects across a wide variety of industries including paper making, railways and aerospace. For the past 14 years he has worked in the field of custom automation and engineering consultancy for the life sciences and FMCG sectors, initially as senior project manager and since 2006 as business development director.



2019/20

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Mar 2020	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 6, 2020
Apr 2020	Pulmonary & Nasal Drug Delivery	Mar 5, 2020
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Nov 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
Dec 2020	Connecting Drug Delivery	Nov 5, 2020

BOX 1: KEY FACTORS FOR PROJECT SUCCESS

The following paragraphs summarise some of the more common issues and pitfalls that 3P has seen occur across many projects and over several years, and – importantly – how to avoid them.

Establish a Multi-Functional Team

Running a “skewed” project team is a common pitfall as it is difficult to form a team that contains the right breadth and depth of skills needed to deliver a whole project. For example, a company’s main focus is on device-drug functionality and efficacy but the aspiration is to develop and industrialise a finished solution, including the drug product. Typically, limited time and focus will be afforded to the manufacturing process, how the device is filled, how it might vary in production and how the device impacts the manufacturing process. The result will be a limited understanding of the variables that can affect both functionality and manufacturing processes. This means that technical risks will remain unaddressed – ultimately resulting in significant project delays, set-backs or even cancellations depending on the nature of the issue.

The solution sounds obvious but is often ignored. Establishing a multi-functional team and bringing in the right expertise at the start will raise the correct questions at the start and will drive a more balanced programme which addresses both drug, device and their interdependencies in parallel.

Specialist life science development and automation companies such as 3P augment project teams, helping to generate a holistic view of the drug, device and manufacturing process interactions leading to a smoother commercialisation/industrialisation path.

Keep the End Goal in Sight

Closely related to the skewed project team issue, projects often suffer from a short-term view, often as a result of the wrong scope of objectives being defined at the start. For example, a device design and development team might focus on achieving key functionality in the device, but without considering how it will be filled or tested. The result is that design changes are often required to enable filling or manufacturing at commercial scale, causing delay and significant on-costs.

The solution is the same as above – a multi-functional team, formed at the earliest stages and involved in project planning and objective setting, as well as in the design and development process from the start, will ensure that all essential aspects of the project are considered at the right time to avoid rework.

Build a Complete Process Understanding

Process understanding is a key aspect in device development. In essence, it involves applying physics and quantifying the range of conditions under which a component (e.g. a liquid, a powder, a plastic component, etc) will behave in the desired way for the product to give the required function. The engineering skills involved are often different to the skills involved in generating new design concepts.

Successful teams will pull in the right mix of resources to ensure science is applied to build a full understanding of every aspect of a new product, including all pertinent processes. Well-proven and tested tools such as failure mode effects and criticality analysis (FMECA), design of experiment (DoE), sensitivity analysis, design for manufacture/design for assembly (DfM/DfA) are invaluable to test design robustness for both function and manufacturability.

Automation and engineering experts such as 3P fulfill a key consulting role in providing support to customers across all of these areas, resulting in an optimised product as well as process for manufacture.

Consider Early How to Manufacture

Don’t wait too late to consider how to manufacture a device. An all too common scenario unfolds when a company has completed the drug and/or device design and development work and is now ready to manufacture initial volumes. This is a critical stage for any project and is often where many finish up cancelled or postponed. The reason for the failure is so often due to lack of attention and resources dedicated earlier on to exploring manufacturing solutions and/or unrealistic estimates of how much a manufacturing solution will cost and how long it will take.

To avoid these issues, engage with equipment suppliers at the earliest stages of the project to provide drug and device development projects with the crucial information required to make the decisions that can influence design and enable a faster, smoother route into clinical manufacture and beyond.

Be Ready to Demonstrate Manufacturing Know-How to Your End Customers

Having a great device or a great drug product in isolation is generally not enough to persuade big pharma to invest and take it forward to commercialisation. As end customers, big pharma companies are looking for and expect the complete package, where drug, device and manufacturing solutions are available, tested and proven.

It is not sensible nor financially viable for a device developer to invest at the outset in the high-speed, fully automated production lines which would ultimately be required. However, what is possible is to show end-customers that the key high-risk production processes have been defined, developed and derisked.

The way to achieve this is by investing in low-volume, bench-top machines. These can be GMP compliant and fully representative of individual process steps, but will typically require operators to complete the lower-risk steps, such as container load/unload and transfer between processes. Portable and versatile, machines can easily be installed in clean rooms and isolators.

Learn to Walk Before You Run

Aiming for a single, fully automated, high-speed machine that will meet volume targets projected for 3-5 years’ time is not always the most sensible approach. Depending on the level of commercial risk that exists on the project, such as untested or unproven market demand, businesses may be better off scaling out, rather than scaling up, to deliver increasing volumes.

Having already provided manufacturing capability through bench-top machines, further volumes can easily be achieved by procuring multiples of the same machine. Obviously, more operators will be required, but this is often faster, lower cost and carries less risk than a high-speed, fully-automated solution.

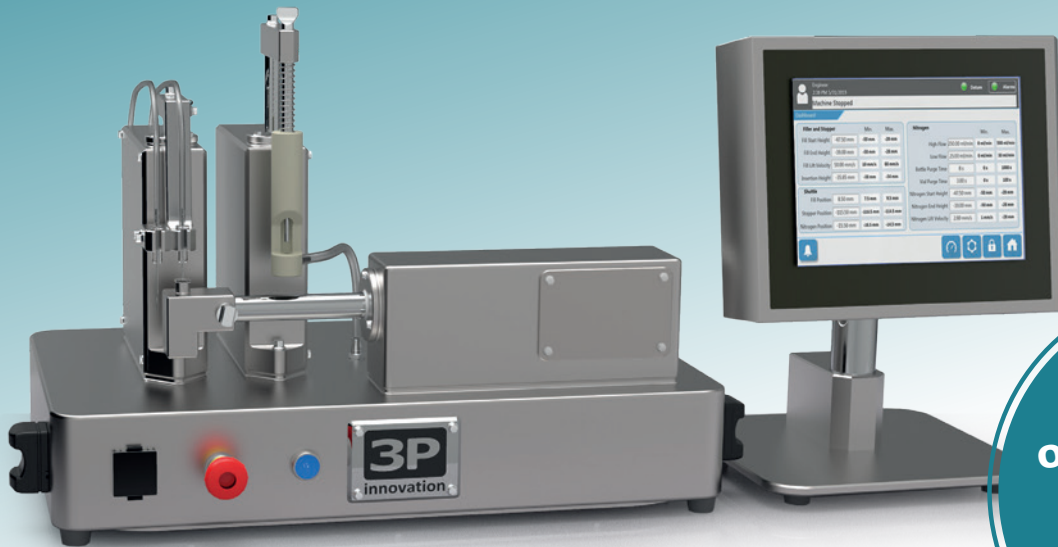
The critical point to understand here is that although the product unit cost may be higher, the ability to match output with growth in demand incrementally using a scale-out approach, rather than by step change (investing in long-lead, high-speed equipment) that comes on stream many years later, means companies can see early growth in their revenue stream.

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PRODUCT SHOWCASE: ZwickRoell Parenteral Device Testing Platform

Zwick / Roell

LATEST ROBOTIC TECHNOLOGY

ZwickRoell's discussions with pharmaceutical companies have identified the need for a single testing system for autoinjectors that can perform the following standard tests in compliance with EN ISO 11608-5:

- Removal force of safety cap
- Activation force and displacement
- Injector timing
- Delivered drug volume, including the last drops
- Effective needle length
- Safety of needle guard

Fully automated solutions range from easy-to-use smart robots only used for feeding and removing the injector, to complex robotic systems which are used to load specimens into multiple testing machines in parallel. With the latter, fully automated daily checks can be implemented, results/events can be uploaded into the customer's IT system and injectors can be sorted by specified tolerances.



Figure 1: Fully automated breakaway force and glide force.

FULLY AUTOMATED BREAKAWAY & GLIDE FORCE DETERMINATION

The glide force test is based on the following standards: ISO 7886-1, ISO 11499 and ISO 11040-4. Breakaway force and glide forces are important parameters used to select the most suitable syringe. These forces may not exceed or fall below defined limits to ensure the delivery of a safe drug dose. Forces are influenced by the viscosity and molecular size of the drug.

ZwickRoell's roboTest offers fully automated breakaway and glide force testing (Figure 1). A robotic gripping arm takes one of the 30 syringes from the magazine table, places it in the testing machine and starts the determination of the glide force. After the test, the robot places the syringe back in its original location in the magazine.

Fully Automated Pen Injector Testing

The most important requirements when testing medical products is the reproducibility of results and the minimisation of operator influences. To meet these requirements, ZwickRoell has developed automated systems for testing pharmaceutical pens. Single-use pens are disposed after the contents of the cartridge are dispensed, whereas reusable pens can be used year after year. ISO 11608 Parts 1-3 define the standard used for quality assurance tests on insulin pens and cartridges. As with autoinjectors, fully automated solutions range from simple smart robots used for feeding and removing to robots that operate multiple machines in parallel.

KEY BENEFITS OF AUTOMATION

Industry 4.0

The autoEdition3 software controls the robotic testing system. It is based on the principles of Industry 4.0: decentralised intelligence, parallel processes, standardised interfaces and real-time optimisation. The roboTest testing systems allow ZwickRoell to achieve higher specimen throughput in comparison with traditional, sequentially controlled systems.

Traceability

Everything must be completely backwards traceable. ZwickRoell's testXpert III testing software allows complete, tamper-proof documentation of all actions performed in testXpert III. The user defines the level at which actions are to be logged and explained according to requirements (e.g. this may mean that each change made to a test-relevant parameter such as test speed is recorded in full). Together with user management already integrated in testXpert III, this option provides the ideal tool for fulfilling the requirements of US FDA 21 CFR Part 11.

Providing easy access to quality characteristics as well as protection from tampering at the same time allows manufacturers to optimise their processes and sustain improvements in product quality for safety-related products.

Automatic Daily Check Tools

Daily check tools are used to check sensors regularly for force, weight, or displacement. They recognise systematic measurement errors in the sensors and notify the responsible person immediately. Normally, this takes place daily. In addition to the manual version in which the user engages and monitors the daily check tool, ZwickRoell also offers a fully automated version in which all steps are handled via automation. The results are traceably recorded in a log file. If the results are bad, the system stops and the user is notified.

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- Manual, semi-automatic and fully automated testing solutions for therapy systems (needles, (pre-filled) syringes, insulin pens, auto injectors)
- Traceable and tamper-proof test results in accordance with FDA 21 CFR Part 11
- ZwickRoell supports customers with DQ, IQ and OQ services

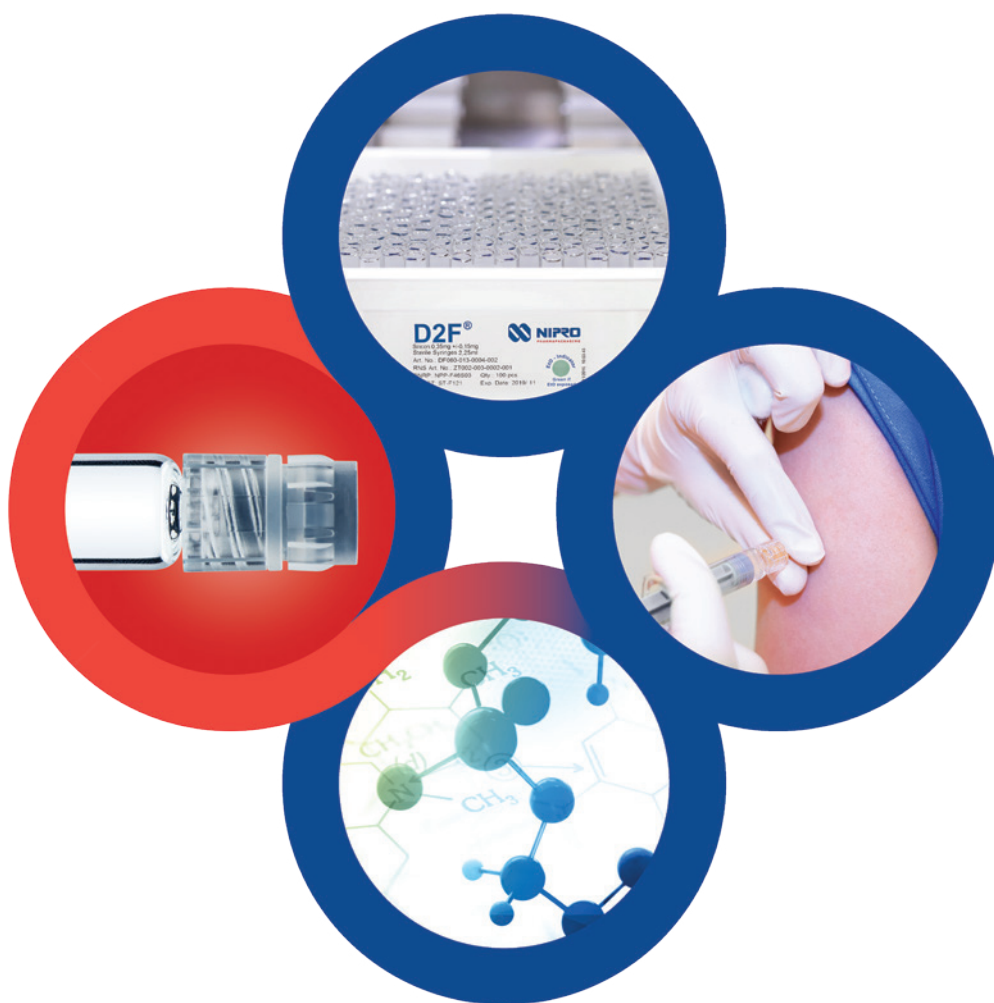
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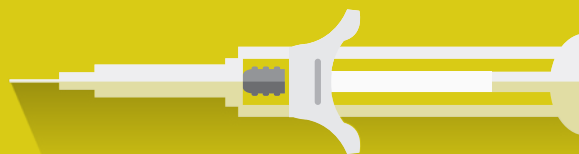
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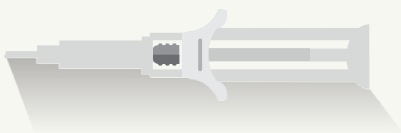
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HOW CONNECTIVITY ADDS VALUE TO INJECTABLE DRUG DELIVERY DEVICES

In this article, in the context of the growing shift in emphasis from improving adherence to the better outcomes that can arise from doing so, Iain Simpson, PhD, Director, Front-End Innovation, Phillips-Medisize, discusses why connectivity is becoming increasingly important in injectable drug delivery, and how it can benefit patients, providers and pharmaceutical manufacturers.

Medication non-adherence is a major issue and represents a barrier to effective healthcare, with the WHO reporting in 2015 that medication adherence among patients with chronic diseases averages only 50% in developed countries.¹ The problem has long been recognised. In 1985, former US Surgeon General C Everett Koop, MD, succinctly observed, “Drugs don’t work in patients who don’t take them.”² Yet over the following 30 years or more, frustratingly little progress has been made in reliably tracking and successfully increasing medication adherence.

However, the arrival of widespread and increasingly low-cost connectivity (the so-called Internet of Things), coupled with the pervasive use of smart devices such as phones and tablets, now creates an opportunity to change this. Furthermore, the use of connectivity has the potential to demonstrate a direct link between medication adherence and healthcare outcomes. The emergence of the IoT is

ushering in a new era of precision medicine and value-based payments – approaches that pave the way to a more personalised and effective healthcare system.

MULTIPLE FACTORS INFLUENCE ADHERENCE

Part of the challenge is that multiple economic and behavioural factors affect adherence. These vary depending on the drug, disease and delivery method, but include patient concerns about side effects, questions about the efficacy of the drug, difficulty using the delivery device properly, insufficient patient education and engagement, and high out-of-pocket costs.

Non-adherence has significant ramifications, both clinically and economically. For patients, it can result in additional hospitalisations and medical visits, contribute to poor health outcomes or even death, reduce productivity and compromise quality of life. It also



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“Clinical trial data might be sufficient to get a drug approved as safe and effective but may not satisfy the needs of payers. They may demand further trials post-approval to assess the value of medication in real-world conditions.”

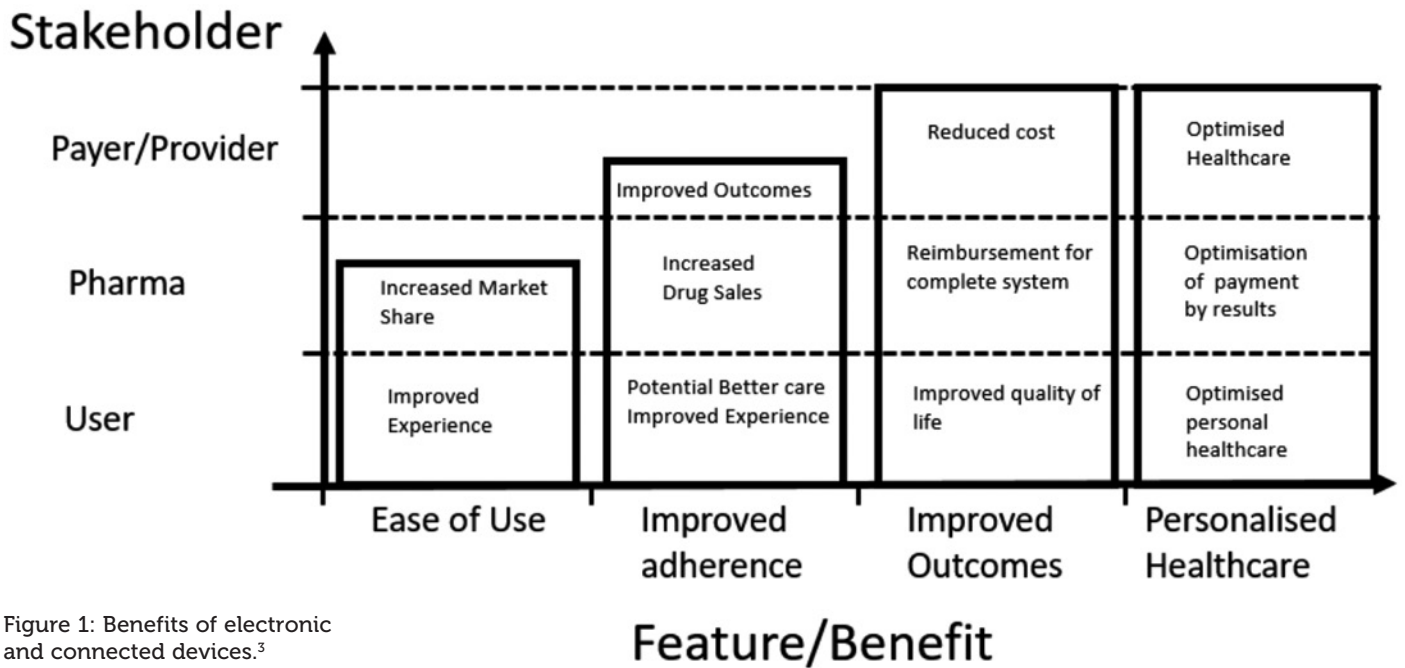


Figure 1: Benefits of electronic and connected devices.³

significantly burdens healthcare systems,³ with estimates of avoidable costs ranging up to US\$290 billion (£233 billion) in the US and €1.25 billion (£1.12 billion) in Europe.⁴ However, accurately estimating the true magnitude of the economic impact on healthcare costs is difficult, due to varying study methodologies and the absence of standardised measures.⁴

Pharmaceutical companies are also affected by non-adherence, losing an estimated 36% in potential sales per drug on average.⁵ This adds up to approximately \$188 billion in annual losses for the US pharmaceutical industry alone.⁶

In the past decade, healthcare has become increasingly digitalised with the implementation of electronic health records (EHR) in many markets, connected devices and equipment in hospitals and laboratories, and smartphones and tablets to support healthcare professionals. At the same time, prescription medication – especially for patients with chronic diseases – is increasingly being taken at home rather than in the hospital, underscoring the need to explore and expand mobile digitalisation outside the hospital as well as within.

Fortunately, the widespread availability of low-cost connectivity such as Bluetooth® and near universal access to mobile technologies such as smartphones have opened the door to new opportunities in this arena. With smartphones already integral to most patients' lives across the globe, the logical next step is to use them as tools to support both medication adherence and disease management.

Belief in the potential of connectivity to improve medication adherence through better usability, medication reminders, remote patient support and other functionalities that support behavioural change has been a primary driver in the development of connected drug delivery devices.

SHIFTING THE FOCUS FROM ADHERENCE TO OUTCOMES

Pharma companies typically establish that drugs are effective by demonstrating therapeutic benefit in controlled clinical trials. However, the outcomes from these studies might be considered “best case” and don't necessarily guarantee similar results under real-world conditions, where complications such as disease comorbidities, variations in treatment pathways, poor education and healthcare funding adversely impact performance. Clinical trial data might be sufficient to get a drug approved as safe and effective but may not satisfy the needs of payers. They may demand further trials post-approval to assess the value of medication in real-world conditions. One approach to resolving this dichotomy is to make clinical trials more representative of real-world treatment, but that risks losing some of the potential offered by new treatments. A better approach is to understand how to address some of the real-world health challenges, such as non-adherence, more effectively.

Where reimbursement is driven by payment by use, improving medication

adherence provides a direct benefit to pharmaceutical companies through increased drug sales and underpins much of their investment in connected delivery systems. It also suggests a better patient experience is making it easier to overcome some of the barriers that negatively impact adherence. However, in isolation, improved adherence is less well aligned to the interests of payers and providers, who are concerned about healthcare outcomes, costs and efficiency.

While it is reasonable to assume that increasing adherence ought to improve health outcomes and move the dial back towards the “best case” results from clinical trials, demonstrating a direct link has proven difficult. Clinical trials have been reported that show a positive impact on outcomes from improved adherence, yet significant doubts remain as to whether this success will scale to real-world healthcare. The cost and complexity of scaling the technology, combined with the real-world healthcare challenges described above, can mask or reduce the benefit. Until these challenges are addressed and more compelling real-world evidence is generated, the likelihood and extent of reimbursement will be limited.

But, as the healthcare industry continues its march towards a value-based payment model in lieu of a volume-based one, the landscape is set to change. Aligning patient, provider and pharma company needs with the healthcare reimbursement process is critical and probably best accomplished by shifting the focus from adherence alone to improving outcomes, as shown in Figure 1.

Adherence is only one part of the story. Developing the quote above from C Everett Koop, it can also be said that drugs don't work in patients who don't respond to them. So, a poor outcome for a therapeutic intervention could be a result of non-adherence and/or non-response. A step beyond value-based healthcare is recognising that patients are not all the same, so prescribing the same dose to all may not be optimal. We need to move toward precision or personalised medicine, where treatment is tailored to individual needs. At present, relatively few drugs beyond insulin used to treat diabetes, are titrated.

As well as providing a better patient experience, connected drug devices can generate reliable data in near real time, allowing providers, payers and pharma companies to understand what works and what doesn't. Medication usage data collected directly from devices and integrated with electronic patient reported outcomes (ePROs) and digital biomarkers can be used to understand medication performance under real-world conditions as

"A step beyond value-based healthcare is recognising that patients are not all the same, so prescribing the same dose to all may not be optimal. We need to move toward precision or personalised medicine."

well as monitor treatment performance on individual and cohort levels.

In addition, these data can be integrated into EHRs, which help aggregate diagnostic data, prescriptions, treatment adherence and outcome measurements. These digital advantages provide a two-fold benefit: the ability to support outcomes-based payment accurately and to deliver more responsive, personalised healthcare.

Looking toward the future, moving from clinical assessments and questionnaire-

based ePROs to smartphone-connected tracking that monitors patient activity, sleep and other behaviour will further quantify medication efficacy. In addition to supporting reimbursement, this data can help healthcare providers tailor and improve the effectiveness of their patient treatment plans – assuming the data can be provided to professionals in an actionable form.

REAL-WORLD RESULTS FROM CONNECTED INJECTORS

Despite the potential benefits, development and adoption of connected drug delivery devices has been relatively limited so far. Typically, connected injection devices are being used for high-value medications for chronic diseases in competitive markets such as multiple sclerosis (MS), human growth hormone deficiency and diabetes, which often already have patient support programmes in place. Integrating connected devices into these existing programmes supports improved patient engagement, enables more evidence-based patient guidance and allows providers to zero-in on patients most in need. However, scaling these interventions and applying them to wider healthcare practice remains challenging.

Four drug-device combination products using electronic autoinjectors have currently been approved for patient use (Figure 2).

A quick look at the BETACONNECT™ Electronic Autoinjector (Bayer, Leverkusen, Germany), developed by Phillips-Medisize, illustrates the advantages of connected autoinjectors. The first connected electronic autoinjector approved in both the US and Europe for the delivery of interferon

"Connected drug devices can generate reliable data in near real time, allowing providers, payers and pharma companies to understand what works and what doesn't. Medication usage data collected directly from devices and integrated with electronic patient reported outcomes (ePROs) and digital biomarkers can be used to understand medication performance under real-world conditions as well as monitor treatment performance on individual and cohort levels."

Integrated Electronic Autoinjectors	Manufacturer	Device Name	CE Mark	License Application	Key Features
	Amgen	AutoTouch®	✗	Supplemental Biological License Application	Electronic drug delivery device for etanercept (Enbrel®). Not currently connected. Audible and visual feedback on injection progress. Battery status indication.
	Bayer	BETACONNECT®	✓ Device CE Mark	Supplemental Biological License Application	Connected, electronic autoinjector for IFN-β-1B that records dosing history (injection date, time, speed, depth). Visual and audible signals indicate that the injection has finished and low battery. Reminder function. Bluetooth transmission to mobile device or USB to computer
	Merck Serono	Easypod®	✓ Device CE Mark	Supplemental Biological License Application	Electronic drug delivery device for rHGH that records dosing history (date, time, dosage) and provides dose reminders. Visual signals plus on-screen feedback with audio cues guide patient through injection process. Data downloaded to the physician's PC via dock.
	Merck Serono	RebiSmart®	✓ Device CE Mark	✗	Electronic drug delivery device for IFN-β-1a that records dosing history (date, time, dosage) and provides dose reminders. Visual signals plus on-screen feedback with audio cues guide patient through injection process. Data downloaded to the physician's PC via dock.

Figure 2: The four approved drug-device combination products using electronic autoinjectors.³

beta-1b for MS, the BETACONNECT system comprises an electronic autoinjector, the myBETAapp™ for patients and the BETACONNECT Navigator, a clinician dashboard (Figure 3).

The connected, patient-centred design offers:

- Ergonomic design with a button in the middle of the device that can be conveniently operated with one hand
- Adjustable injection speed and depth, plus automatic needle insertion and retraction
- Bluetooth connectivity that ensures data on injection time, volume and body location sync with the patient app and clinician dashboard, either wirelessly to a mobile device or via USB to a computer
- Personalised, localised messages and reminders for patients on their device and in the app
- A wellness tracker where patients can record their well-being and selected health parameters.

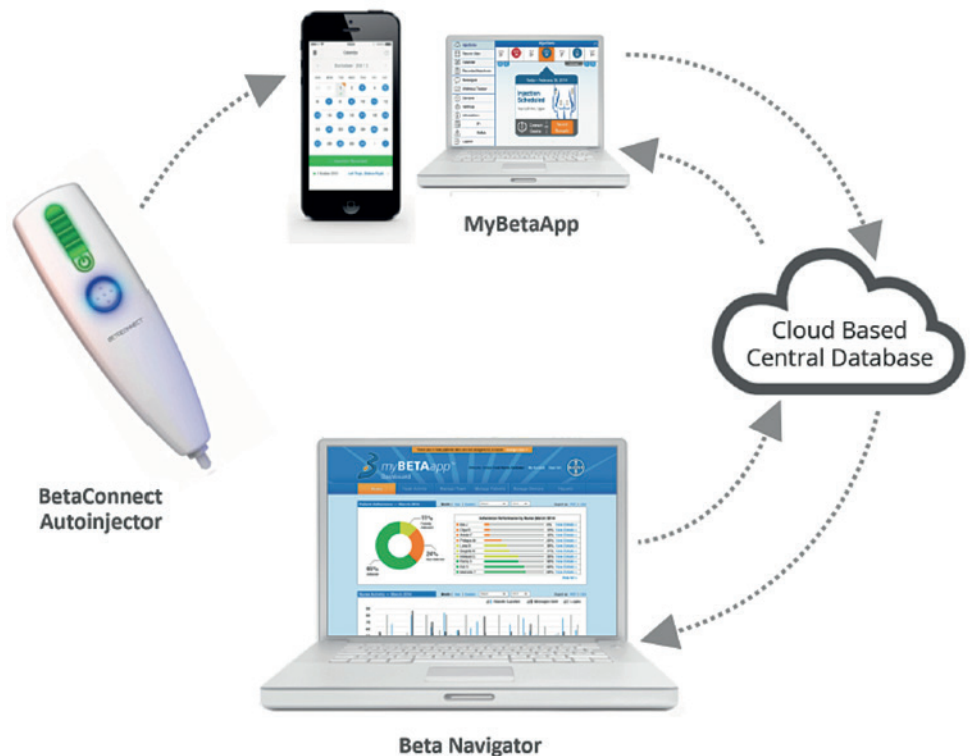


Figure 3: The BETACONNECT system for the treatment of MS.

Research results have been positive. Nearly three-quarters of participants were still using the autoinjector and nearly 60% achieve adherence levels above 80% by the end of one study.⁷ In another study of the myBETAapp, 93% of those who used the app considered it helpful and 87% said it supported their therapy.⁸

As this emerging evidence demonstrates, BETACONNECT has been well-received by patients and can improve medication adherence. However, outcomes-related evidence remains limited, with no head-to-head study data yet published that might show the incremental benefit of connectivity and digital service. Further studies are being conducted to evaluate

long-term adherence as well as treatment outcomes in order to support reimbursement and better identify patients at increased risk of exacerbations or relapses so that timely intervention can be provided.

The pioneering model of BETACONNECT and other current connected health solutions, which link a drug delivery device to an app and cloud data system for a particular purpose such as providing drug usage monitoring or supporting disease management, has opened the door to much wider use of the technology. The approach has been shown to work well for current business models operating in conjunction with patient support programs, demonstrating

the value of the collection of quantitative and actionable data. It is also creating an infrastructure that, once technical, clinical and commercial challenges are overcome, can be utilized more widely, by integrating the approach into healthcare, scaling to larger real-world patient populations and addressing more complex disease management situations, involving multiple medications and comorbidities.

Models that solely rely on pharmaceutical companies getting a return on their investment through increased drug sales, and not through reduced healthcare costs, need to evolve to realise the wider potential of the approach in addressing non-adherence and improving other aspects of healthcare.

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“Models that solely rely on pharmaceutical companies getting a return on their investment through increased drug sales, and not through reduced healthcare costs, limits the wider potential benefits of the approach.”

Greater integration with outcome measures, analytics and the wider healthcare system will enable future connected devices to more effectively engage all the key healthcare stakeholders, including patients, payers, clinicians, pharma companies and technology providers.

CAPITALISING ON CONNECTED HEALTH EXPERIENCE & EXPERTISE

Trailblazers who are willing to invest in the development of additional innovative connected injectable drug devices have a unique opportunity to create a win-win situation for all stakeholders. As with any development project, the right partner is key.

Phillips-Medisize is one of the few companies that has partnered with pharma manufacturers to bring a connected injectable drug delivery system to market successfully. Its end-to-end development and manufacturing capabilities streamline design and production, speeding time to market. In addition, the company's deep knowledge and experience regarding different rules and regulations across global markets enables proper configuration of the product to help reduce project costs and support regulatory approval.

In addition, Phillips-Medisize's ability to manufacture the electronics internally makes connectivity for drug delivery devices far more affordable, supporting wider deployment.

In the four years since BETACONNECT came to market, the company has also created a highly scalable connected health platform that offers numerous benefits, including comprehensive information-sharing and analytics, robust cybersecurity and a modular approach that can be easily customised to multiple therapeutic areas. The company plans to introduce

an app framework that can be tailored to link patients and devices to the platform in a wide range of disease areas. This configurability can reduce the regulatory burden of needing to have the solution reapproved for each new application.

CONCLUSION

Increasingly, evidence demonstrates that connecting injectable drug delivery devices results in higher levels of patient medication adherence and persistence longer term. Consistently high adherence certainly adds value, since medications cannot help patients who don't take them. The next challenge, however, is to generate databased evidence that better adherence improves outcomes.

Although achieving this goal presents challenges, connected injectable drug delivery devices are already playing a critical role in capturing reliable real-world data on medication usage, supporting better decision-making, and more effective use of relatively expensive resources in areas such as patient support programs and healthcare pilot studies. This work is building the infrastructure as well as the evidence base for the linkage between adherence and outcomes, creating the opportunity and investment case for wider uptake in healthcare, with better alignment of reimbursement to the real-world value a therapeutic brings. But most importantly, combined with patient-reported outcomes and digital biomarker data from wearable biosensors, connected drug delivery devices have powerful potential to improve outcomes and quality of life for patients living with chronic disease.

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Iain Simpson is a Director of Front-End Innovation at Phillips-Medisize. He is part of a global team of engineers, designers, researchers and business analysts developing industry leading solutions for drug delivery, digital medicine and Connected Health systems.

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ACCELERATING THE ADOPTION OF CONNECTED COMBINATION PRODUCTS: PATIENTS, MANUFACTURERS & PRACTITIONERS CAN LEAD

In this article, Napoleon Monroe, Managing Director, New Directions Technology Consulting, asks why connectivity has failed to advance rapidly, and argues that many stakeholders can benefit if the adoption of connectivity for drug delivery can be accelerated. While this article will centre on pharmaceutical combination products, the essential points also relate more broadly to pharmaceuticals and medical devices.

As discussed in “*Combination Products Can Benefit Most from Serialisation*”, our October 31, 2017, PDA Letter article, “Four years after the rulemaking and legislation for standardised automatic identification and data capture (AIDC) requirements for prescription pharmaceuticals and medical devices, scanning is minimal.”

Now, six years down the line, this still holds true, scanning is still minimal. Yet enablers for connectivity are in place: device-connected smartphone apps, open APIs regulated by FHIR are known, standardised AIDC including serialisation for the US prescription pharmaceuticals is bound by law, investments in the Internet of Healthcare Things (IoHTs) including remote diagnostic devices have been made, cloud-based big data processing capability is real, and well-developed security systems including blockchain technologies are part of supply and information chains.

Accelerators for connectivity abound: the biotech revolution necessitating patient-used combination products (wearables, implantables, pens, inhalers, autoinjectors, kits) has redefined the point of care to be “wherever the patient is”; regulators are fast-tracking approval; compliance problems and related costs are well publicised; regulators demand real-world evidence; drug price reduction pressures are in the press daily and payers ask for payment-for-outcome programmes; pharma and other stakeholder consolidations provide economies of scale; and disruptors are fundamentally changing healthcare and pharma market structures.

Nonetheless, the tenor of the healthcare connectivity discussions, especially at the

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most recent conferences, has convinced me that the approach of everyone trying to connect everything in healthcare will continue to fail.

There must be a far better way to start somewhere and implement meaningful connectivity, especially for expensive, fragile combination products in patients’ hands. A focus on achievable goals would be more beneficial.

Connecting combination products in the US healthcare systems can be achieved by manufacturers supporting their prescribers and patients. Patients who are prescribed combination products have diseases which are expensive to treat. Capturing



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information on combination products is useful and societally beneficial in the short and longer term.

The global healthcare industry and governments have spent billions of dollars on manufacturing, tracking and regulating pharma and medical devices; and on highly unpopular electronic medical records / electronic healthcare records (EMRs/EHRs). Healthcare manufacturers and distributors have spent millions on placing barcodes, including serialised barcodes, on their prescription products and on devising software to report the data. Yet, thus far, practitioner scanning product bar codes into EMRs and fully integrated supply-chain use by manufacturers and distributors are exceptions, not the accepted best practice standards, meaning that the returns on all these investments are miniscule.

At conference after conference, practitioners, pharmacy benefit managers (PBMs), pharmacies, manufacturers, distributors, patients and patient advocates, industry, taxpayers and their advocates, plan sponsors, regulators, payers, lawyers, lobbyists and other experts bemoan the fact that none of these investments have yielded meaningful improvement in outcomes. And all the while, self-evidently, everyone wants better patient outcomes.

EVERYONE WANTS BETTER PATIENT OUTCOMES

Patients most especially, need help to improve their outcomes. Patients and the combination product manufacturer have the greatest combined financial and outcome interests in the information about the treatment.

The real world is now full of consumer healthcare recording tools, connected medical devices, patient portals, journals and logs, environmental monitors and connected combination products. Consumer behaviour is becoming better recorded, analysed and understood from their combination products, medical devices, consumer devices patient medical records. Every patient is different to some extent.

Patient ownership of their EMR information is finally being promoted in the US by federal policies. But the patient cannot easily aggregate their own data, nor may they understand it fully. Patient data is a major revenue source for the aggregators, but patients are becoming ever more wary of the use of their data.

Practitioners (prescribers), nurse practitioners and physicians' assistants are usually not pharmacists. Patients have multiple prescribers. Patient memory and knowledge is faulty. Compliance is known to be terrible. "Patients lie about the taking of medications", is a rough translation from Hippocrates. Patients forget, they have little experience with medication, and little knowledge of brand and generic names and dosage strengths. This often makes medication reconciliations, when the prescriber asks, "Has anything changed with your meds?", a pointless exercise. Even a review of a previous list of medications for updates is often a waste of time. While practitioners may want to be able to help patients and help limit patient costs, payments to practitioners for drug follow-up are poor.

Clearly, any data captured in a manufacturer-sponsored program should be transferred to the practitioner and the patient's record. Trust in pharma is such that pharma manufacturers may wish to train and reimburse provider call-centre pharmacists.

Pharma manufacturers' profitability is largely tied to specialty drugs, often combination products. Manufacturers want patient and prescriber loyalty, better control of their products, and means to prove and improve the value of products. In many countries, pharma manufacturers have lost much of the control of pricing to the numerous intermediaries that have (in different ways in different countries) structured opaque pricing schemes outside of pharma's control. Pharma manufacturers, while not blameless, get more than their fair share of the blame for price increases.

Direct pharma to patient communication is usually limited (in the US) to non-targeted

DTC advertisements and practitioner office media. In other countries there is no such direct contact at all. Patient communication should be available to practitioners and pharma as well as to the patients and their designated caregivers. Data sharing could, and arguably should, be limited to the manufacturer, the prescriber and the patient and their approved persons.

Manufacturers and their distributors want to secure returns on their investments in products and AIDC.

Combination products are used outside institutions and are therefore subject to myriad human factors issues. Adding connectivity and professional advice can help address the human factors questions. Connectivity allows practitioners and manufacturers to understand the outliers.

Patient package inserts are generally not read. Even if they attempt to read them, the inserts are not understood by the average patient. Patient website searching gives general information which may or may not be applicable to the patient. Manufacturers can assist the practice of medicine and pharmacy by providing truthful professional advice. Such professional advice is not regulated in most countries (e.g. it's not regulated by the FDA in the US). Pharma has an interest in having patient information quickly. Preferably in near real time. This can enable information and assistance to be provided before an adverse event or before someone unknowledgeable misinterprets patient information and starts making erroneous assumptions. Professional intervention through connectivity could allow the pharma company to provide great value while not having to address every regulatory "What if...?"

Pharma is already being asked to assume payment risk in outcomes-based payment plans. Is connectivity costly? Yes, but not so costly as the inability to manage the business. One of the largest manufacturers repeatedly asks me "where is the value in connectivity?" That company just began offshore trials of connectivity.

Connectivity does add cost and complexity to already complex, costly and profitable, combination products. Connectivity also allows manufacturers to avoid the hidden costs of existing system complexities.

Regulators want to improve product safety and efficacy and there is pressure on them to approve new treatments rapidly. Behavioural and social variables are factors in adherence and, in this regard,

"The limitations and costs of randomised clinical trials are moving regulators toward demanding that stakeholders collect and analyse observational real-world data to build real-world evidence for safety and efficacy."

regulators have realised that the prospective approaches of randomised clinical trials are inadequate. In particular, they often do not fully capture information on subsets of populations, which relate to age, ethnicity, sex, co-morbidities, genetic variations, and other factors. This, and other limitations of randomised clinical trials, and also their high costs, are moving regulators toward demanding that stakeholders collect and analyse observational real-world data to build real-world evidence for safety and efficacy. The great unstudied subset is those patients whose social circumstances or behaviours are unusual. There is a clear case for adopting connectivity as soon as possible to get the most favourable outcomes from approved combination products.

Payers want to limit costs. And in the same way that regulators are getting behind real-world data, the trend with regard to payers is also toward building real-world evidence for comparative cost effectiveness. If the manufacturer of a combination product cannot prove their case, the manufacturer of that combination product will suffer. Or, looking at it the other way around, if one manufacturer can demonstrate their product's cost-effectiveness unequivocally by using real-world data, and another cannot, the manufacturer who can is at a distinct advantage. These are realities even before the announced programmes from the US Department of Defense, Veterans' Affairs and EU's Pan-European Public Procurement Online (PEPPOL) initiatives I discussed in my previous ONdrugDelivery articles (see bibliography) take full effect.

Retail pharmacists, PBMs, pharmacy technicians and sales clerks are not diagnosticians. Often the patient-pharmacy interaction is perfunctory: "Do you have any questions today? Next customer please." Home health visits by nurses and pharmacists can be helpful but are just snapshots, not ongoing views, of the patient or of medication performance. Such visits do not update for adverse reactions or lifestyle changes between visits.

Insurers for commercial employee plans are largely processors for plan sponsors. Provider payer insurers are true insurers. Insurers for commercial employee plans are not driven primarily by the patient's needs nor by the patient history. They do not prescribe, but can limit access to certain drugs and can disintermediate other stakeholders from the decision process.

EMR/EHR Companies' products might function well in theory but in practice the data inputted is often incomplete, out of date, inaccurate, inaccessible across providers and to patients, and far from interoperable across multiple providers and pharmacies. The products are not designed to interpret important evidence, and the data is often only accessed at the time of healthcare practitioner (HCP)-patient interaction.

Many EMRs were built primarily to manage payment and, as reported in a March 2019 Fortune Magazine article, are viewed by practitioners as "*Death by a Thousand Clicks*". EMRs contain professional information and are not integrated with personal health records. 99% of daily life for the non-hospitalised patient takes place *in between* their interactions with HCPs but EMRs don't log this or reflect it in any meaningful way. Immediacy of information capture is often essential. Memories fail. You can't write it all down. Yet complete, meaningful medication histories and reconciliations, and an understanding of symptoms and behavioural variables would be valuable to all stakeholders. Connected devices, especially connected combination products, can help deliver this.

Legislators are under political pressure to reduce the total cost of pharmaceuticals, which is building rapidly. And some of the regulatory changes which would enable and incentivise connectivity require legislation. Legislators want to help constituents, they also want to be re-elected. These are sometimes mutually exclusive. The US legislative process is currently at a virtual standstill, lawsuits abound, the cost to achieve legislative resolution will be high, the wait long, and the outcomes uncertain.

Many Other Stakeholders have their own interests. Even not-for-profit entities have financial imperatives and desires to expand. Stakeholders are not monolithic. There are silos of interest within each.

QUESTIONS AND CONCLUSIONS

We are at an inflection point. Expensive specialty products are key to improved health, pharma profitability and healthcare cost containment, and all stakeholders naturally want their own needs to be met. Yet the

"The patient, their prescriber and the pharma company are better positioned to improve the value of a treatment than the myriad other intermediaries. A patient, prescriber pharma co-operation can be better and more effective in promoting compliance and improved outcomes and lowering cost."

complexities of the healthcare marketplace and of healthcare information systems boggle the mind. It seems everyone is collecting data but few are able extract and interpret meaningful evidence. Medical records and prescription medical products are becoming like banking records. Your chequebook and each cheque in it are serialised and prescription drug products are as well.

Connected systems offer a route toward making sense of the real world situation and a route to meeting the needs of many stakeholders. Questions of who has the most to gain or lose from connected systems may determine outcomes for the future of connected healthcare, and the words healthcare systems overall:

- Q. Which stakeholder really has the true patient relationship?
- A. Arguably, in our current reality, no one.
- Q. Who has the most at stake in each patient situation?
- A. The patient.
- Q. Who knows the most about a given drug?
- A. The pharma manufacturer.
- Q. Who knows or should know the most about each individual patient, their activities and related human factors?
- A. Prescribing doctors.
- Q. How can the data received, especially from patients, be validated, secured, understood and used to improve patient and population health?
- A. By pharmacists who are knowledgeable about the drug and the patient receiving and interpreting the data for the patient and the pharma company.

The patient, their prescriber and the pharma company are better positioned to improve the value of a treatment than the myriad other intermediaries. A patient, prescriber pharma co-operation

can be effective in promoting compliance and improved outcomes and lowering cost. Meddling by unknown, unknowing, uninformed data collectors cannot.

One can envisage a new paradigm with software proprietary to pharma (or other) companies, shared with the informed approval of the patient at the time treatment begins and as necessary with prescribing practitioners first and others as treatment progresses. Obviously, the patient and other stakeholders must be assured that their information is secure. An example of a company developing sophisticated security and privacy platforms which could enable this focused data sharing, and linking it with identity proofing and transparency to the blockchain, is WebShield (San Francisco, CA, US).

As discussed in my June 2019 ONdrugDelivery article, “Connectivity Restoring Trust in Pharma Communications”, much trust in pharma has been lost. Becoming more patient centric and better supporting and, within ethical limits, controlling, their products can allow pharma to build trust. Pharma will be well served if it seizes the opportunities presented by connectivity and applies connectivity in its specialty and combination products to make outcomes better.

Transformational medicine requires a focus on achievable goals. In the US healthcare system, and in an increasing number of healthcare systems further afield, connecting specialty and combination products has become an achievable goal, and it can be transformational. Pharma, along with practitioners and patients can lead in the transformation.

ACKNOWLEDGEMENT

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Napoleon Monroe, Managing Director of New Directions Technology Consulting, has a diversified background that extends from developing and producing pharmaceutical product delivery systems, to managing thousands of private brand products for a Fortune 500 company, to building and managing the IP portfolio for a company that is now part of Pfizer. His expertise includes product development, licensing, regulatory processes as business opportunities, risk management and international marketing, with experience managing business relationships in more than 30 countries. Mr Monroe has led teams that have invented and commercialised major products, such as the (pre-Mylan) EpiPen, and nerve agent antidote autoinjectors for the US and allied countries. New Directions holds patents related to medication telemanagement.



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ADDING VALUE TO PREFILLED SYRINGES: SAFETY AND CONNECTIVITY

Here, Chantal Wierckx and Arnaud Guillet, both Business Development Directors at Biocorp, provide an update on Newguard™, the company's integrated safety device for prefilled syringes, and explore the possible advantages connectivity can bring in the context of traceability for anti-counterfeiting, in clinical trials and in vaccination campaigns.

The prefilled syringes (PFS) market keeps growing according to the estimates given by various market forecasts, now reaching a global value of around US\$5 billion (£4 billion). The main driver underlying the observed trend is the growth of the list of injectable products with more biologic products than ever being approved by regulatory bodies. A wider geographic coverage of PFSs is also driving the growth of the market in emerging countries.

In addition to this, prefilled syringes offer multiple benefits to pharmaceutical companies, healthcare professionals (HCPs) and end-users to treat or prevent illness. This includes being ready to use, which provides a quick way to inject medications in an emergency. The fact that no drug needs to be transferred from a vial to a delivery system is also beneficial as it is easy to use and leads to a reduction in dosing errors and potential contamination. Furthermore,

the prefilled syringes contain the precise quantity to be delivered, resulting in a big reduction in wasting valuable product.

INTEGRATING A SAFETY DEVICE

Safety is an important consideration with prefilled syringes. Any person handling sharp devices such as needles are exposed to injuries that could lead them to being infected with blood-borne pathogens. To meet this need, Biocorp has developed Newguard™, which is a reliable, integrated safety device compatible with standard prefilled syringes

“Wireless technologies such as Wi-Fi, Bluetooth low energy (BLE) and near field communication (NFC) are now being increasingly used in healthcare.”

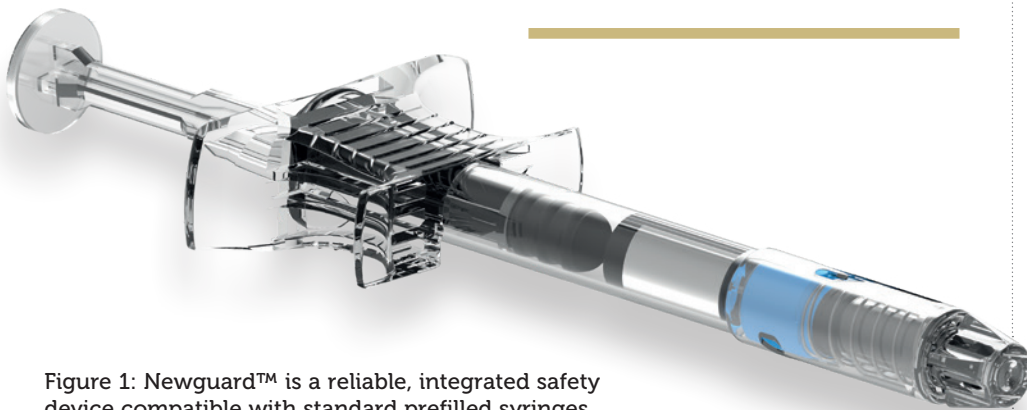


Figure 1: Newguard™ is a reliable, integrated safety device compatible with standard prefilled syringes.



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designed to prevent accidental needlestick injuries and any unintended re-use (Figure 1). Its user benefits include:

- Ease of use
- Passivity of the system
- Guarantee of safety before, during and after the injection
- Compact size for optimal storage
- Transparency to correctly see the needle tip (Figure 2).

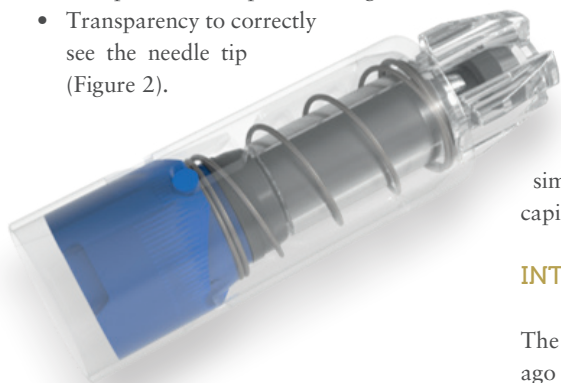


Figure 2: The needle-safety mechanism of Newguard™ is transparent to allow the tip to be seen.

In terms of manufacturing benefits, Newguard™ meets the requirement to fit the standard PFS nests and tubs, it is compatible with various sterilisation processes, fits the conventional packaging formats and respects the conventional filling equipment and processes.

Adding a safety device to a syringe may have significant consequences for the manufacturer and lead to the need for changes of the industrial production and filling processes of the PFS. However, Biocorp took this requirement into consideration during its development, and made sure that the assembly of the Newguard™ safety

“Adding traceability to a PFS could play a key anti-counterfeiting role, minimising the spread of fake medicines. Other benefits include monitoring the delivery of expensive biologics, ensuring the efficacy of vaccination campaigns and improving the efficiency of clinical trials.”

“Many pharma companies are looking for innovative technological solutions to ensure the protection and traceability of products, to identify fake products and to secure the supply and distribution chain.”

system together with a PFS doesn't require any specific investment. For this reason, this product is ideal for companies that haven't invested yet in safety systems but need simple solutions to implement with low capital expenditure requirements.

INTRODUCING CONNECTIVITY

The move to e-health began a while ago when providers started to look for ways to diagnose, monitor and treat patients with connected medical devices. Wireless technologies such as Wi-Fi, Bluetooth low energy (BLE) and near field communication (NFC) are now being increasingly used in healthcare.

Biocorp is very proud to have been at the forefront of developing drug delivery device applications of these cutting-edge technologies and is now leading the way delivering connected solutions to pharma. For example, the Biocorp Mallya™ device (Figure 3) is a smart sensor that turns conventional injection pens into connected devices by recording key treatment information (selected dose, date and time of injection) and sending the data in real time to a dedicated mobile application. Biocorp recently obtained a CE0469 mark for Mallya™ as a medical device class IIb, with the first launch being scheduled for insulin pens. It is also easy to adapt Mallya™ to other pen applications such as fertility, weight loss, multiple sclerosis, growth hormone and Parkinson's disease. Furthermore, with innovative technological changes, more medical devices such as connected infusion pumps, glucose monitors, inhalers, blood pressure monitors or thermometers will be able to generate, collect, analyse or transmit data.

However, this important connectivity feature for standard prefilled syringes is still missing. There is no way to gather key information automatically about the appropriate usage and delivery of the drug in a PFS format. It would be useful to know – for both the physician and the patient – whether the syringe was correctly used, if the drug was totally delivered, and the time and date of injection.

USING CONNECTIVITY TO IMPROVE TRACEABILITY

Many pharma companies are looking for innovative technological solutions to ensure the protection and traceability of products, to identify fake products and to secure the supply and distribution chain.

Biocorp is currently exploring the possibilities offered by tracing PFS devices using the Unique Device Identification (UDI), which can be included into the readable data of the connected device. The American and European Medical Devices Regulation introduced the need for a device traceability system based on UDI to allow for the unambiguous identification of a specific device on the market.

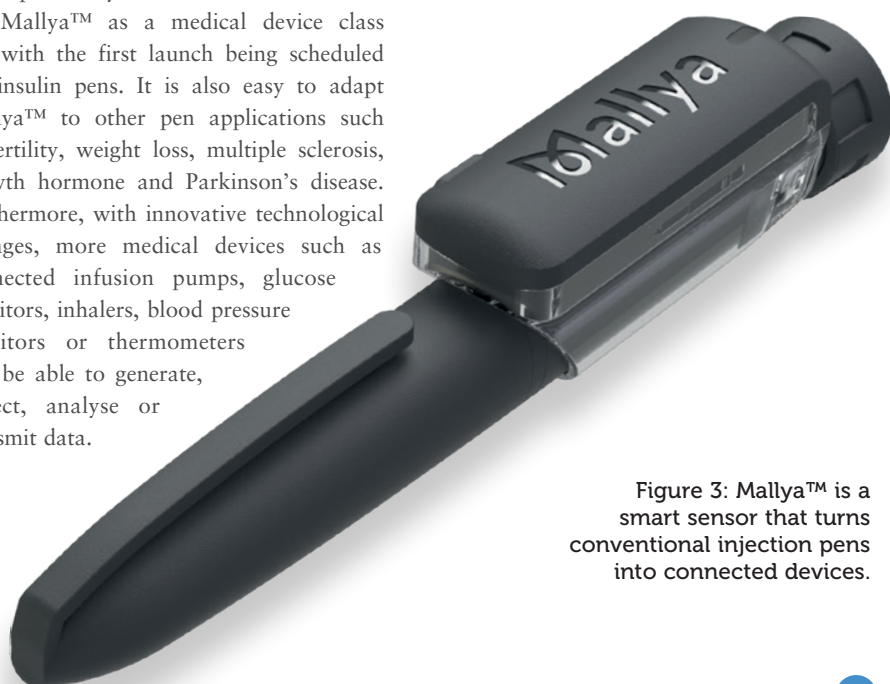


Figure 3: Mallya™ is a smart sensor that turns conventional injection pens into connected devices.

BENEFITS OF PROVIDING TRACEABILITY

Adding traceability to a PFS could play a key anti-counterfeiting role, minimising the spread of fake medicines. Other benefits include monitoring the delivery of expensive biologics, ensuring the efficacy of vaccination campaigns and improving the efficiency of clinical trials.

Anti-Counterfeiting

A UDI includes a device identifier (DI) – a static part of the UDI number that identifies the specific device among a product range. It also includes any applicable production identifiers (PIs) such as lot number, serial number, manufacturing date and expiration date. Such identifiers could also be linked to key information and documents such as certificates, declaration of conformity and technical documentation. A companion software application linked with the connected syringe could potentially detect if the PFS is on the administration list or may be part of a possible counterfeit medicine.

Delivery of Drugs

It would be particularly useful to know if biologic drugs are delivered successfully as they are very expensive, especially for pharma companies and payers who have a direct incentive to know if a drug has been correctly administered. Medication errors happen too often, even with treatments administered by professionals. For each injection, careful attention must be paid to ensure it's the right patient, the right drug, the right time, the right dose and the right route. Therefore, connected technology would help decrease errors in administration as patients can be better monitored and linked with the drug administered. This leads to more efficacious therapeutics and better cost control for payers.

Vaccination Campaigns

In terms of vaccination campaigns, a connected PFS would significantly help to ensure traceability. Mass immunisation campaigns pose specific traceability challenges, due to their objective of immunising large populations over a short period of time and the fact they are often conducted outside the normal healthcare setting. As a result, the coverage of highly recommended vaccines is frequently inadequate and incomplete, which leaves significant portions of the population at risk.

“With a connected PFS, pharmaceutical companies can consider alternative study designs, such as organising clinical trials in real-life conditions. Instead of bringing patients into clinical facilities, they could provide a batch of connected PFS and remotely monitor treatment delivery at home.”

Instead, with connected PFSs, immediate upload of vaccine data becomes possible, directly filled in to an application associated with the patient's name. This would enable HCPs to maintain thorough and up-to-date vaccination records for each patient and avoid missed or incomplete immunisations. The data collected could feed directly into vaccine management systems or patient's electronic health records (EHR).

Clinical Trials

There is also an evident opportunity for connectivity in collecting dose delivery data during clinical trials and observational studies to better follow and understand treatment efficiency results and potential underdosage incidents. Clinical trials may compare a new medical approach: with a standard one that is already available; with a placebo that contains no active ingredient; or with no intervention. Some clinical trials compare interventions that are already available. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful or no different than available alternatives. The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants.

The automated detection and collection of the key treatment delivery information would be a real advantage in this situation. This would save time and avoid loss of data, incomplete records and gaps in the information collected. The collection and reporting of treatment delivery information and the aggregation of data into the clinical file would be much simpler and faster. Thus, the solution is likely to reduce the number of clinical operators involved in the study, making it more cost effective.

With a connected PFS, pharmaceutical companies can consider alternative study designs, such as organising clinical trials in real-life conditions. Instead of bringing patients into clinical facilities, they could provide a batch of connected PFS and remotely monitor treatment delivery at home. If some issues with treatment compliance are observed, the clinical operators can quickly interact with patients to remedy the situation and put them back on track. Studies in real-life conditions can help pharma companies identify all the factors that negatively impact drug efficacy and provide the appropriate services and corrective measures before commercial launch. They could also give precious information for potential post-approval/Phase IV studies.

ABOUT THE AUTHORS

Chantal Wierckx is Business Development Director at Biocorp in charge of the innovative non-connected and conventional pharmaceutical devices range. She leads sales and client relations, proposes new strategic partnerships and tracks new market opportunities and emerging trends to recommend new product development. Ms Wierckx studied at the HEBO (The Hague, The Netherlands), a unique, international and interdisciplinary European Studies School, teaching knowledge and skills to start international careers in business management, marketing, communications and/or policy advice.

Arnaud Guillet is Business Development Director at Biocorp, in charge of finding partnerships and license opportunities for Biocorp's range of connected devices. Previously, Mr Guillet worked for a healthcare consulting firm with a strong focus on connected health strategies for pharma and insurance companies and has additional past experience in the pharmaceutical industry (with Sanofi) and the insurance industry (with AXA). He graduated from HEC Paris, a major European business school.

DEVELOPING A CONNECTED PREFILLED SYRINGE

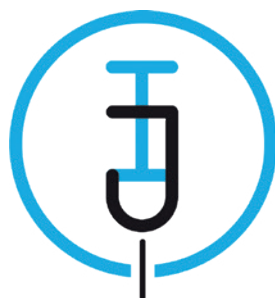
Earlier this year, Biocorp put together its teams to generate innovative ideas that meet the existing needs for an e-PFS. Team members care passionately about doing work that helps others, and commit to ensuring a high level of quality during the design, development and manufacturing phases of a new product. Biocorp has the strength and the ability to adapt to ever-changing techniques and constraints maintaining a keen focus on delivering user-friendly products with maximum simplicity.

To be successful, a connected PFS must meet various functional requirements. It must collect essential information such as injection completed, time and date, type of drug, its batch number and expiration date. In addition, it must meet user requirements such as ergonomic handling, being intuitive and leveraging existing prefilled syringe features. On the manufacturing side, the components required for adding connectivity must be validated and fit the conventional nest and secondary packaging.

Moreover, similar to the Newguard™ safety device, the connectivity components should not interfere with the filling line process.

CONCLUSION

Biocorp is planning to commercialise connectivity features for PFS as early as the beginning of 2020. More detailed information will be revealed during the product launch at the *PDA Universe of Pre-Filled Syringes & Injection Devices* conference in Gothenburg, Sweden, on October 21, 2019, and during the event on October 22-23, 2019.



Biocorp will then continue to extend its range of products and intends to

supply combined safety and connectivity solutions “all-in-one” for standard prefilled syringes to serve the needs of our customers around the globe, for the benefit of their patients.

ABOUT THE COMPANY

Biocorp specialises in the development and manufacturing of medical devices and innovative drug delivery systems. With nearly 25 years of experience, more than 30 million units produced each year and 12 patent families, Biocorp is a key player in the industry, providing drug delivery solutions that meet the evolving needs of patients. Biocorp is constantly innovating on medical plastics, its core business and to market traditional devices (alternative to aluminum capsules, syringe and vial administration systems). Our strong expertise and innovative capacity have also allowed us to develop a range of connected products, including Mallya™, a smart cap for pen injectors that captures injection data and automatically transmits data to a mobile app.

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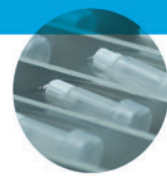
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SIMPLIFYING THE PROCESS OF DEVELOPING PREFILLED SYRINGES

The use of cyclic olefin polymer delivery systems is gaining in popularity because of the benefits they have over glass systems for complex drug applications. Tibor Hlobik, Senior Director, Product Management, West Pharmaceutical Services, explains what this advance in technology can offer drug manufacturers and how the company can simplify the process of drug development.

Selecting the best materials for packaging and delivering drugs is critical in improving stability and performance risks. Sensitive drugs, and in particular biologics, are often complex entities and more challenging to administer. Choosing materials that present the lowest possible risk of interaction, such as low surface energy cyclic olefin barrels and barrier-coated elastomeric plungers, is critical for success.

Delivery systems based on cyclic olefin polymers (COPs) are therefore becoming increasingly popular because these materials can meet the challenges of providing the quality, safety and reliability needed for complex therapeutic applications.

Whether preparing for clinical trials or drug product commercialisation, there is now a wide platform of polymer systems commercially available and ready to use off-the-shelf, to meet unique user requirements, and complimentary support and service offerings to help navigate work required during development of

products, for commercialisation and drug lifecycle management. The variety of options and treatment applications (Figure 1) include:

- Vial systems in a range of sizes with low extractables and low subvisible particles for storage at low temperatures for cell and gene therapies
- Small volume 0.5 mL and 1 mL prefillable Luer lock syringes used in ocular injections with ophthalmic treatments where there is high sensitivity to silicone oil
- 1 mL long and 2.25 mL prefillable insert needle syringes used to administer treatments with auto-injectors where syringe breakage is a concern for high viscosity drugs
- 3.5 mL and 10 mL cartridges for wearable large volume, on-body patient-controlled injectors that enable precise drug delivery over longer time periods for biologic pipeline drugs and intravenous to subcutaneous product conversions.

“West is uniquely positioned to provide fill/finish support services and can assist drug developers with small-scale sample preparation for product testing, line implementation at a customer site, third-party clinical and commercial filling, support testing and programme management.”



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Figure 1: West's offering of polymer base primary containers and delivery systems includes vials, prefilled syringes, and cartridges.

BENEFITS OF POLYMER SYRINGES

COPs offer advantages over glass thanks to a number of attributes and design features. High-quality COPs such as the Daikyo Crystal Zenith® syringe systems, are designed to overcome complex challenges, provide solutions for unique user requirements and add value to complex and sensitive biologics. This includes the absence of silicone oil in Daikyo Crystal Zenith® syringes, which results in decreased interaction with the drug product and enhanced cleanliness.

The Daikyo Crystal Zenith® Insert Needle Syringe system supplied with Flurotec® pistons is designed to maintain the purity, integrity and efficacy of premium biopharmaceutical therapies and can be coupled with an autoinjector device that provides greater patient convenience and ease of use through self-administration.

The syringe system minimises the potential contamination issues associated with other container materials and helps to reduce the risk of product interactions and performance issues. This helps to meet drug product performance needs that include:

- Tighter dimensional tolerances
- Higher break resistance
- Silicone oil-free barrels
- Tungsten and glue free
- Repeatable functional performance
- Higher fill volume threshold.

Ophthalmic applications present a whole new set of challenges. The majority of intravitreal injections are anti-VEGF drugs packaged in either a vial format, using either a polypropylene, heavily siliconised syringe, or a siliconised Luer lock prefilled syringe with attached needle. However, silicone oil has been associated with

floaters in patients' vision. The Daikyo Crystal Zenith® Luer Lock 0.5 mL syringe system can provide improved dose accuracy and higher final drug product quality. It is also silicone oil free, has low endotoxin limits, low sub-visible and visible particle limits, and offers repeatable functional performance.

MANAGING THE DEVELOPMENT OF COMPLEX PRODUCTS

West provides a complementary support service to help with the development of products for commercialisation and drug lifecycle management (Figure 2). Partnering with a company that not only provides the product, but also expertise in material science, primary packaging, delivery systems and experience in services to support pharmaceutical companies has many advantages.

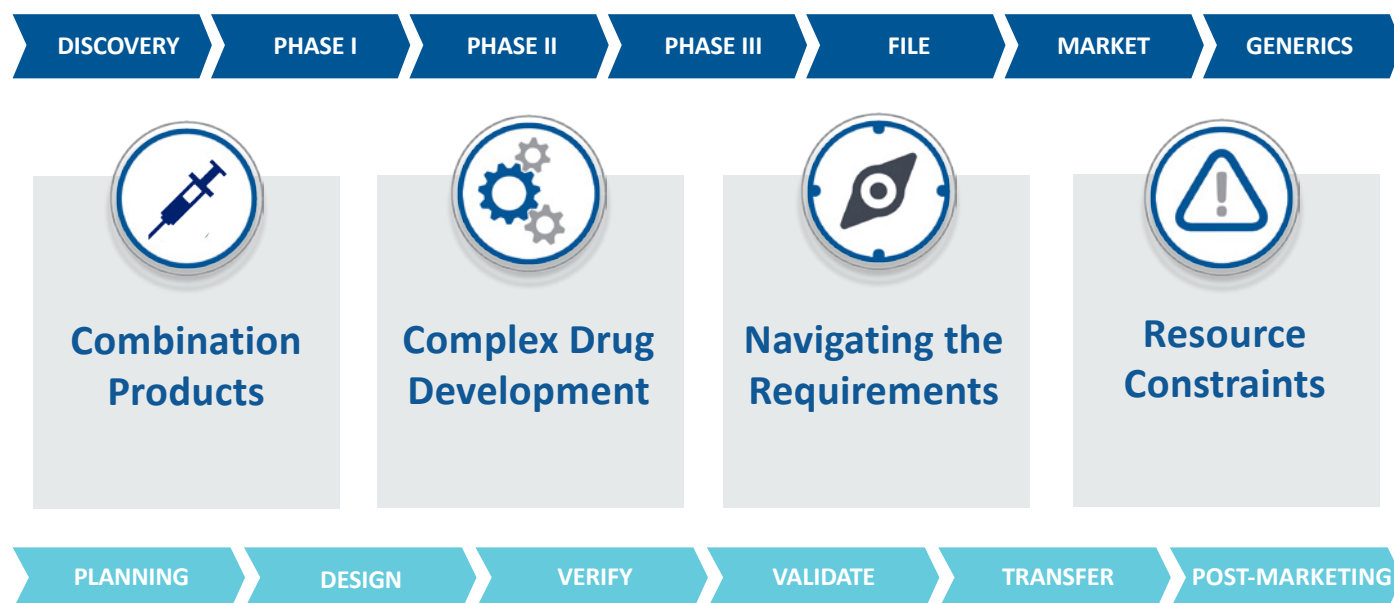


Figure 2: With programmes designed for any stage of the drug development lifecycle and across all injectable formats, West can help you Simplify the Journey™.

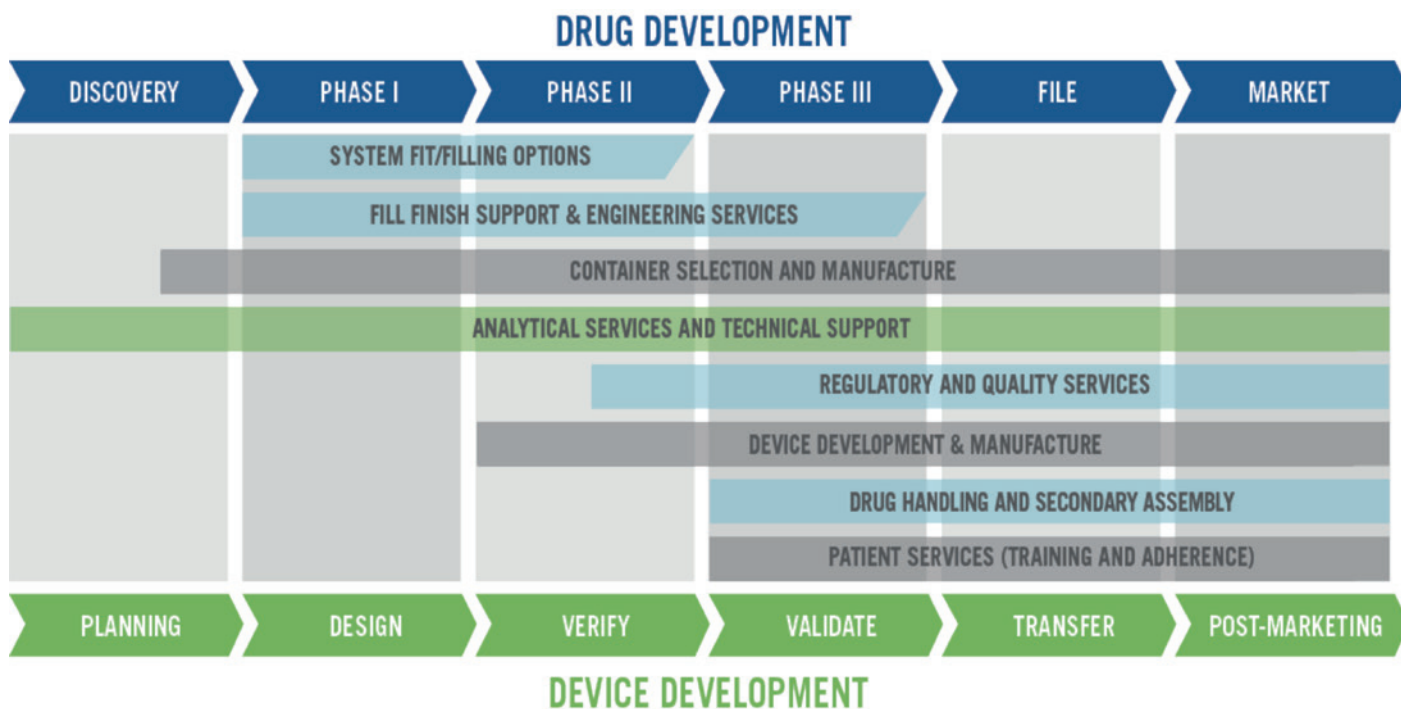


Figure 3: West can provide its clients with services throughout the drug development process.

“Partnering with a company that not only provides the product, but also expertise in material science, primary packaging, delivery systems and experience in services to support pharmaceutical companies has many advantages.”

A single partner can reduce development and supply risk, reduce total cost of ownership and accelerate your path to market. West now offers a comprehensive approach of integrated solutions to Simplify the Journey™ (Figure 3).

Evaluation from Development to Commercialisation

It is important to document the early baseline verification data, typically generated in Phase II studies. These studies should show that the selected syringe system meets intended user requirements and should include performance evaluation, functionality characterisation as well as identify any associated chemical compatibility concerns.

The packaging and delivery system also needs to be evaluated against the baseline data and defined critical quality attributes (CQAs), before the drug product/device manufacturing is scaled-up for regulatory submission.

Phase III studies include performance testing of the drug product and syringe

system during both real-time and accelerated conditions over the shelf-life of the product (Figure 4). Real-time conditions should include test intervals up to 36 months and accelerated conditions up to six months for functionality and performance, extractables and leachables, particulate and silicone oil analysis, dose accuracy and system integrity evaluations.

Other tests available, depending on programme requirements, include bacterial endotoxin, biocompatibility, and shipping simulations based on ASTM standards. The latter includes:

- Environmental conditioning
- Shipping and handling
- Low pressure, high altitude testing
- Post shipping analyses, including:
 - Particles in solution
 - Container closure integrity testing
 - Helium leak detection
 - Inspection (plunger placement and leakage, and needle shield or tip-cap placement and leakage).

Fill/Finishing Solutions

Finding fill/finish options for the broad variety of drug product packaging and containment options on the market can be a challenge for drug developers, particularly for novel formats that provide differentiation and improved patient experience but may have unique fill/finish requirements.

West is uniquely positioned to provide fill/finish support services and can assist drug developers with small-scale sample preparation for product testing, line implementation at a customer site, third-party clinical and commercial filling, support testing and programme management. This is because West has lab-scale fill/finish capability, an established third-party network and expertise in fill/finish requirements for innovative containment systems such as the Daikyo Crystal Zenith® polymer syringe technology.

Post-Market – Continuing the Journey

It is important to use the data and knowledge gained in product development and scale-up to keep improving the product and process. The standards that need to be met in technical transfers and change control processes are provided by the CQAs of the drug and the delivery system output requirements. In addition, ICH Q12 outlines the regulatory expectation for continuous management of a product over its lifecycle. The following services can also be offered:

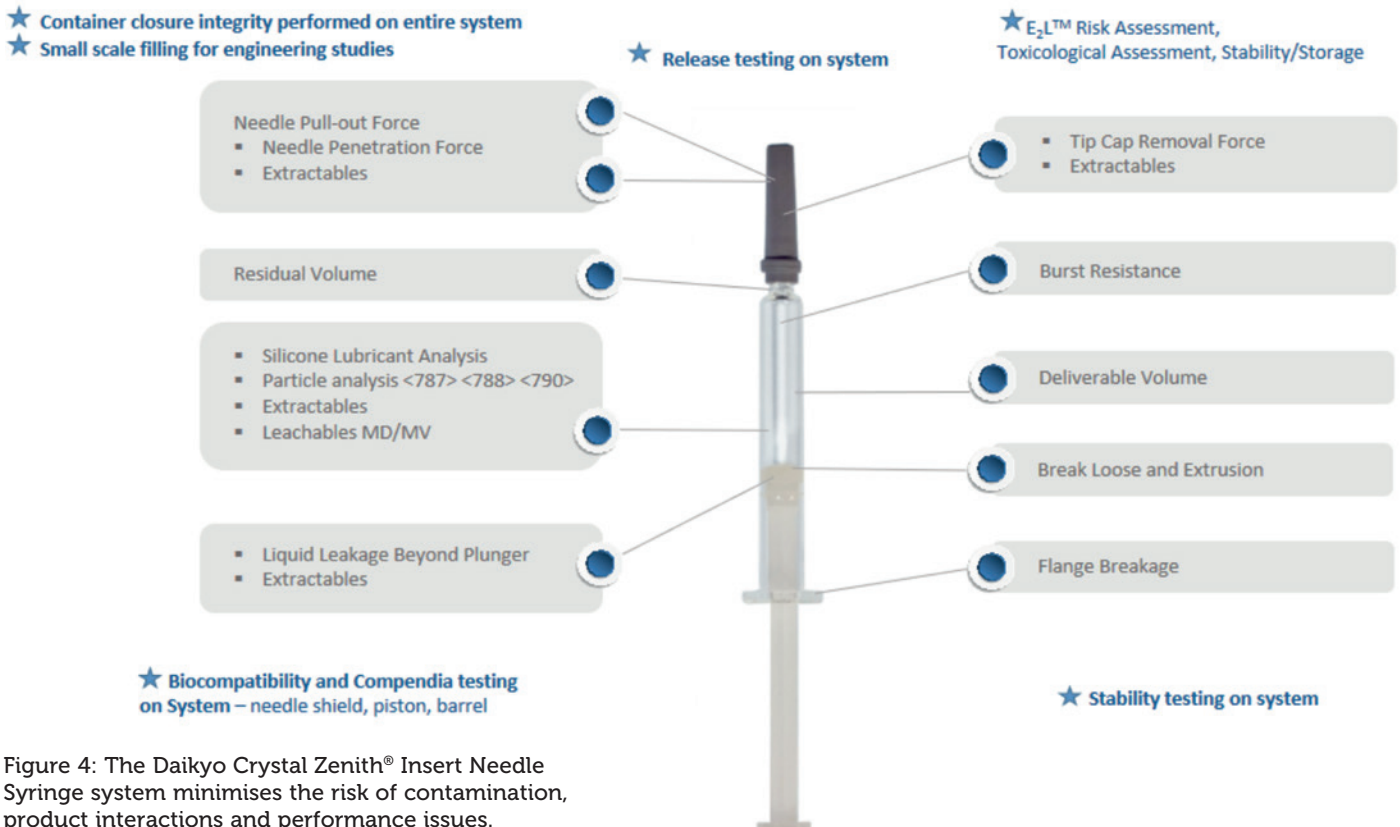


Figure 4: The Daikyo Crystal Zenith® Insert Needle Syringe system minimises the risk of contamination, product interactions and performance issues.

- Device manufacturing and assembly
- Drug and device packaging solutions
- Device serialisation
- Drug handling, including cold storage
- Quality control release testing
- Regulatory services
- Support of tech transfers or change management
- Release testing based on customer requirement.

CONCLUSION

Greater scrutiny needs to be paid to the interaction between a drug and its container closure system. Drug stability over its shelf life, particulate burden, the prevention of breakage and ease of delivery are important factors to consider. In addition, regulatory agencies and pharmaceutical companies have increased quality expectations to enhance patient safety.

Through break resistance, superior functional performance, highly reduced extractables and the availability of sterile formats, polymer syringes present

attractive benefits that are gaining increased attention from manufacturers seeking new answers to increasing drug delivery and administration challenges.

The West Integrated Solutions programme brings together West's primary packaging, device, analytical, regulatory and contract manufacturing expertise in a single-source solution. With programmes designed for any stage of the drug development lifecycle and across all injectable formats, West can help you Simplify the Journey™ at any stage of drug development.

ABOUT THE COMPANY

West Pharmaceutical Services, Inc. is a manufacturer of packaging components and delivery systems for injectable drugs and healthcare products. Working by the side of the world's leading pharmaceutical, biotechnology, generic drug and medical device producers from concept to patient, West creates products that promote the efficiency, reliability and safety of the global

pharmaceutical drug supply. In addition, West provides a comprehensive Integrated Solutions Program that combines high-quality packaging and delivery systems with analytical testing, device manufacturing and assembly, and regulatory services to support customers throughout the drug development lifecycle.

West is headquartered in Exton, PA, US, and supports its customers from locations in North and South America, Europe, Asia and Australia. West's 2018 net sales of US\$1.7 billion reflect the daily use of approximately 112 million of its components and devices, which are designed to improve the delivery of healthcare to patients around the world.

SmartDose® is a registered trademark of West Pharma. Services IL, Ltd., a subsidiary of West Pharmaceutical Services, Inc., in the United States and other jurisdictions.

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ABOUT THE AUTHOR

Tibor Hlobik is Senior Director, Product Management at West Pharmaceutical Services. He has worked within the pharmaceutical packaging industry for thirty years in areas of research and development, corporate quality, technical services and marketing primarily at West Pharmaceutical Services. He has extensive knowledge and experience with prefilled syringe systems and cartridge-based solutions, and related technologies.

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ASSESSING USABILITY EARLY FOR OPTIMAL INJECTION PEN DESIGN

To meet the need for effective delivery systems that optimise the benefits of new drugs and the growth in patient self-injection, combination drug delivery represents a significant opportunity. However, it is important to undertake a full use-related risk analysis for these products to assess their usability and identify any risks. Using the example of Haselmeier's D-Flex system, David Fink, Vice-President Strategic Development at Ximedica, and Stefan Gaul, Head of Strategic Product Management at Haselmeier, highlight the importance of considering usability right from the start.

Mistakes in the dose or method of using a drug were recognised almost two decades ago as significant errors in patient treatment, carrying serious consequences.¹ Adverse drug events (ADEs) may number in the millions across the US alone in care settings ranging from hospitals to long-term care facilities.² Adding to the milieu is the growth in self-injection, with effective treatment dependent on patients understanding the correct application process.

To address this risk, the rise in human-centred engineering practices in medical device development, combination drug delivery and associated treatments is acknowledged to be a key factor in improving treatment safety and efficacy. Regulatory bodies are leading that process, tying approval to effective application of human factors and usability engineering (HF&UE) practices through guidance documents³⁻⁶ for both the product and its associated packaging and labelling.

One element of this guidance is the application of use related risk analysis for effective product design and clear presentation (e.g. labelling, packaging and instructions for use) to the defined end users. Undertaking this analysis requires an understanding of the intended user, use environment and use flow of the selected device, and assessing the risk of anticipated errors that will guide potential solutions to mitigate those risks.

To understand how this process works, we will focus on a novel injection device design (Haselmeier D-Flex) that presents a flexible injection platform ideally suited to targeted therapies where HF&UE and consideration of potential usability issues were applied from the inception of the concept.

DEVELOPING A USE-CASE APPROACH

Haselmeier, with a long history of developing and producing injection pen devices, viewed emerging market trends as an opportunity to identify unmet or hidden needs which could be addressed in terms of improving usability and reducing injection errors.

Haselmeier's strategic product management team investigated the market to identify indications of strategic relevance to be considered in the development of an innovative platform. This strategic consideration³ was matched with general trends such as changes in administration method, volume and viscosity, the frequency of administration, as well as comparisons

"Fixed-dose pens are limiting, while variable-dose pen injectors have such a broad array of dose choices that this may create confusion and errors. Haselmeier saw this as an opportunity to strike a new path."



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with other devices available on the market. These insights comprised a basis to identify any promising business opportunities, resulting in a corresponding use case.

In order to design and develop an effective and valuable product or service that is desired in the market, the design team needs to consider the relevant use cases to know what needs to be developed. The use case is a full definition of the process including:

- The involved stakeholders
- The patient journey including use flow of the intended system
- The use environment
- Motivations, needs, opportunities and especially risks in effectively administering treatment.

During this exercise, the patient must be in the centre of all considerations and this is the success criterion to generate a valid value proposition which translates into a positive and beneficial business case. In effect, an effective use case will drive the business case.

Haselmeier's disposable D-Flex pen for subcutaneous injection is a good example of how the injection treatment success rate could be increased by following a market and use case-driven, patient-centred approach. The identification and understanding of the involved stakeholders, patient journey, needs and risks led to a unique device platform not currently available on the market.

HASELMEIER'S D-FLEX SYSTEM

D-Flex (discussed further in this issue, pp 82-86) is a manual injection pen platform for the administration of a small number of selected doses (Figure 1). But what makes the D-Flex a unique manual injection pen?

In some therapies, a finely adjusted variable dose is specified. Typically, a variable dose injection pen will be used for that kind of application. However, those injection devices have myriad injection volumes for the patient or healthcare practitioner to use accurately. Presenting too many choices opens up significant potential for use error in applying the wrong dose. Other therapies require just one fixed dose. In this case a fixed-dose injection pen is used. However, an increasing number of therapies prescribe a limited number of fixed doses. The emergence of biologics and targeted, patient-specific treatment regimens accentuate that need.



Figure 1: The D-Flex injection pen is designed for the administration of a small number of selected doses.

So, fixed-dose pens are limiting, while variable-dose pen injectors have such a broad array of dose choices that this may create confusion and errors. Haselmeier saw this as an opportunity to strike a new path and leverage the needs of different kinds of therapies, pharmaceutical customers and patients. The D-Flex manual injector pen platform brings the worlds of fixed-dose and limited variable-dose pens together with a design that makes it very easy to select one fixed or several fixed doses on the same device and includes a mechanism which prevents the selection of unintended doses.

The final D-Flex solution reveals just one internal component which determines the dose regimen – the dose selector

(Figure 2). Each specific dose regimen can be easily accommodated by only changing the dose selector.

Additionally, the internal D-Flex torsion spring reduces misuse and incorrect dose selection by using the tactile feel of a distinct “click”, thereby significantly reducing the potential error rate. That means that users cannot set a dose between two fixed doses as no clicks secure these in-between doses and the torsion spring turns the setting back to the next lower dose which is built into the device. It represents a significant design contribution to reducing potential use errors.

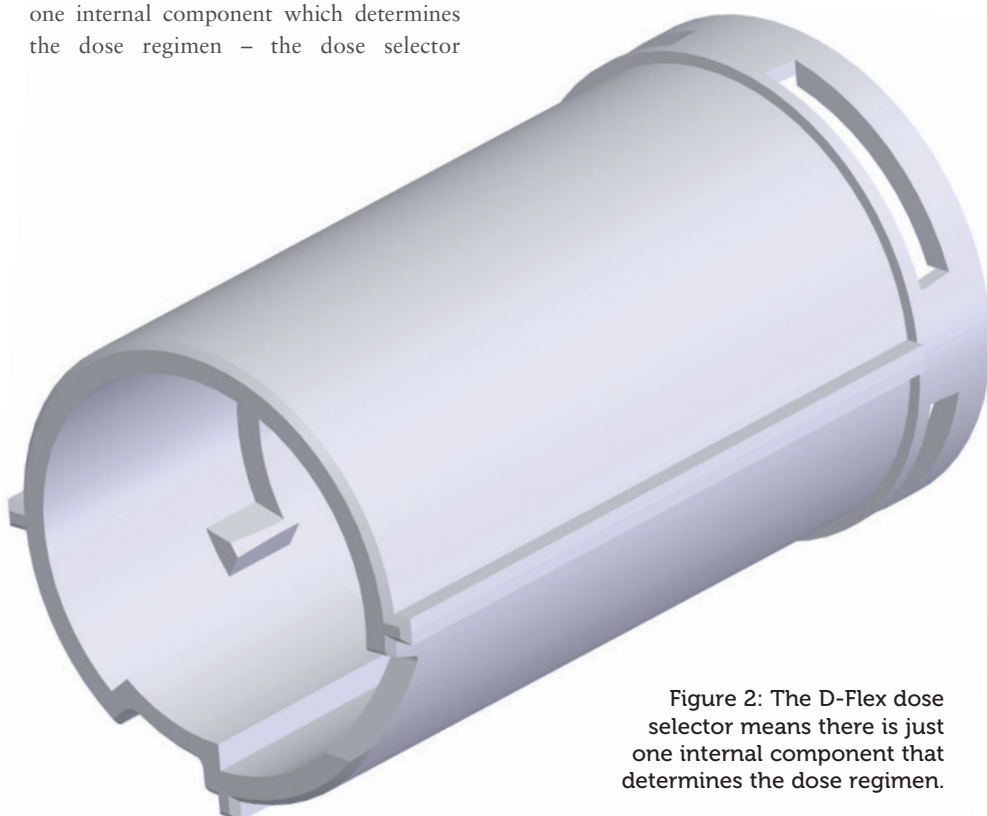


Figure 2: The D-Flex dose selector means there is just one internal component that determines the dose regimen.

From a business perspective, D-Flex offers a flexible platform that accompanies customers through their entire product development process, product launch, platform lifecycle phases and even in cases of new applications. The dose setting can easily be adjusted throughout every phase of the clinical study with the one-part change in the pen assembly. Customers can use one variant in Phase II and another variant in Phase III of the clinical trials. The attractive usability features of the D-Flex remain unchanged across that clinical continuum. The D-Flex platform also allows for variation in total volumes in the pen assembly to accommodate a larger number of potential drug options. This level of flexibility reduces risk, saves money and reduces time to market.

A HUMAN FACTORS STUDY OF THE D-FLEX SYSTEM

Early on in the innovation project, the design was tested in a human factors study (HFS) to consider potential design changes and concept adaptations to be integrated in corresponding design loops.

One of the potential applications of D-Flex device is for the delivery of GLP-1 receptor agonists such as liraglutide in diabetes. Liraglutide is taken daily starting at 0.6 mg for one week to help gastrointestinal tolerability then moving to a maintenance dose of 1.2 mg, or 1.8 mg depending on the need for further glycaemic control. D-Flex is an attractive device to use for this application as the three doses could be set

“The encouraging results of the D-Flex human factors study confirm the importance of the early research and show the value of gathering a deep understanding of the corresponding use case...”

in the factory using the previously described dose selector so that patients could not select a dose in-between one of these three specified doses.

Aim

Haselmeier elected to run an HF study to assess the usability of the dose-setting feature and to check for usability risks. The priority of the study was to assess the dose-setting, dose-correction and injection force features. Other features addressed in this study were:

- Patient training
- Contents and presentation of the instructions for use (IFU)
- Overall handling of the device (including flow check and needle management)
- Quality and force of dose-setting click
- Legibility of dose scale, dose scale font size
- Design (e.g. size, appearance, anti-rolling feature)
- Cartridge container printing
- Flow check symbols and symbol between set doses
- Patient last dose approach (i.e. what happens if there is insufficient drug to complete their dose).

The aim was to inform Haselmeier of the overall functionality of the pen and identify potential improvements related to specific findings.

Method

The study of D-Flex assessed functional samples and the IFU. The participants were made up of 17 Type 2 diabetes patients. Ten patients used GLP-1 injectable drugs and seven patients were naïve to GLP-1 treatment (four were injection naïve, two were insulin users and one was using an injectable growth hormone therapy). The participant acquisition also considered patients with some level of visual impairment or some level of dexterity impairment or a combination of both. Four diabetes specialist nurses (DSN) were recruited to give their professional opinions on the usability of the device.

The study consisted of 60-minute individual in-depth interviews with the patients, which included several injections with the D-Flex device into an injection pad. A 45-minute individual interview with each nurse was conducted at the beginning and end of the study days, and the nurses observed the patient interviews.

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Results

Overall, the D-Flex pen was well received by nurses and patients. It was relatively straightforward for nurses and patients to use D-Flex for the delivery of GLP-1 drugs. Users found the dose setting and correcting easy and agreed that the inability to select intermediate doses was a good safety feature. The nurses also agreed that the dosing mechanism could prevent dose errors.

Furthermore, patients liked the distinct setting of the dose and the proper click sound and haptic feel was perceived as reassurance that the set dose is correct. Users became familiar with the device after a short time and the handling of the pen was considered easy to dial, to set and correct doses.

Some smaller remarks were received with regards to making the design and content of the IFU less complex and providing clearer instructions for the flow check.

The encouraging results of the D-Flex HF study confirmed the importance of the early research and show the value of gathering a deep understanding of the corresponding use case by considering all relevant stakeholders to work on the right solution which serves the hidden needs.

CONCLUSION

Innovative applications of human-centred engineering principles to the devices that administer biologics, biosimilars and other novel and existing drugs, will serve to accelerate the already rapid emergence of these molecules onto the market.

With patients now taking an increasingly active role in their care, the need to focus

on reducing errors in medication delivery has never been greater. Incremental yet meaningful improvements in delivery systems devoted to reducing use errors is vital. The next wave of user centric drug delivery designs like Haselmeier's D-Flex will certainly make a meaningful impact in that quality of patient care.

ABOUT THE COMPANIES

Ximedica is a product research and development consultancy with an exclusive focus on the development, evaluation and commercialisation of medical and drug delivery products and systems. Its work in a variety of fields over the last 29 years has helped Ximedica develop many best practices in evaluating use scenarios, determining user and stakeholder needs, and regularly evaluating the user experience in its intended use environments during the design and development process. Against this historical context, Ximedica has helped its clients stay in front of the increased emphasis on qualitative and quantitative data in medical device product marketing submissions in the US and EU. However, of equal or greater importance, Ximedica's experience suggests that successful human-centred design often results in innovative products that are superior in functionality and uniquely differentiated for end users.

Haselmeier is a developer and manufacturer of innovative self-injection devices featuring proprietary designs, technology and intellectual property. With over four decades of medical device experience, Haselmeier has built up a world class design and development team

– working in compliance with regulatory requirements – for the creation, design and industrialisation of innovative self-injection systems used by pharmaceutical and biotechnology companies worldwide. The Haselmeier Group employs approximately 240 team members worldwide, has its headquarters in Europe, with a presence in the US, India and China. Products are manufactured at state-of-the-art sites in Buchen im Odenwald (Germany), Dnesice (Czech Republic) and Bangaluru (India).

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ABOUT THE AUTHORS

David Fink has more than 40 years of successful new product development experience in the medical device industry ranging from early phase research, strategy and business development through detailed design to commercial launch. His role at Ximedica is working closely with client companies to align their project needs effectively with Ximedica's extensive development capabilities. Prior experience includes over 20 years at Covidien/Kendall, most recently serving as Director of Research & Development managing multiple development groups in the fields of cardiology, radiology, respiratory care and advanced wound care. Mr Fink's experience includes 12 years in antimicrobial device platform development.

Stefan Gaul has deep knowledge and insight regarding the development and successful implementation of new and innovative products. He was already active in various business areas, focussing on product innovation, strategic positioning, project management and market implementation. Mr Gaul joined Haselmeier in 2014 and took over the responsibility for strategic product management in 2016. Mr Gaul has a strong, patient-centred approach, which drives product definition, roadmap and development. His current role takes into account the whole journey of a new and innovative product from intense market analysis and the identification of market opportunities through the product definition and execution of innovation projects to proof of concept of the various programmes.

CO-PACKAGED COMPONENTS IMPROVE PATIENT EXPERIENCE AND ENSURE CONSISTENT DRUG DELIVERY

In this article, Chris Franzese, Clinical Leader, and Amy Rinaldi, Insights Associate, both of Matchstick, explore the challenges and benefits of co-packaging for manufacturers, healthcare workers and patients.

A growing combination-product market and regulatory focus on patient-centred drug development has brought human factors engineering to the forefront of the pharmaceutical industry. Whereas the term “delivery device” previously signified traditional needle and syringe systems, today significant resources are allocated to ensuring drug delivery devices reflect user-centred design principles and can be used safely and effectively.

The prefilled syringe (PFS) developed to deliver UCB’s Cimzia (certolizumab pegol) was one of the first devices to exemplify this change, leveraging usability principles adapted from OXO’s kitchen utensils. Since then, many PFS devices, autoinjectors (AIs), on-body injectors (OBIs) and inhalation devices have been purposefully developed with the user in mind. Connected delivery devices that communicate with the user’s smartphone or other technology represent the next horizon for improving usability and patient-centricity.

While device usability has made a step-change in recent years, device packaging has not always followed suit. With few exceptions, parenteral medications – even those that are delivered with complex devices – are typically supplied in standard cartons with no additional design features or affordances. This is somewhat understandable, given the stringent labelling and child-resistance requirements for pharma packaging.

“Unlike other packaging strategies, co-packaging has the potential to directly impact medication administration, as opposed to strictly improving usability.”

“While device usability has made a step-change in recent years, device packaging has not always followed suit.”

In lieu of altering the packaging design itself, some manufacturers of oral medications have adopted co-packaging strategies to improve the user experience. One of the most prominent examples is the Kisqali (ribociclib) and Femara (letrozole) co-pack from Novartis, which supplies one 28-day cycle of both medications in a single box for the treatment of metastatic breast cancer – Kisqali is supplied in weekly blister packs alongside Femara, which is supplied in a bulk bottle.

Novel packaging configurations, such as those that employ “poka-yoke”¹ or “stepwise reveal” design elements, have been shown to improve usability,² but these approaches often face substantial manufacturing hurdles. In other cases, “smart packaging” that incorporates video instruction and/or audiovisual feedback has been conceptualised.

Still another strategy is to use more commonplace packaging designs and supplement this approach with co-packing, whereby delivery devices are provided alongside ideal (and tested) supplies to facilitate a drug’s proper and intended use. Unlike other packaging strategies, co-packaging has the potential to impact medication administration directly, as opposed to strictly improving usability.

Including simple disposable devices (needles, syringes, transfer



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“When co-packaged supplies are not available, similar populations have been shown to require significantly more time and steps to reconstitute their medications, and deviate from the product’s IFU more often.¹⁰”

devices, vial adapters and closed-system transfer devices) in drug product packaging may confer several benefits, some of which are specific to the user and others to the manufacturer. Users may benefit most from co-packed supplies when their drug product requires some degree of manipulation (e.g. reconstitution, volume pooling or multiple transfers) before it can be administered. In these cases, several and/or specific types of supplies may be needed to facilitate the manipulation.

Some of the most well-known examples of this are found in haematologic conditions – such as haemophilia and hereditary angioedema – where many of the approved medications require reconstitution prior to administration.³⁻⁸ As a result, these drug products are often co-packed with supplies such as diluent vials, vial adapters, transfer needles and/or injection needles to aid in reconstitution and administration.⁹

When co-packaged supplies are not available, similar populations have been shown to require significantly more time and steps to reconstitute their medications, and deviate from the product’s instructions for use (IFU) more often.¹⁰ In addition, these populations may need to procure the appropriate supplies on their own, which not only increases the probability for error but can also create a burdensome supply excess, as they must often buy these items in bulk. In some cases, dispensing pharmacies (e.g. specialty pharmacies) may provide the components they deem necessary but these supplies may not be designed for non-healthcare provider user groups and/or may not have undergone human factors or compatibility testing with the drug product.

For manufacturers, co-packing offers a means to direct users to supplies that

have already been vetted for physical and chemical compatibility with a specific drug product and primary container. This is not only relevant for patient- or caregiver-administered medications but also particularly important in the acute care setting. In practice, drug products and primary containers are subject to an enormous variety of ancillary supplies, ranging from standard steel blunt and sharp needles of different lengths and gauges to large-bore plastic dispensing pins, plastic cannulae, stopcocks, vented needles and closed-system transfer devices (CSTDs).

Such variety can be problematic – a 2018 study found that variation in chemotherapy vial spike characteristics (e.g. dimensions and design) and user practices (e.g. off-centre stopper puncture) produced unpredictable stopper collapse when spikes were tested with different stoppers.¹¹ This finding will be increasingly relevant as the regulations and recommendations for management of hazardous drugs (e.g. NIOSH, USP Chapter <800>) are enforced. For example, the prescribing information for some chemotherapy products specifically advises against the use of chemotherapy dispensing pins or similar devices, which is at odds with USP <800> recommendations for the use of CSTDs.

Moreover, dead space is not consistent amongst supplies commonly used in the hospital environment and may result in persistently inaccurate drug dosing, depending on the product used and any adjustments made by clinicians to account for lost volume. While it is probably unnecessary and unreasonable to co-package supplies with every manufactured drug distributed to a hospital, drugs with high physicochemical sensitivities, those packaged in primary

containers with stoppers prone to collapse or particulate generation, or those that require very precise dosing for therapeutic effect may be at risk when ancillary supplies cannot be controlled. This may be particularly relevant during investigational studies, where standardisation is critical to preserve internal validity.

In addition, there is some evidence to suggest that use of CSTDs may reduce microbial ingress into primary containers and yield extended microbial stability.^{12,13} Although this has not yet been reflected in standards such as USP <800>, co-packing with CSTDs to increase in-use time without the need for antimicrobial preservatives or complex formulation changes may represent a competitive advantage in the future.

Although co-packing offers tangible benefits to users and manufacturers, some manufacturers may be hesitant to employ a co-packing strategy, as it could present an incremental variable and potential risk in the drug development process that would need to be managed. While this is certainly a valid concern, new risks have emerged in recent years that may swing the balance in favour of co-packing.

In addition to the usability/convenience benefits to users and compatibility/consistency benefits to manufacturers mentioned previously, increasing human factors scrutiny may make co-packing a requirement for some products in the future. This is largely dependent on the clinical situation in which the product will be used and the reliability of safe and effective use with the supplies available in the use environment.

Examples include medications used in emergency situations, where access to appropriate supplies may be limited and delayed treatment would be deleterious, medications with narrow therapeutic indices that require precise and consistent dose preparation and administration, and medications that may present a high risk for the healthcare provider or patient harm if a specific supply is not used (e.g. a particular type of infusion set or a CSTD).

One such product is the Emergency Gynecologic Methotrexate Kit (EmGyn



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"It will not be surprising if more products begin to launch with co-packed supplies, especially as medical care continues to transition to the home, medication regimens become increasingly complex and the marketplace becomes more crowded."

Kit), compounded and sold by Edge Pharma (Colchester, VT, US), a US FDA-registered 503B outsourcing facility. This system employs a CSTD to allow for closed transfer and disposal of unused methotrexate (after an appropriate body surface area-based dose has been set) in facilities without access to a USP <800>-compliant compounding area (e.g. obstetrics and gynaecology clinics).

CONCLUSION

All strategies to enhance patient and healthcare provider experience and usability inherently involve risk/benefit analyses, as well as time, cost, manufacturing and supply chain trade-offs. Overall, it will be interesting to see how this topic evolves moving forward, although it will not be surprising if more products begin to launch with co-packed supplies in the near future, especially as medical care continues to transition to the home, medication

regimens become increasingly complex and the marketplace becomes more crowded.

ABOUT THE COMPANY

Matchstick is a specialty consultancy focused on pre-concept and concept stage development of combination products, including devices, patient support and engagement programmes, training and lifecycle strategies. Matchstick helps firms understand unmet patient and caregiver needs, invent useful and relevant product and service solutions, and deliver compelling business cases to drive programmes forward within their organisations.

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ABOUT THE AUTHORS

Chris Franzese is Clinical Leader at Matchstick. He manages a team of clinicians supporting client projects related to combination product development and usability testing, leads the company's clinical training and is accountable for making clinical knowledge accessible and relevant to client projects. An experienced clinical trial researcher, Mr Franzese has numerous peer-reviewed publications related to usability research for connected drug delivery devices, devices for medication preparation, biomarkers and antiplatelet therapies in coronary artery disease, and clinical laboratory and diagnostic testing. He earned a BS in Biology from Loyola University (MD, US) and a concurrent PharmD and MHS in Health Informatics from Fairleigh Dickinson University School of Pharmacy and Health Sciences (NJ, US). He is a practising pharmacist in New Jersey.

Amy Rinaldi is an Insights Associate at Matchstick. She is responsible for executing user research projects, patient, caregiver and clinician empathy workshops, and innovation challenges. A talented user researcher, Ms Rinaldi is recognised for developing novel approaches to collect rich data from study participants. She has led several projects related to patient and caregiver experience with oral adherence packaging and lyophilised parenteral medications, and has published on these topics. Ms Rinaldi earned a BS in Chemical Engineering from Manhattan College (NY, US) and is currently pursuing a Graduate Certificate in Human Factors Engineering and Ergonomics at Penn State University (PA, US).



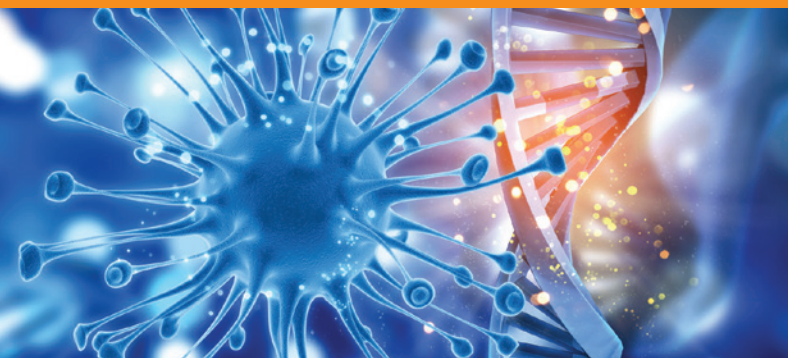
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DEVELOPMENTS IN SELF-INJECTION DEVICES FOR COMBINATION PRODUCTS

In this article, Fred Metzmann, PhD, Vice-President Sales & Marketing, Haselmeier Group, reports on the latest state-of-the-art developments in innovative injection devices for combination products in subcutaneous self-application. He outlines Haselmeier's product platform strategy for single-use (D-Flex) and re-usable (i-pen²) injection-pen systems, and related services. He also looks at the company's connected digital solutions, which support point-of-care data collection and transfer by patients, as well as data management by stakeholders in the care environment.

High cost-pressure in the healthcare sector means that to launch a new combination product successfully, a drug must not only be safe and effective, but the combination of drug and device must also guarantee reliable and beneficial therapy and, of course, be economical.

Many biopharma companies are currently looking for solutions that enable rapid drug development, smooth conduct of clinical trials and fast device development for commercialisation of their combination products. For drugs that require subcutaneous application, self-injection pens offer an ideal opportunity to reduce time and risk.

ADVANTAGES OF SELF-INJECTION PENS

Self-injection applications are an effective way to minimise the costs associated with managing and treating a broad spectrum of diseases. This means self-injection pens are increasingly the first choice for new, subcutaneously administered pharmaceutical agents. These biopharmaceutical products are being developed through a combination of industry innovations and new pharma companies.

Self-injection solutions also have the potential to greatly improve the quality of care from the patient's perspective. Self-administering by the patient – for example, with injection pens – offers

“For drugs that require subcutaneous application, self-injection pens offer an ideal opportunity to control the time factor and reduce risk.”

several advantages. The patient has more flexibility in terms of place and time of treatment, thereby substantially reducing therapy costs.

Therefore, where it is possible for medication to be administered using an injection pen, the devices should be used as the pharmaceutical form as early as possible in clinical studies.

Generally during the clinical phase, medication is stored in vials and administered to the patient through a disposable syringe. However, vials can be inconvenient to use and harbour safety risks, especially in terms of shelf-life after opening, contamination and injury to staff due to the cannula. An alternative is the prefilled syringe, but this does not permit any dose adjustment and, as such, would mean substantial additional demand for the trial drug. Moreover, common to both vial-and-syringe administration and prefilled syringes is that they are unsuitable for use by non-medical laypeople. Administering a drug once or several times a day would require substantial nursing care potentially including hospital treatment.



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The D-Flex product platform: ready to support your needs

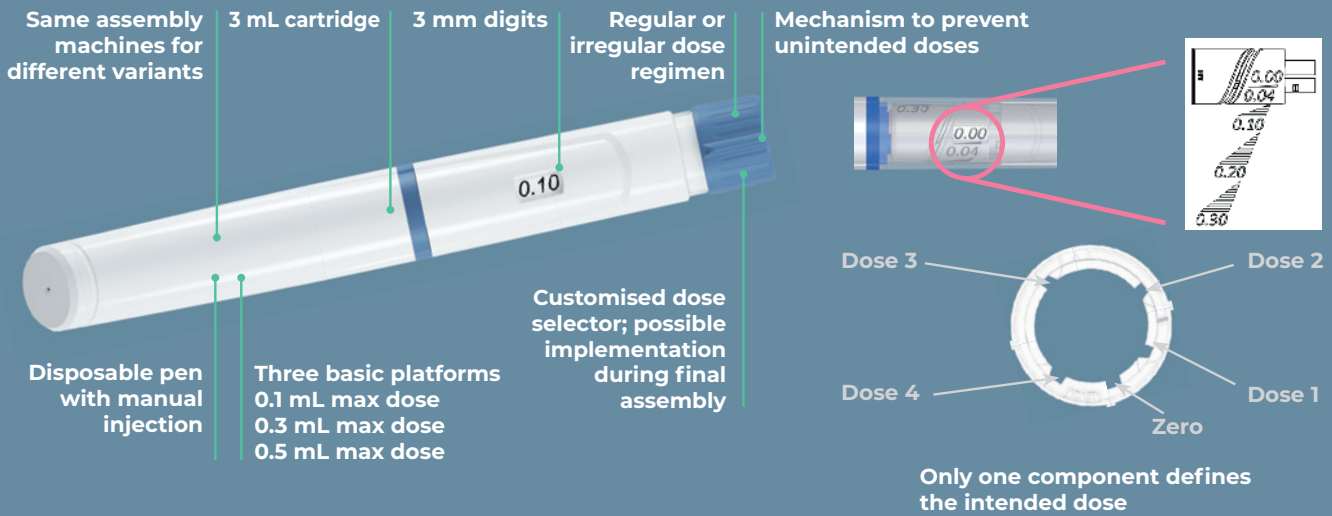


Figure 1: The D-Flex product platform has a range of beneficial features.

“Haselmeier’s new D-Flex product platform strategy offers innovative technical features that enable customers to accelerate product development with a drug agent and delivery pen that are combined during development rather than sequentially, as is traditionally the case.”

DEVELOPMENT OF IMPROVED COMBINATION PRODUCTS

It is important to develop not only pen technology and manufacturing methods, but also focus particularly closely on how to improve the engineering process for new self-injection pens.

Haselmeier is constantly adapting its offerings to meet customers’ needs – in

response to the factors that drive their markets and patients. It has always been Haselmeier's top priority to be a strong, proactive partner, which has been demonstrated with its recently released injection pen system, the D-Flex product platform. Together with a connected digital solution, D-Flex Connect, and a pharma packaging solution, Haselmeier offers a comprehensive service, helping its partners

save time and reduce risk in the development and market launch of combination products.

THE D-FLEX PRODUCT PLATFORM STRATEGY

Haselmeier’s new D-Flex product platform strategy offers innovative technical features that enable customers to accelerate product development with a drug agent and delivery pen that are combined during development rather than sequentially, as is traditionally the case.

This makes the D-Flex product platform an ideal, flexible platform for adapting to set doses in accordance with therapy. It has been developed and validated so that only minimal drug- and customer-specific adjustments are necessary (Figure 1). These can be seamlessly integrated into the clinical



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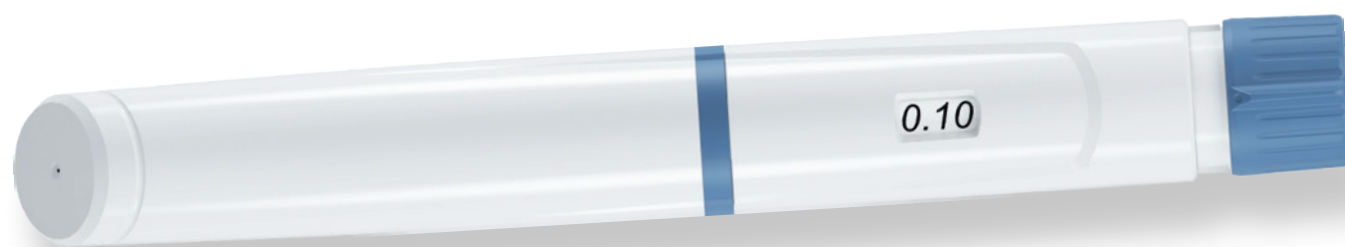


Figure 2: The Haselmeier D-Flex pen is designed for use with 3 mL cartridges but can be configured for several fixed doses.

supply chain process up to serial production following market authorisation.

Use in Clinical Trials

The requirements of an injection pen for clinical studies are:

- Simple and safe to use, and permits a predefined flexibility in the adjustment of the dose in Phases II and III
- Permits therapy-appropriate labelling, including re-labelling for dose adjustment as well as the option of multilingual labels
- Can be used continuously or with minimum adjustments for all phases of the clinical study up to drug approval
- Can be delivered ready-to-use to trial participants without having to establish in-house manufacturing competence.

The new product platform is therefore highly suitable for clinical trials. The disposable pen for use with 3 mL

cartridges can be configured for several fixed doses, bridging the gap between fixed- and variable-dose pens. These dose values can be freely selected when designing the pen. This is especially of interest for dose-escalation studies, for example. The pen system does not allow any intermediate steps between the set doses, significantly reducing the risk of a wrong dose and enhancing patient safety.

The D-Flex product platform pen can also be quickly and cost-efficiently adjusted to customer needs or their requirements for clinical-trial design, by replacing just one single part of the device. Modifications after Phase II are possible and the drug delivery device can be adjusted to the requirements of other products in the drug development pipeline (Figure 2).

D-Flex can be flexibly configured to suit the desired dose values from the first clinical study to series production, significantly reducing capital expenditure and time-to-market.

THE D-FLEX PRODUCT-SERVICE SYSTEM

The D-Flex Product-Service System (also known as the D-Flex ecosystem) consists of the D-Flex pen with an optional smart cap that enables Bluetooth data collection and transmission as well as data management to an optional platform to develop health management applications. These components are combined with Haselmeier's engineering services, which support the parallel integration of drug and delivery pen development processes, plus a pharmaceutical packaging service (Figure 3). Haselmeier's D-Flex ecosystem significantly accelerates time-to-market while simultaneously reducing risks during the platform pens' initial development phases.

The parallel development of drug and delivery platform can start as early as Phase II. The disposable pen can be used during trials as it can easily be adapted to

The D-Flex injection pen system: shorter time-to-market

The D-Flex ecosystem accompanies customers throughout the entire development and commercial life of a drug using the same platform



Figure 3: The D-Flex ecosystem comprises the D-Flex pen, an optional smart cap that enables Bluetooth connection (with associated software/apps), and engineering and pharma packaging services.

different dose requirements and improves the trials' quality by lowering the risk of manual handling errors and simultaneously reducing the required investment. The pen uses the information and outcomes gathered from the trials to simultaneously adjust and engineer the final delivery pen. This shortens development cycles while minimising the customer's investment risks.

The D-Flex product platform offers two versions of the final pen solution. Depending on the patient's needs or the doctor's prescription, the pen can deliver different doses. The dose can either be continuously adapted, or the correct dose can be selected from a range of presets.

DATA MANAGEMENT AND MONITORING IN CLINICAL TRIALS

The option to equip the D-Flex pen with Haselmeier's smart cap D-Flex Connect enables bio-pharmaceutical partners to collect data at the point of care and improve the quality during clinical trials by monitoring compliance with study design during Phase II and III trials. This makes a sustainable contribution to increasing and demonstrating therapy efficiency. In addition, the smart cap lets you help patients to manage their personal health by combining pen delivery with appropriate user-friendly apps (Figure 4).

The flexibility of the D-Flex injection system together with the pharmaceutical packaging, the possibility to produce small quantities and the D-Flex Connected digital solution make the system a very promising solution for cost saving and time reduction in drug development and improvement of therapy efficiency.

In short, the D-Flex is ready for our pharma partners to apply to their specific application needs – quickly and easily.

THE i-PEN² PRODUCT PLATFORM

Haselmeier's i-pen² product platform solution can help pharmaceutical companies to accelerate time-to-market for their injection pens if this needs to



Figure 4:
The D-Flex
connected
digital solution.

be balanced against cost pressures. This reusable variable-dose injection device is designed for use with standard 3 mL cartridges – and so combines the Haselmeier platform concept with the benefits of an established infrastructure for production and certification processes (Figure 5).

The Haselmeier i-pen² solution was specifically created to provide a high-quality pen at a low economic cost and offers an affordable alternative to fully customised pens. Although it is a platform solution, the i-pen² offers high flexibility and variability in design and appearance. Haselmeier operates a production facility for the i-pen² in India to meet the needs of self-injection patients across the world and applies certified German manufacturing and quality standards.

ENSURING QUALITY DRUG DEVELOPMENT PROCESSES

Quality of care is defined by two key aspects: the latest quality and safety requirements for healthcare products, and patient-centric approaches that address the convenience of products, safe usage and treatment compliance. This is a challenge for market participants

throughout the entire product lifecycle. At Haselmeier, customers are supported with quality assurance processes by working closely together with them at every stage – from initial design specifications to user feedback integration, production, product delivery and continuous quality control measures. This carefully co-ordinated approach helps ensure the best possible outcome for the quality of care that patients receive.

ABOUT THE COMPANY

Haselmeier has been established in the healthcare marketplace for almost a century. It is a family-owned business with approximately 240 employees and has been pioneering the development of injection pens for subcutaneous application with its own IP since the 1960s. To this day, we continue to drive innovations in self-injection pens from development and manufacturing to packaging and delivery. We have developed solutions in scalable volumes for numerous pharmaceutical partners, always following state-of-the-art engineering practices – and we aim to evolve even further.



Figure 5: The Haselmeier i-pen² is a reusable variable-dose injection device.

i-pen² – a reusable injection pen with a high quality

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Z.BLIZZARD AUTOMATION SYSTEM FOR PFS: IMPROVING THE LIVES OF PATIENTS

With the ultimate objective of improving patients' lives, Berthold Schopferer, Product Manager, System Technology, ZAHORANSKY Automation & Molds, provides an overview of the company's customer-specific automated manufacturing and assembly equipment offering for prefillable polymer syringes.

Readily packaged, ready-to-fill staked-needle syringes have one goal: making handling medication easy. After all, the chronically ill are already burdened enough by their state of health. Cumbersome handling of their daily dose of medication – often more than one – would place an even greater burden on these patients. Not to mention the fact that dosing would be challenging. Prefilled syringes (PFS) actively contribute to making life easier for patients.

This places a demand on industry as well. Mould and mechanical engineering specialist ZAHORANSKY builds automation systems in different, very customer-specific variants for serial production. In doing so, the business implements the desired and required elements of modularity one by one. It goes without saying that this is based on the premise that the finished product will meet the high quality standards required and demanded in medical technology to ensure that the systems built protect the integrity of the product and thus the safety of patients.

GREATEST FREEDOM OF CHOICE FOR A TAILOR-MADE SYSTEM

Z.BLIZZARD (Figure 1), is the automation system from ZAHORANSKY that includes injection-moulding, and is therefore specially equipped with a sophisticated quality-assurance system: in current systems and upon request, more than ten camera systems ensure ongoing product

"If Z.MISTRAL, which handles downstream processing, and the Z.LODOS palleting system are added, the system covers the full process from COC/COP granulate to prefillable syringe."

control in the production process while an integrated 100% X-ray system ensures product control after assembling. More comprehensive quality assurance according to modern-day standards is barely possible. However, ZAHORANSKY does not rest on this success: and its mechanical engineering specialists are currently testing the use of an additional CT module in future systems for even finer quality control.

The same careful procedure is also applied to clean-room modules. In this area, ZAHORANSKY relies on industry-proven systems to enable its customers to produce their products hygienically.

Customers can determine numerous specifications:

- Orientation of the needle – is it straight or bent?
- Areas covered by integrated X-ray examination
- Z.BLIZZARD configured with additional access doors.



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Figure 1: Z.BLIZZARD produces ready-to-fill, stacked-needle-syringes from COC/COP polymers with a very high autonomy time.



From early in the process, these and other details are determined and subsequently executed precisely in close co-operation with the customer, who is consulted throughout the design and production process, which usually takes 12 months. Close collaboration throughout provides the customer with the best possible product.

Further customisation is made possible with additional integrated systems. A system that covers the full process chain from cyclic olefin copolymer/ cyclic olefin polymer

(COC/COP) granulate to prefillable syringe (Figure 2) is formed when Z.MISTRAL, which handles downstream processing, and the Z.LODOS palletising system are connected with Z.BLIZZARD (Figure 3).

ZAHORANSKY CUSTOMERS CHOOSE POLYMER SYRINGES

Why do ZAHORANSKY customers choose plastic as their preferred material for their prefilled syringe products? The greatest advantage COC/COP syringes have over their glass counterparts is that the needle is over-moulded and not melted in or glued in. In the melting process for glass syringes – in which a heat-resistant material such as tungsten is used in temperatures of more than 1,000 °C – heavy metals can enter the glass container and may later be found in the product, despite the containers subsequently being washed, dried, and sterilised.

These aspects are crucial when it comes to ensuring that the already impaired health of patients is not burdened further by their treatment. Other persuasive aspects of the plastic version are its minimal risk of breakage and greater freedom in design.

NO HUMAN CONTACT FOR CLEAN-ROOM CONFORMITY

The Z.NFS needle feeding system (Figure 4) ensures the first-in-first-out principle, which means that the system is filled with the required number of cannulas and works in series. This prevents needles from remaining in the system for long periods of time. Z.NFS can process up to 32 needles or cannulas with up to 12 cycles per minute, i.e. 400 units per minute.



Figure 2: Z.BLIZZARD manufactures COC/COP prefillable syringes with distinct advantages over their glass counterparts, e.g. the needle is over-moulded, not welded or glued in.

“Customers can contribute their own know-how to specific assemblies or technologies required for the production of the final product. ZAHORANSKY gladly provides comprehensive advice to its customers and makes recommendations in accordance with cGMP guidelines.”



Figure 3: Z.MISTRAL and Z.LODOS connected with Z.BLIZZARD to form a system that covers the entire process chain, from polymer granulate to prefillable syringes.

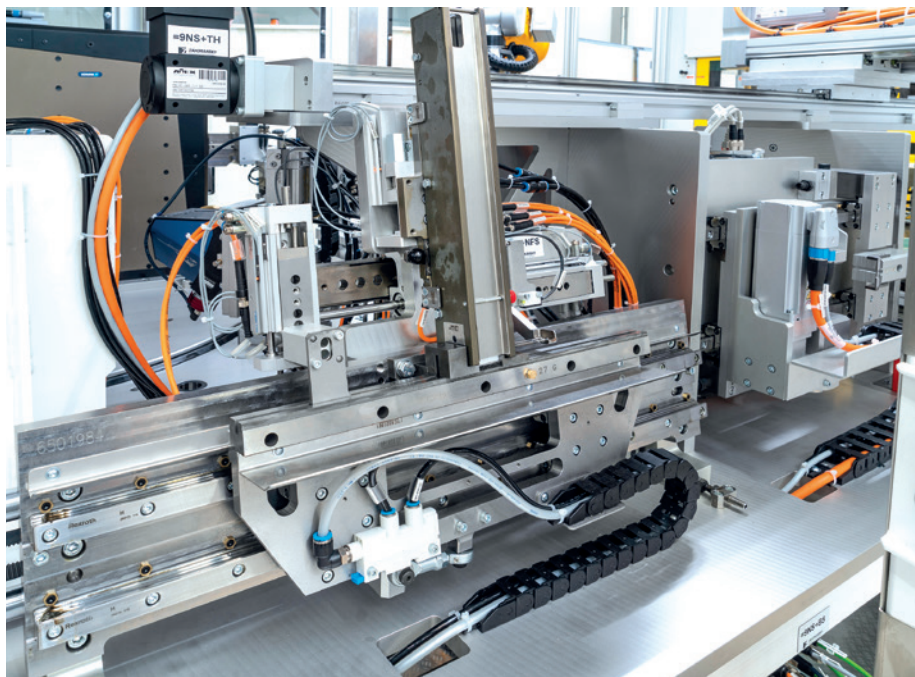


Figure 4: The combination of the Z.NFS with the Z.BLIZZARD, as shown here, forms an integrated system which guarantees maximum purity in the production process, since there is no human contact and the process is cleanroom compatible.

“The clinical characteristics and requirements of their ultimate customers – patients – are highly individual. In turn, ZAHORANSKY ensures that its pharma customers have maximum freedom in the design of their automation and production systems.”

Currently, the system can process diameters from 0.2 mm upwards, and lengths of up to 45 mm. In addition to this, Z.NFS is an integrated system that guarantees the highest levels of cleanliness in the production process since no human touches the product, and the process can run in accordance with clean-room conditions. This is a decisive plus in the production of particularly sensitive

prefillable syringes. A higher quality in the production of a product for medical technology is barely conceivable.

FULL-SERVICE CONSULTING

The entire pharma and biopharma industry is geared towards guaranteeing the well-being of patients through the highest-quality production of medication solutions. The clinical characteristics and requirements of pharma companies' ultimate customers – patients – are highly individual. In turn, ZAHORANSKY ensures that its pharma customers have maximum freedom in the design of their automation and production systems.

For example, customers can contribute their own know-how to specific assemblies or technologies required for the production of the final product. ZAHORANSKY gladly provides comprehensive advice to its customers and makes recommendations in accordance with cGMP guidelines, always mindful that just because something works in the laboratory, it does not necessarily

work in an industrial setting. Evidence is provided that the solutions suggested are implemented in a manner that customers can have audited. Should customers already have a firm idea of units or technologies that have proven their worth and that they would like to see integrated in their systems, this can be arranged. ZAHORANSKY thoroughly validates such integrations.

ALWAYS WITH A FOCUS ON IMPROVING THE LIVES OF PATIENTS

Customers receive support even after the system has been delivered to ensure that they have an innovative and future-proof mould and machine. Because even if pharma is not known for making quick changes due to the heavily regulated environment in which it operates, the industry does continue to evolve with modern demands. Likewise, machine manufacturers and producers must continuously optimise their products. This is the basic prerequisite for further and constant improvement of the lives of patients.

ABOUT THE COMPANY

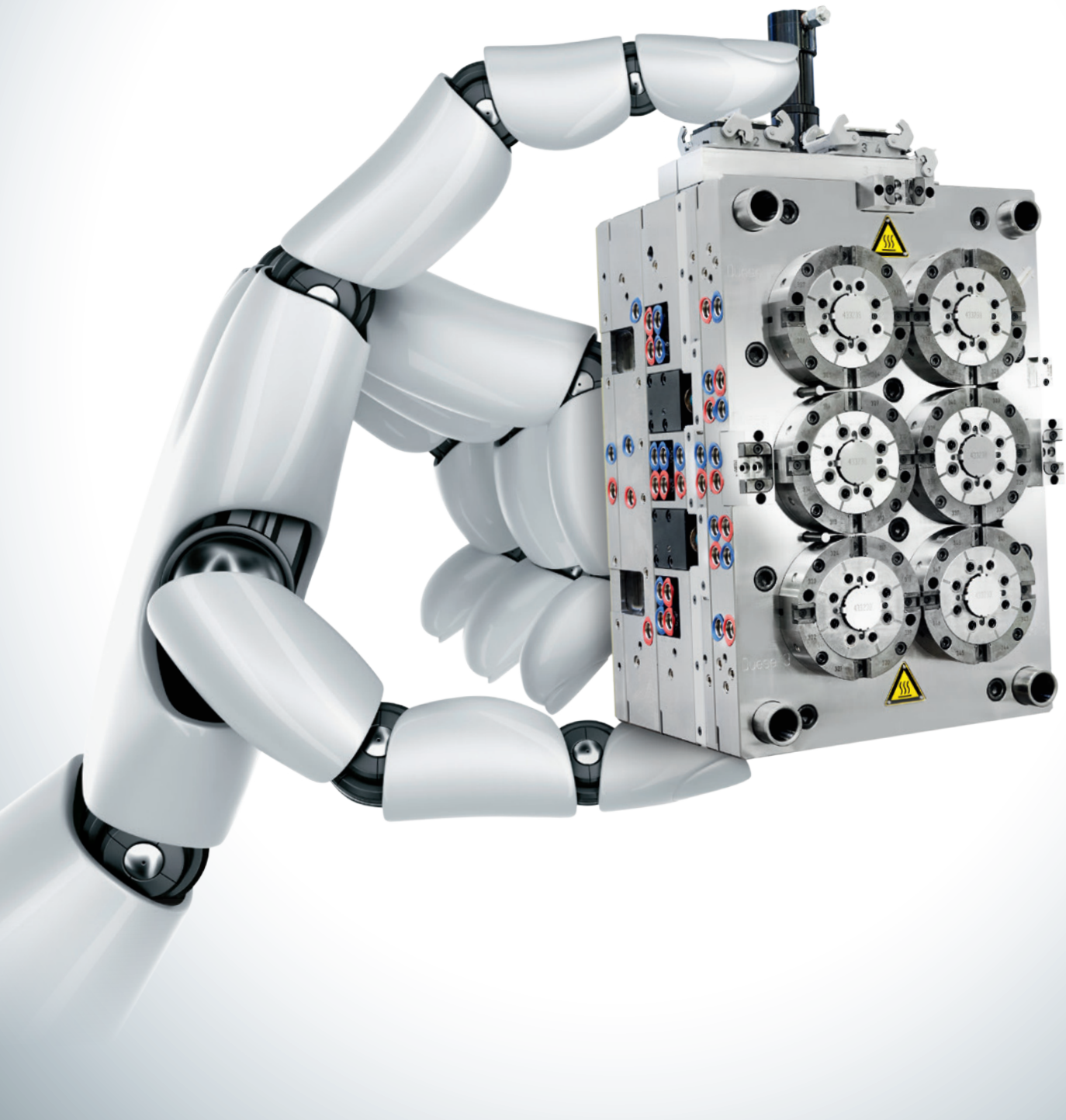
ZAHORANSKY AG is a full-range supplier in machinery and production lines, sophisticated, innovative injection moulds and automation equipment. The company operates with over 700 associates at production sites in Germany, Spain, China, India and the US. System Technology offers across-system solutions for the injection-related automation. These systems are based on injection moulds by ZAHORANSKY Automation & Molds GmbH and on established systems from different modules of automation. Intelligent and injection-related automation solutions can be composed with these modules. ZAHORANSKY Automation & Molds GmbH serves the areas Industrial Automation and Medical Devices, with pre-configured solutions provided for medical engineering. Z.BLIZZARD, for example, is an integral solution for making ready-to-fill prefillable polymer syringes as primary medical packaging.



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LATEST UPDATE ON OXYCAPT™ MULTILAYER PLASTIC VIAL AND SYRINGE

Tomohiro Suzuki, Associate General Manager at Mitsubishi Gas Chemical Company, gives an update on the development of the OXYCAPT™ multilayer plastic vial and syringe – highlighting the results of recent tests comparing it with existing glass syringes.

OXYCAPT™ is a multilayer plastic vial and syringe. It consists of three layers (Figure 1): the drug contact layer and outer layer, both made from cyclo-olefin polymer (COP);

and the oxygen barrier layer, which is made from a proprietary, novel polyester.

Thanks to its state-of-the-art multilayer technology, OXYCAPT™ has excellent oxygen barrier and high water vapour barrier properties, very low extractables, low protein adsorption, excellent ultraviolet (UV) barrier properties, high break resistance, high pH stability and a silicone-oil free barrel.

Although COP is the most promising candidate when it comes to replacing glass with plastic, the oxygen barrier

“We have recently decided to invest in a facility for the stacked-needle syringe. The necessary equipment will be installed during 2020.”

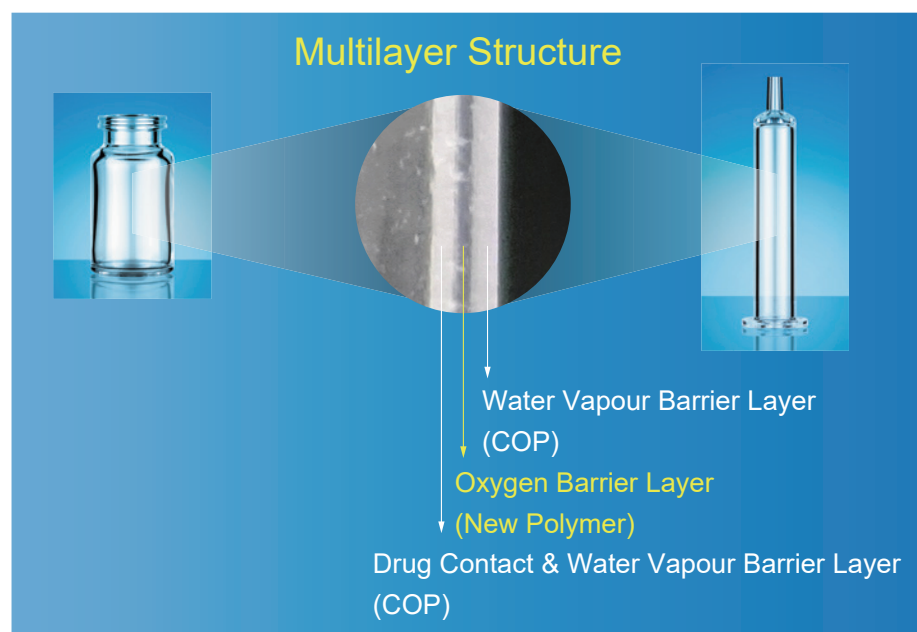


Figure 1: Multilayer structure of OXYCAPT vial and syringe.



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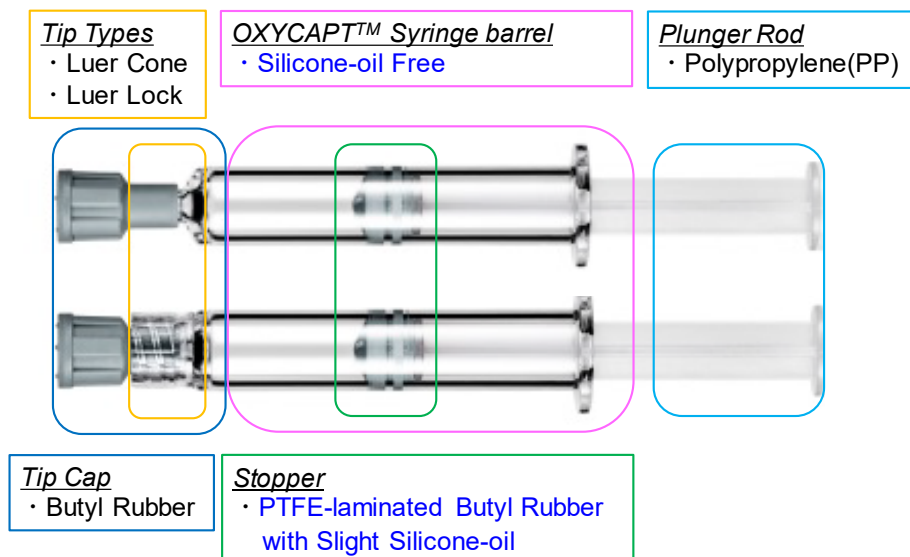


Figure 2: Components of OXYCAPT syringe.

is insufficient for oxygen-sensitive drugs. According to one of our experiments, the oxygen barrier of COP is more than 100 times worse than the existing glass-syringe system. We therefore started developing multilayer plastic vials and syringes about seven years ago to ameliorate the disadvantages of a COP vial and syringe.

To begin with, as a manufacturer of special polymers, we developed a new polymer that has excellent oxygen barrier properties and is suitable for multilayer injection moulding. The new polymer

for the middle layer is a kind of polyester filled in US Drug Master Files and compliant with US and European pharmacopoeias.

In parallel with the new polymer, we developed innovative multilayer injection moulding techniques. Such injection moulding technology has been applied to beverage bottles for many years – it contributes to preventing oxidation and carbon-dioxide evaporation of drinks. Our idea was to transfer the technology to the vial and syringe in the pharma industry.

The OXYCAPT syringe consists of several components (Figure 2). There are two types of tips, and the stopper is made of polytetrafluoroethylene (PTFE)-laminated butyl rubber with a small amount of silicone oil. To minimise the protein-aggregation problem (Figure 3) caused by silicone oil, no silicone oil is baked on the inside of the barrel.

We tried to confirm the influence of minimised silicone oil on biologics, and conducted protein aggregation studies. The commercially available antibody was filled into OXYCAPT and Type 1 glass syringes, and the syringes were shaken at 500 rpm for one week at room temperature. A week later, tiny sub-visible particles were measured by resonant mass measurement (RMM), and large sub-visible particles and visible particles were measured by dynamic image analysis

“The amount of silicone oil leached from the OXYCAPT™ syringe was about seven times less than that from the Type 1 glass syringe.”

Sample preparation

Sample solution

- Well-known antibody, Surfactant removed, Dialysis treatment performed, Adjusted to pH 7 and diluted

Syringe barrels and stoppers

- Type 1 Glass (with silicone)
- Stoppers (with slight silicone)
- OXYCAPT™ (silicone-free)

Test method

- Filled with 1 mL solution and 5 mm headspace
- Shaken at 500 rpm for 1 week at room temperature
- Measured by Resonant Mass Measurement (RMM) for sub-visible particles
- Measured by Dynamic Image Analysis (DIA) for sub-visible and visible particles

Particles

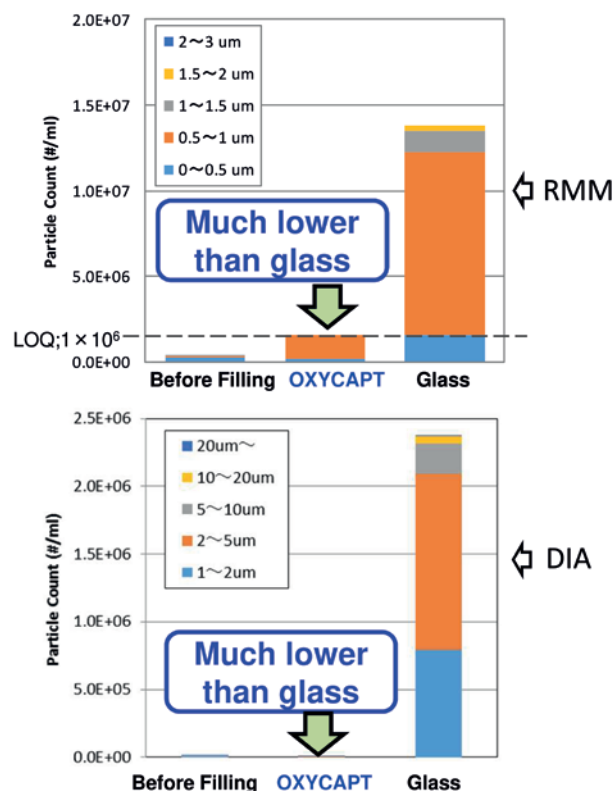


Figure 3: Protein aggregation studies.

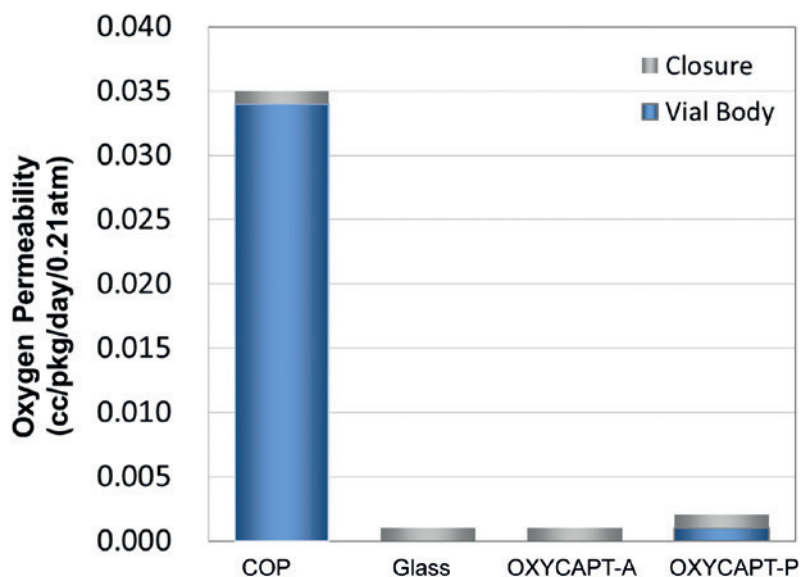


Figure 4: Oxygen barrier of OXYCAPT.

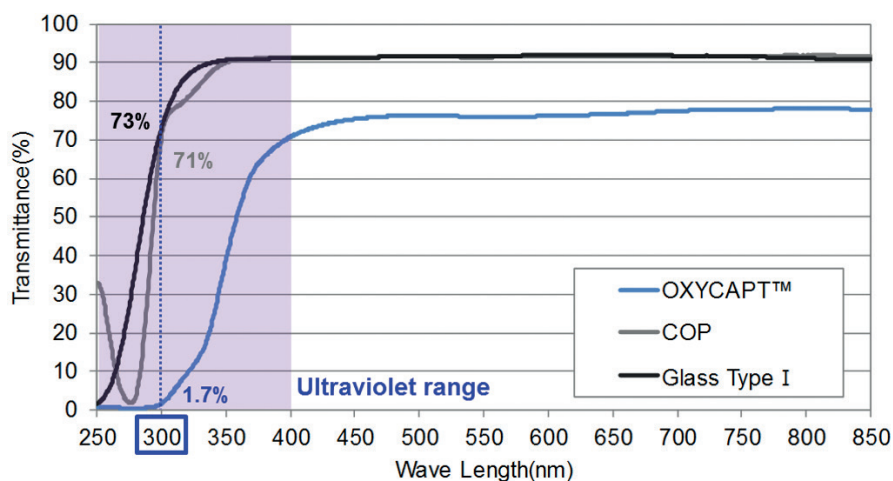


Figure 5: Ultraviolet barrier of OXYCAPT.

(DIA). We found the minimised silicone oil significantly contributes to preventing protein aggregation of the antibody.

There are two types of OXYCAPT multilayer plastic vial and syringe

– OXYCAPT-A and OXYCAPT-P. OXYCAPT-A has achieved a glass-like oxygen barrier (Figure 4). According to some internal studies, OXYCAPT-A can maintain a lower oxygen concentration in

the headspace than Type 1 glass, thanks to its oxygen-absorbing function.

Although there is no oxygen-absorbing function, OXYCAPT-P has also achieved an excellent oxygen barrier. For example, the oxygen barrier of the OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial. OXYCAPT-A is particularly suitable for oxygen-sensitive drugs and OXYCAPT-P is recommended for other less oxygen sensitive drugs.

OXYCAPT also has a UV barrier. For example, although about 70% of UV light of 300 nm transmits through glass and COP, only 1.7% of UV light transmits through OXYCAPT (Figure 5). We have confirmed this feature also contributes to the stability of biologics.

As for the product portfolio, there are four volumes for the OXYCAPT vial and two volumes for the OXYCAPT syringe (see Table 1). All the dimensions of the OXYCAPT vial and syringe are designed in accordance with the ISO standard. We can offer bulk vials, ready-to-use (RTU) vials and RTU syringes. The RTU vials and syringes are placed in ISO-based nest and tub formats and packed with a Tyvek® lid, a Tyvek bag and a high gas-barrier bag (Figures 6 & 7). All the RTU containers are sterilised by gamma.

Recently, we measured the amount of silicone oil leached from the OXYCAPT syringe and the existing Type 1 glass syringe. Each syringe was filled with distilled water and then shaken at 100 rpm for one week at 30°C. A week later, the quantity of leached silicone oil from each syringe was measured by proton nuclear magnetic resonance imaging (¹H NMR). The results showed the amount of silicone oil leached from the OXYCAPT syringe was about seven times less than that from the Type 1 glass syringe (Figure 8).

Container closure integrity (CCI) is one of the important requirements for prefilled syringes. Although dye ingress testing is popular at present, other quantitative analysis such as helium gas testing is also now conducted. In addition to dye ingress testing, we have conducted helium gas testing to confirm the CCI of the OXYCAPT syringe. Results from helium testing showed that both the OXYCAPT 1 mL and 2.25 mL syringes meet the required CCI criteria (Table 2).

As we have been asked to develop stacked-needle multilayer plastic syringes (Figure 9) by some customers, we started tackling the development a few years ago.

Type	Volume	ISO	Parts	Option
Vial	2 mL	ISO 8362-1	Vial	Bulk or RTU
	6 mL	ISO 8362-1	Vial	Bulk or RTU
	10 mL	ISO 8362-1	Vial	Bulk or RTU
	20 mL	ISO 8362-1	Vial	Bulk or RTU
Syringe	1 mL "long"	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU
	2.25 mL	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU

Table 1: Product portfolio.



Figure 6: Nest and tub for RTU vials.



Figure 7: Nest and tub for RTU syringes.

Test Condition

- Filled with 1 mL water and 5 mm head space
- Shaken at 100 rpm for 1 week at 30°C

Analysis Methods

- ¹H NMR

Test samples

- 1 mL “long” syringe
- 10 samples



OXYCAPT™
1 mL syringe

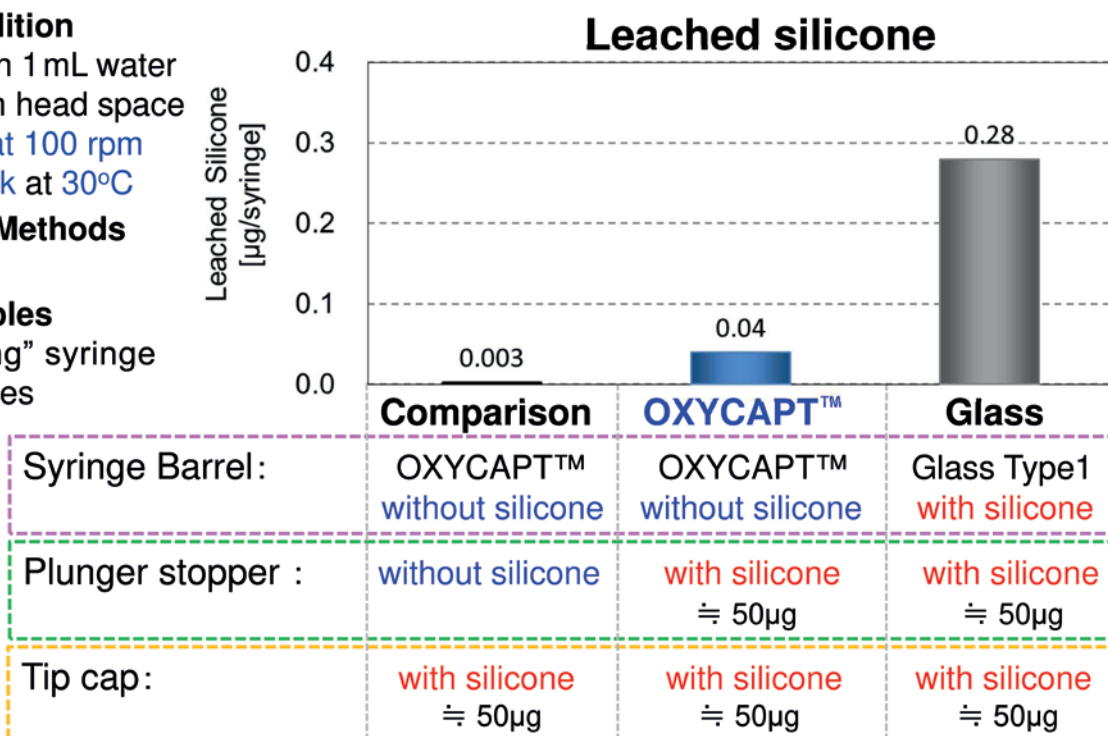


Figure 8: Silicone oil from Type 1 glass syringe and OXYCAPT syringe.

	OXYCAPT S1	OXYCAPT S2.25
Syringe Size	1 mL long	2.25 mL
Stopper	PTFE laminated stopper	PTFE laminated stopper
Sample Quantity	10	
Acceptance Criterion for Helium CCI	<1 x 10 ⁻⁷ [Pa m ³ /s]	
Leak Rate between Stopper and Barrel	< 1 x 10 ⁻⁸ [Pa m ³ /s]	< 1 x 10 ⁻⁸ [Pa m ³ /s]
Leak Rate between Tip Cap and Nozzle	< 1 x 10 ⁻⁸ [Pa m ³ /s]	< 1 x 10 ⁻⁸ [Pa m ³ /s]
Compliance with Helium CCI acceptance criterion?	YES	YES

Table 2: Container closure integrity test results.

We have recently decided to invest in a facility for the staked-needle syringe. The necessary equipment will be installed during 2020. The OXYCAPT syringe with a needle has some special features – it is tungsten free, glue free and adhesive free, and several gauges and lengths will be available.

CONCLUSION

OXYCAPT has been developed to overcome the current problems the pharmaceutical industry is experiencing with syringes and vials made from traditional materials. In addition to special features of COP – such as a high water vapour barrier, high break resistance,

- ✓ OXYCAPT™ multilayer plastic syringe with staked needle
- ✓ Several sizes of gauge and needle length
- ✓ Tungsten-free, Glue-free (This adapter is made by insert molding)
- ✓ Ultrasonic welding with syringe barrel and adapter with needle
- ✓ Adhesive-free
- ✓ ISO 7864 (Needle), ISO 7886-1 (Syringe)



Figure 9: Staked-needle syringe (under development).

very low extractables and low protein adsorption – OXYCAPT can offer a high oxygen and UV barrier. Also, we have conducted extensive testing and developed

innovative products based on customers' requests. We believe OXYCAPT offers numerous substantial benefits to the rapidly growing pharma industry.

ABOUT THE COMPANY

Mitsubishi Gas Chemical (MGC) operates in a wide range of fields, from basic chemicals to fine chemicals and functional materials. MGC established the Advanced Business Development Division in 2012 as a centre to create new businesses, and developed OXYCAPT™ Plastic Vial & Syringe as an alternative to glass containers.

ABOUT THE AUTHOR

Tomohiro Suzuki joined Mitsubishi Gas Chemical in 1998. He worked in the oxygen absorbers division until 2011, before moving to the advanced business development division in 2012 to be a member of the OXYCAPT development team. Since then, he has been in charge of marketing the OXYCAPT plastic vial and syringe. His current position is associate general manager.



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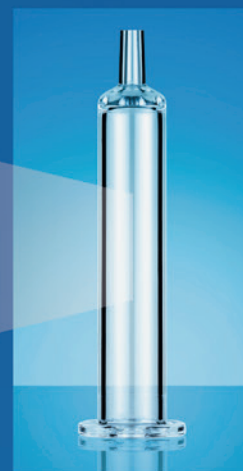
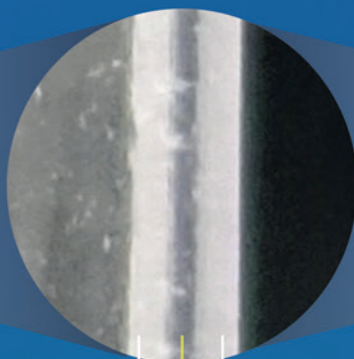
Assessing the risk of interaction between E&Ls and therapeutic proteins

Kim Li, Amgen

Transformation of toxicology data into specific PDE's

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



- Excellent Oxygen Barrier**
- High Water Vapor Barrier**
- Very Low Extractables**
- Low Protein Adsorption**
- Excellent Ultraviolet Barrier**
- High Break Resistance**
- High pH Stability**
- Silicone Oil Free Barrel**
- Pre-sterilized Vial & Syringe**
- Customizable**
- Suitable for Biologics**

Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)



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DEVELOPING DEMONSTRATORS TO INCREASE PATIENT CONFIDENCE AND REDUCE ANXIETY

In this article, Joe Reynolds, Research Manager at Noble, using Noble's collaboration with BD as an example, discusses the value of demonstrators for making patients comfortable and effective with their prefilled syringe, leading to a significant improvement in treatment adherence and patient quality of life.

According to recent research, the global prefilled syringe market is estimated to reach US\$22.5 billion (£17.3 billion) by 2025. Driving forces in the market's expansion include technological advancements in drug delivery and the growing use of prefilled syringes for biologic and large molecule medications.¹ While these medications can significantly improve patient quality of life, the WHO estimates that 50% of patients diagnosed with chronic conditions do not take their medications as prescribed.² Whilst myriad factors influence patient adherence and outcomes, research has shown that demonstrators and education can positively influence patient acceptance and adherence to treatments using prefilled syringes, safety systems and other forms of drug delivery.

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

From experience, Noble has found that confidence and anxiety are two key variables that influence a patient's perception toward drug delivery devices and their overall therapy. The onboarding period (or the

"Through advancements in usability and human factors engineering, the overall understanding of patient adherence and, in particular, the value of device demonstrators and onboarding education has greatly improved."

first 30, 60, 90 days of treatment) is where these attitudes and usage behaviours are first established, becoming key predictors of long-term adherence and outcomes (Figure 1). During the onboarding phase, 45% of patients skip or avoid injections due to needle anxiety or fear,⁴ which can subsequently lead to ingrained avoidance behaviours and, ultimately, the discontinuation of treatment.

REDUCING NEEDLE ANXIETY THROUGH THE USE OF DEVICE DEMONSTRATORS

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



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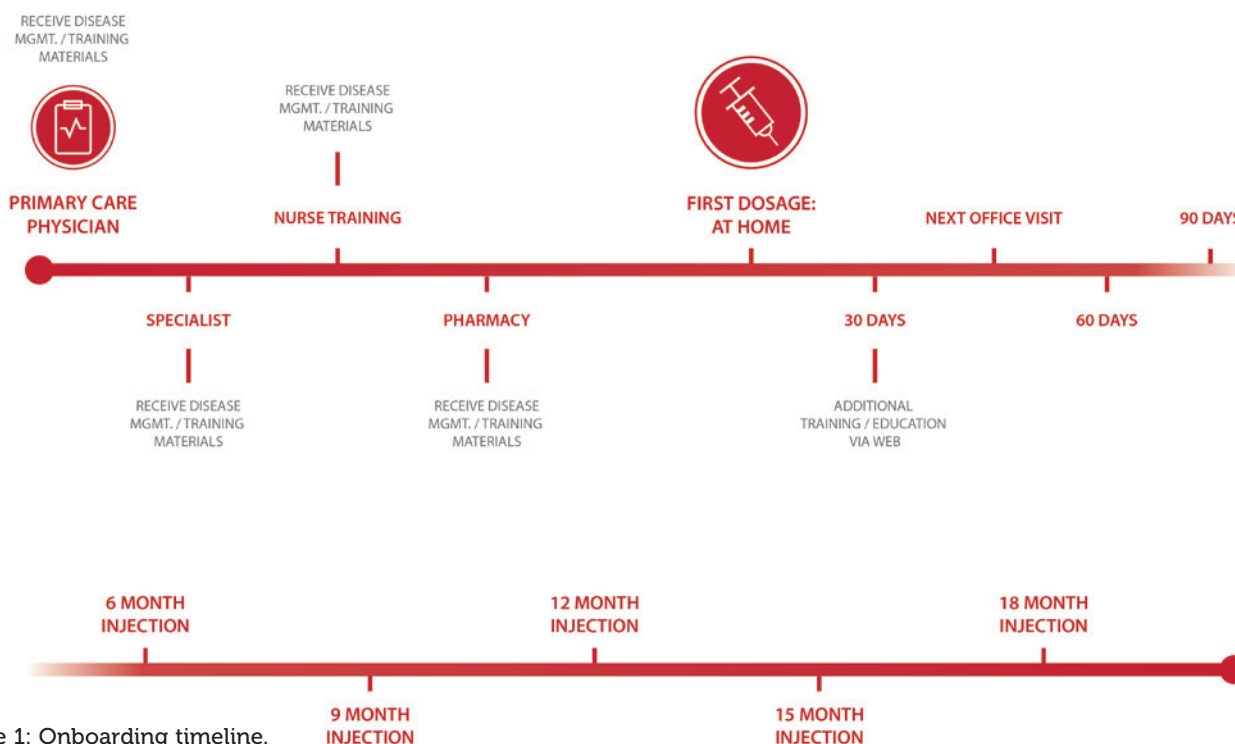


Figure 1: Onboarding timeline.

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

COLLABORATIONS THAT FOCUS ON PATIENT SUCCESS

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

Noble collaborates with Becton Dickinson (BD) to provide advanced patient onboarding solutions, including demonstration devices (Figure 2). Through the ongoing collaboration, Noble leverages its onboarding solutions to develop novel demonstrators based on BD UltraSafe™ technology, thereby improving the patient experience and confidence. Noble's market expertise and BD's passive needlestick safety devices allow for a platform approach for drug delivery devices and access to

dedicated onboarding systems. BD has been an early innovator in developing safety-engineered solutions for the market, partnering with numerous customers to ensure product success.

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

One example of how this collaboration benefits patients is BD's UltraSafe Plus™ Passive Needle Guard. The overall design of the product was validated by performing handling studies with both nurses and self-injecting 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. Noble's device demonstrators will compliment BD's syringe and help instill another level of confidence during the onboarding process through hands-on experience that fully mimics the actual device (Figure 3). Device demonstrators have become the foundation for effective education and onboarding strategies, allowing patients and healthcare providers to safely learn how to use prefilled syringes and other forms of drug delivery.

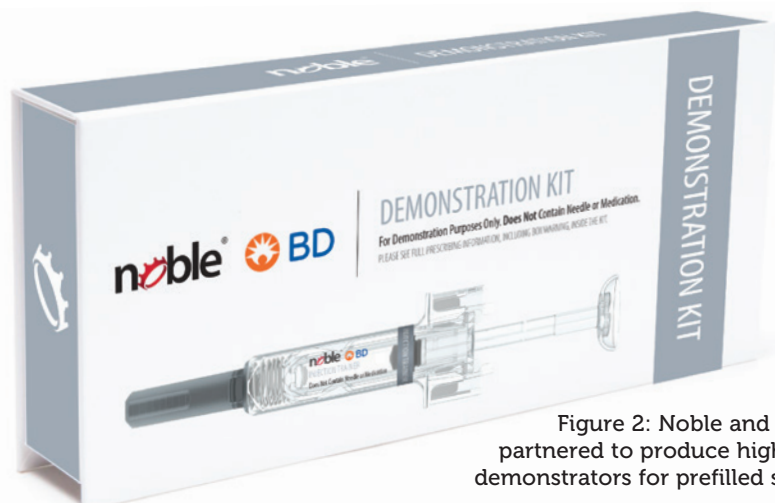


Figure 2: Noble and BD have partnered to produce high quality demonstrators for prefilled syringes.

DEVELOPMENT OF DEMONSTRATORS FOR PREFILLED SYRINGE SYSTEMS

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

These demonstrators are custom developed to mimic standard prefilled syringes and prefilled syringes with safety systems. A few key features include:

- **Locking Needle Shield & Resettable Safety Mechanisms** – Demonstrators are intended to replicate the device safety and shielding systems with the capability for users to reset the mechanisms for repeated use.
- **Replication** – Demonstrators are designed to be true to form and function of the real prefilled syringe, able to simulate all aspects of the patient experience including form, colour adjustments, window size and actuation force.
- **Needle Tip Simulation Option** – Demonstrators should also offer the option to exhibit realistic injection simulation designed to simulate the feel and forces involved with an injection.

BEST PRACTICES IN QUALITY

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

The industry will continue to evolve, giving patients the opportunity to gain confidence in their treatments, overcome adherence barriers and, in the end, achieve an improved quality of life. Through partnerships and collaborations that put the patient at the centre, like the relationship between Noble and BD, patients will have a better onboarding experience for

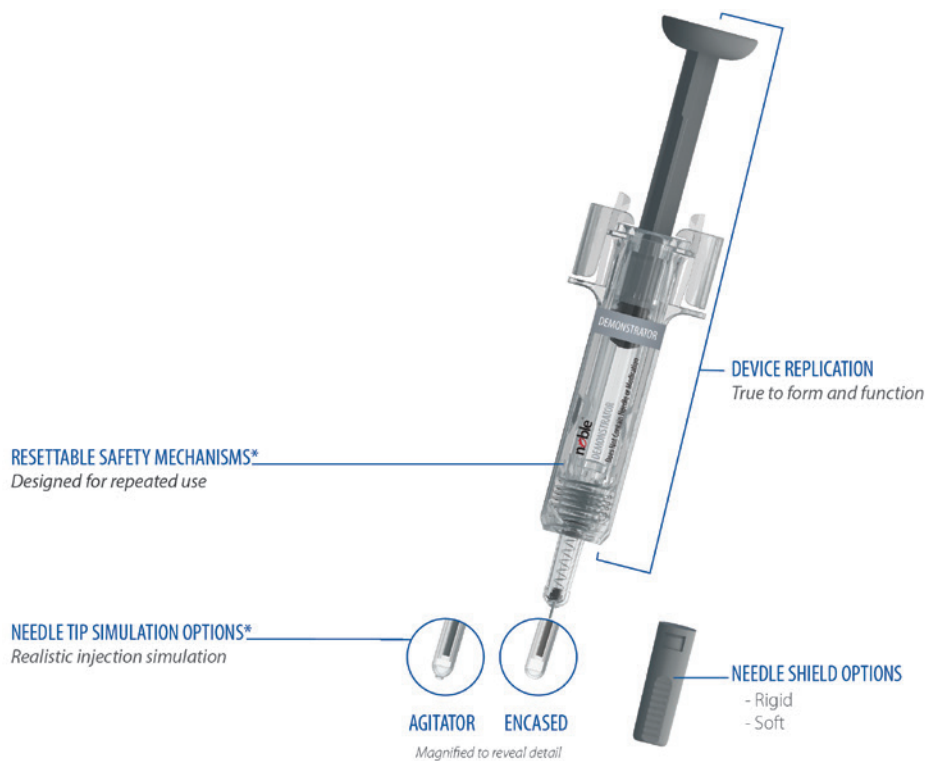


Figure 3: Noble offers a variety of innovative features designed to simulate BD UltraSafe™ technologies with the goal of familiarising and preparing patients to self-inject.

treatment all the way to the last step as they administer their medication. Industry leaders like BD and Noble, partners who know the power of incorporating human factors into engineering and experiential training, inspire the industry to innovate design and onboarding practices and ultimately provide patients with better overall treatment options.

ABOUT THE COMPANY

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

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ABOUT THE AUTHOR

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

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