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# Contents

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## PREFILLED SYRINGES & INJECTION DEVICES

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

### EDITORIAL CALENDAR

| | |
|---|---|
| Oct/Nov 2022 | Drug Delivery & Environmental Sustainability |
| Nov | Pulmonary & Nasal Drug Delivery |
| Dec | Connecting Drug Delivery |
| Jan 2023 | Skin Drug Delivery: Dermal, Transdermal & Microneedles |
| Feb | Prefilled Syringes & Injection Devices |
| Mar | Ophthalmic Drug Delivery |
| Apr | Pulmonary & Nasal Drug Delivery |
| Apr/May | Drug Delivery & Environmental Sustainability |
| May | Injectable Drug Delivery: Formulations & Devices |
| Jun | Connecting Drug Delivery |
| Jul | Novel Oral Delivery Systems |
| Aug | Industrialising Drug Delivery |
| Sep | Wearable Injectors |
| Oct | Prefilled Syringes & Injection Devices |

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*Front cover image, "syriQ BioPure® 5.5 mL", courtesy SCHOTT Pharma (see Ypsomed's article in this issue, Page 6). Reproduced with kind permission.*

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# THE NEW YPSOMATE® 5.5 – TAKING HANDHELD SELF-INJECTION BEYOND VOLUMES OF 2 ML

In this article Reto Jost, Innovation and Business Development Director at Ypsomed, introduces YpsoMate 5.5, the staked-needle-syringe-based, two-step autoinjector for injection volumes in the 2.0–5.5 mL range. Mr Jost discusses the drivers of the demand for high-volume, high-rate subcutaneous drug delivery using handheld autoinjectors and explains the design rationale of this new injection device.

## AUTOINJECTORS FOR THERAPEUTIC PROTEINS

The success story of autoinjectors for the subcutaneous administration of therapeutic proteins began in 2006 with the introduction of devices for Amgen's Enbrel (etanercept) and AbbVie's Humira (adalimumab).[1] With the increasing number of biologic and biosimilar drug approvals, the number of marketed autoinjectors has grown continuously over the last few years. Today, approximately 300 million prefilled autoinjector devices are sold annually, and this number is increasing. Today's prefilled autoinjectors are typically platform products, such as the YpsoMate device family – which is characterised by simple push-on-skin needle insertion and automatic initiation of the injection process.

Until 2020, all marketed autoinjectors had a maximum injection volume of 1 mL. Over the last five to seven years, much of the demand for new device innovations for subcutaneously delivered drugs has been dominated by the need to inject larger volume injections. This has spawned demand for larger volume handheld autoinjectors, as well as a new device class – patch injectors. With regard to this demand, Ypsomed has increased its YpsoMate autoinjector family with the addition of two new variants, YpsoMate 2.25 and YpsoMate 2.25 Pro, for standard and more viscous drugs respectively. Two examples of recently approved drugs delivered in YpsoMate 2.25 mL autoinjectors are Teva's migraine product, Ajovy (fremanezumab), which was approved in 2020, and Novartis' Cosentyx (secukinumab), which was approved in 2021 for psoriasis. Moreover, Ypsomed is industrialising its YpsoDose patch injector for its first clinical trials, acknowledging the growing interest in larger-volume wearable injectors.

> "Pushing the limits of today's injection devices has the potential to provide significant benefits to patients, providers, payers and pharmaceutical companies."

## LARGE-VOLUME, HIGH-RATE HANDHELD INJECTIONS

Pushing the limits of today's injection devices has the potential to provide significant benefits to patients, providers, payers and pharmaceutical companies. Larger dosing volumes allow larger payloads and less frequent injections, reducing the therapy-burden for patients and caregivers. They offer new options in formulation development and, therefore, foster the transition from intravenous to subcutaneous delivery, enabling a shift from hospital to home administration.

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"YpsoMate 5.5 represents the newest member of the YpsoMate autoinjector family, extending the design space of today's handheld autoinjectors and enabling the administration of injection volumes in the 2.0–5.5 mL range."

Today's autoinjectors are capable of injecting volumes of up to approximately 2 mL in around 10 seconds, which are medium-volume, high-rate injections. Recent work on increasing the volumes of autoinjector-based injections has been published in preclinical and clinical studies that explore the new field of large-volume, high-rate injections.[2–6] The results of these studies indicate that high-rate injections of volumes beyond 2 mL are feasible, paving the way for the development of autoinjectors for volumes above 2 mL.


Figure 1: The new YpsoMate 5.5 large-volume autoinjector.

## YPSOMATE 5.5 – THE NEW AUTOINJECTOR PLATFORM FOR VOLUMES ABOVE 2 ML

YpsoMate 5.5 represents the newest member of the YpsoMate autoinjector family, extending the design space of today's handheld autoinjectors and enabling the administration of injection volumes in the 2.0–5.5 mL range (Figure 1). YpsoMate 5.5 is based on the proven YpsoMate 2.25 Pro technology and leverages a similar type of constant force drive mechanism. This ensures that large drug volumes are injected reproducibly, even with higher-viscosity formulations, which would not be possible using a conventional compression spring. Different spring configurations with different force profiles allow the system to be adapted to accommodate a broad range of drug viscosities, up to 30–50 cP. Furthermore, it allows the adjustment of the flow rate to the desired target value. Configurable injection times are in the range of approximately 10–60 s for an injection volume of 5 mL.

| Attribute | Specification |
|---|---|
| **Primary container** | Staked-needle prefilled syringe |
| **Fill volume** | 1.5–5.5 mL |
| **Viscosity** | 1–30 cP, with 27G STW<br>12.7 mm needle, up to 50 c<br>with larger bore needles |
| **Injection time** | 10–60 s |
| **Needle insertion depth** | 5–8 mm |

Table 1: The platform design space of YpsoMate 5.5.


Figure 2: The YpsoMate autoinjector family.

The YpsoMate 5.5 autoinjector features the market-proven and broadly accepted two-step handling principle: the user removes the cap and injects the drug by pushing the device against the skin. As with the other YpsoMate family members (Figure 2), the design is suitable for fully automated manufacturing. YpsoMate 5.5 can be leveraged for a broad range of applications, and offers quick time-to-market and attractive pricing models. The platform design space of the YpsoMate 5.5 is described in Table 1.

## NEED FOR DEDICATED DESIGN AND USER INTERFACE

Larger-volume injections raise questions about the user's physical and cognitive capability to hold the device in place during longer injections. Initial evidence for 2 mL autoinjectors confirmed that injection times of up to approximately 30 seconds are feasible in terms of patient's physical capabilities.[7] However, the question remained whether or not long injection times have an impact on the user requirements and whether injection times beyond 30 seconds are feasible.

Therefore, Ypsomed's development team conducted a series of explorative user studies to assess user capabilities and needs in conjunction with handheld injections of more than 2 mL. The findings of this research confirmed that even users with medium-to-severe hand impairments were capable of holding an autoinjector in place for injections of up to 70 seconds. Additionally, they indicated that a well-designed grip is essential for convenient handling and a stable hand position during the entire injection. Continuous visual and audible user feedback was preferred over the current "start and end click" feedback for short injections, as well as having plunger-travel visible in the drug window.

These findings are designed into YpsoMate 5.5 – the waisted and textured gipping area, along with the contour, allows for a broad variety of grip styles and enables stable handling during the injection. The rotating dial and continuous clicking communicate to the user very clearly the start and the end of the injection, and that


Figure 3: Enhanced grip design and rotating visual injection indicator.

> "One of the main goals of the development was to leverage existing standards and components where possible, with the intent to minimise time-to-market, reduce development risks, ensure suitability for sensitive drug products and facilitate compatibility with existing filling lines."

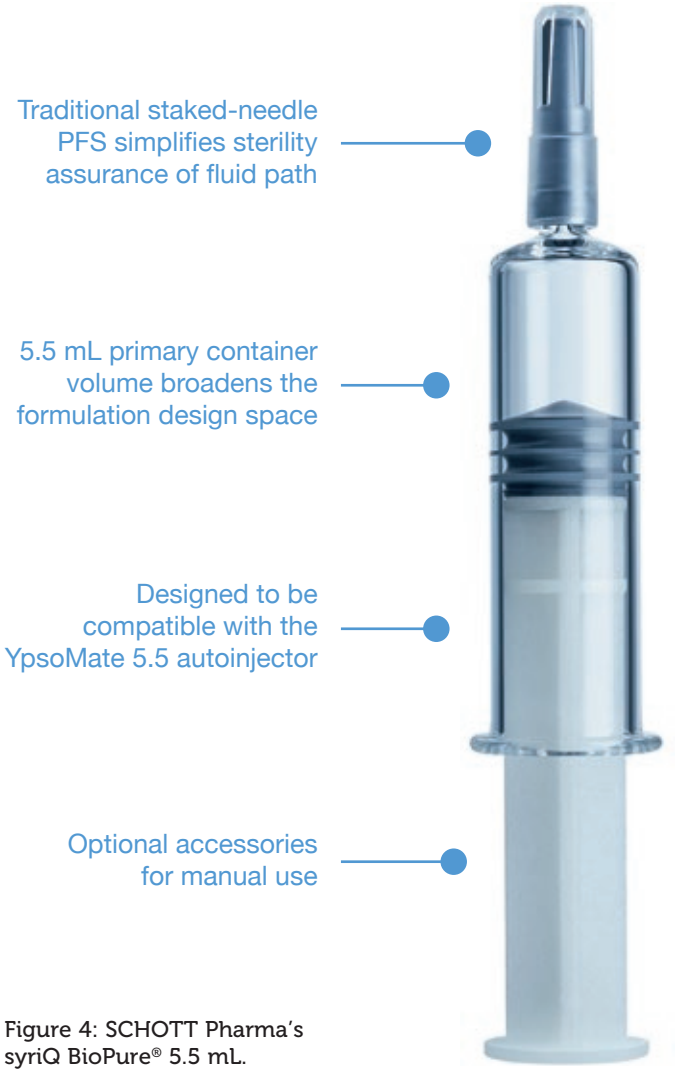


Figure 4: SCHOTT Pharma's syriQ BioPure® 5.5 mL.

the injection is progressing as intended. The design of YpsoMate 5.5 takes into account the particular user needs associated with large-volume handheld injections and supports the user in successfully completing the injection steps, providing the patient with confidence during drug administration (Figure 3).

## THE STAKED-NEEDLE READY-TO-USE SYRINGE

The staked-needle ready-to-use (RTU) syringe has become the primary container format of choice for use in autoinjectors. The integrated needle with rigid needle shield has a proven track record with respect to container closure integrity and sterility. The pre-sterilised format, packaged in a standard nest-and-tub, is well established and has been successfully industrialised on a wide array of filling lines. Different product presentations are possible based on the same syringe, be it as a stand-alone prefilled syringe (PFS), a safety syringe or an integrated syringe in an autoinjector.

Ypsomed has adopted the same prefillable syringe format for YpsoMate 5.5 and, therefore, expanded its existing collaboration with SCHOTT Pharma (Mainz, Germany) to develop a large-volume syringe. One of the main goals of the development was to leverage existing standards and components where possible, with the intent to minimise time-to-market, reduce development risks, ensure suitability for sensitive drug products and facilitate compatibility with existing filling lines. The result of this joint development is syriQ BioPure® 5.5 mL, the large-volume prefillable syringe with staked needle for sensitive drugs (Figure 4).

## CONCLUSION

With YpsoMate 5.5, Ypsomed extends the limits of current handheld autoinjectors and opens up the new segment of large-volume, high-rate injections in combination with SCHOTT Pharma's syriQ BioPure® 5.5 mL RTU PFS. As such, YpsoMate 5.5 offers new administration options for biologics in therapy areas such as autoimmune diseases, rare diseases and immuno-oncology.

After successful completion of extensive concept and human factors testing, Ypsomed has initiated a development and industrialisation programme, together with its lead customers, to bring YpsoMate 5.5 into clinical studies. Non-GMP devices and syringes are available for feasibility testing with further drug candidates.

## ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms consist of autoinjectors or PFSs in 1 and 2.25 mL formats, disposable pens for 3 and 1.5 mL cartridges, reusable pen injectors, ready-to-use prefilled wearable patch injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio.

With over 30 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare providers, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients'

lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases and integrating these insights with digital therapy management ecosystems.

The company leverages its in-house capabilities in electronics, software and connectivity for the development of new devices and digital product systems. Ypsomed is ISO 13485 certified and all its processes comply with design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by pharma customers and regulatory agencies to supply devices for global markets, including the US, Europe, Japan, China and India.

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## ABOUT THE AUTHOR


**Reto Jost** is Innovation and Business Development Director with Ypsomed Delivery Systems. He has been with Ypsomed since 2014 in a number of roles in product management and business development, working with pharma companies to develop and bring to market innovative self-injection systems. Since 2018 his main focus has been on new product innovation, with particular focus on large-volume injections. Mr Jost holds an MSc in Mechanical Engineering from ETH Zurich, Switzerland, and a CAS in Business Administration from HES-SO, Fribourg, Switzerland. He has broad experience in medical devices, having worked in the industry since 2006.

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# AUTOINJECTORS: HISTORICAL ACHIEVEMENTS AND COMPELLING NEEDS DRIVING NEXT-GENERATION DEVICES

In this article, Richard Whelton, Head of Business Strategy and Marketing, and Philip Green, PhD, Senior Consultant, Head of Business and Commercial Development, both at Congruence Medical Solutions, summarise the history of autoinjectors, highlight success stories to date, review the unmet needs that remain and consider emerging needs that could drive continued innovation in autoinjectors to ensure safety, patient satisfaction and pharma commercial success.

The needle-based autoinjector market has grown significantly since the first commercial release in the 1980s and is now one of the most important modes of drug delivery. In 2021, six of the 30 top-selling drugs worldwide were delivered in an autoinjector format, representing around 50% of the total sales. The growth of the autoinjector market is expected to continue, with a projected 18.1% compound annual growth rate from 2019 to 2027.[1]

Autoinjector devices themselves have evolved significantly to address multiple and changing self-injection needs. However, several unsolved problems remain and, as the pharma market itself continues to evolve, additional compelling unmet needs continue to arise.

## HISTORICAL PERSPECTIVE

### Enabling Self-Injection Through Ease of Use and Safety

The needle-based autoinjector was originally invented in the 1970s to help protect soldiers in the event of chemical warfare (Figure 1). In 1987, the EpiPen (Mylan, part of Viatris, PA, US) for emergency adrenaline (epinephrine) delivery was approved by the US FDA, typically for intramuscular delivery, and did not include a prefilled syringe (PFS). It was followed by other emergency applications, such as for naloxone and glucagon delivery.

> "Autoinjector devices themselves have evolved significantly to address multiple and changing self-injection needs."

In the mid-2000s, following a dramatic increase in the number of frequently dosed biologics, autoinjectors for regular home use were developed and introduced. Disposable autoinjectors for Aranesp (darbepoetin alfa; long-acting erythropoietin) (Amgen, CA, US) and Neulasta (pegfilgrastim) (Amgen) launched around 2005, although neither stayed on the market for very long, with devices for Humira (adalimumab) (AbbVie, IL, US) and Enbrel (etanercept) (Immunex, CA, US) launching in 2006. Much of the design work was focused on improving the patient experience, primarily via a reduction in the number of user steps and by improving safety features – such as hidden needles and automatic needle shields.

In the 2010s, human factors testing also became a major driver for design improvement, propelled in part by the FDA and other regulatory bodies placing emphasis on human factors across all medical devices.[2] Examples include the incorporation of multiple indicators (visual, audible, tactile) to signal dose initiation and


Figure 1: MARK I nerve agent antidote kit.

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end-of-dose. Patient training materials – such as instructions for use, online videos, talking trainers, realistic device trainers – have all been improved dramatically over the last ~20 years.

Overall, two common modes of injection actuation arose – push-button and push-on-skin. The two-step push-on-skin has become the more popular approach today. Furthermore, some devices have a stationary PFS with the needles inserted into the injection site by the patient, while in others the PFS is shuttled within the device for automatic needle insertion actuated by the patient. Reusable and disposable autoinjectors were both introduced but, over time, disposable has become the most common modality due to ease of use, easy disposability and reliability, as well as lower upfront cost, fewer reimbursement complexities and many therapies not being injected daily or weekly.

### Reliability and PFS Compatibility

As the use of autoinjectors grew in the late 2000s and 2010s, so did incidences of glass syringe breakage and malfunctions. Indeed, one of the very first autoinjectors, for Neulasta, was recalled in 2006 because of incomplete injections/slow injection times.

Use of the original glass prefilled syringes (PFSs) was never foreseen in an autoinjector. Hence, ensuring PFS compatibility became a major point of emphasis. Various approaches to modifications in the design of both autoinjectors and PFSs have improved the reliability of autoinjectors,[3] and continue to do so.

### Viscous and High-Volume Drugs

The increasing viscosity and/or volume of pharmaceutical formulations has been a well-recognised trend over the last several years, driven by a number of factors, such as the move to high-strength biologics, long-acting therapies, the shift from intravenous (IV) to subcutaneous (SC) administration, etc. In addition, many patients do not always wait for their biologic medications to reach room temperature prior to use, which effectively increases formulation viscosity.

Conventional autoinjectors have struggled to inject these drugs due to the high forces required. This has led to the development of new autoinjectors with increased spring strength, but they, in turn, initially experienced quality/reliability issues, such as syringe breakage, device malfunctions and increasing device size. In addition to considering increasing the number of injections, mitigating approaches were taken to strengthen the PFS accordingly and expand available needle sizes (<25G), while also increasing the drug volume to 2.25 mL to help reduce the viscosity (and therefore the force required). However, this has generally resulted in less user-friendly devices – often with larger form factors, higher weights, physical recoil, loud sounds and uneven delivery rates. It is possible to reduce the size of a device by moving away from automatic needle-insertion to manual.

> "Autoinjector growth will be propelled by patent expiration of biologics, leading to the need for more differentiation, potentially including differentiated autoinjector design."

These drugs also tended to have longer injection times (over 15 seconds) to help avoid patient pain and injection site leakage associated with larger delivery volumes. Long wait time was seen as a potentially major negative for hand-held delivery devices and, in part, this has given rise to a new category of devices – wearable injectors – that can help address some of these needs by delivering even higher volumes over a longer time period. However, these too come with their own set of cost, reformulation, disposal and user challenges.

An alternative approach has been to move away from spring-based autoinjectors to alternate power-sources.[4] This has included gas-based autoinjectors, which typically can deliver very high forces yet still offer a smooth delivery-rate and a compact size. Despite their many advantages, however, adoption of gas-based autoinjectors has been low to date, perhaps due to reliability and cost concerns and the potential for the release of greenhouse gases in some instances (similar to concerns raised with inhalers).[5] Electromechanical devices, such as Enbrel's AutoTouch device, have also been developed, which offer similar benefits, as well as the potential to integrate connectivity and other digital features, but tend to have a high-cost, large size and need to be reusable, going against the prevailing single-use disposable trend.

### Platform Autoinjectors

Development of the early autoinjectors for specific drugs was a highly elongated process. As the biologics revolution continued into the 2010s, and more and more molecules entered the pharma pipeline, speed to market was key – pharma customers no longer wanted devices to be the rate limiting step, especially for drugs such as generics and biosimilars.

Autoinjector manufacturers have responded by introducing platform products, which consist of base devices that can be relatively easily customised to accommodate different specifications within a predefined standard range. This has dramatically cut development times and costs. Pharma companies also tend to view platforms with at least one commercially launched product as "de-risked" options, further increasing their appeal.

## CURRENT AND FUTURE MARKET DRIVERS FOR AUTOINJECTORS

Trends within the pharma pipeline will ultimately have a major influence on the next generation of autoinjectors. These include the continued shift towards less frequent dosing and more viscous/high-volume drugs, the emergence of immuno-oncology drugs, increased shift of therapy to home settings, subcutaneous rare disease products and drugs with variable dosing needs. Additionally, autoinjector growth will be propelled by patent expiration of biologics, leading to the need for more differentiation, potentially including differentiated autoinjector design. The continued drive to switch from IV to SC, especially in oncology, and conversion from lyophilised to liquid-stable formulations will expand the autoinjector market. High-strength biologics and longer-acting products will drive the need for autoinjectors capable of injecting more viscous formulations.

Pharma's strategic needs are also shifting, with a greater emphasis being placed on sustainability[6] and cost-effectiveness, as well as disease management, through integrated solutions and interventions, and a desire to gather real-world data and evidence about their drugs.

### Higher Volume Devices, Longer Hold Time

Currently, the majority of marketed autoinjector products instruct patients to wait up to around 15 seconds before removing them from the skin. However,

"Development of devices leveraging alternate power sources such as compressed gas or electromechanical systems can be expected, due to their ability to deliver highly viscous drugs in a small volume (<2.25 mL)."

there is some evidence to suggest that longer delivery times, and therefore higher volumes (2.25–5 mL), could be acceptable for autoinjectors.[7] Indeed, recently 5- and 3-mL cartridge-based autoinjectors were offered for testing. The anti-migraine autoinjector product Ajovy (fremanezumab) from Teva (Tel Aviv, Israel) was recently approved in the US with a 30-second hold/dwell time (including 10 seconds after the end of injection).

For even higher volumes (>10 mL), it is likely that wearable devices will still be required, and several devices are in development to cater to this need.

### Alternate High-Power Sources

Although the use of springs for higher-volume delivery may be acceptable, patient preference will likely always be for shorter injection times. Therefore, development of devices leveraging alternate power sources, such as compressed gas or electromechanical systems (including micro-electromechanical systems), can be expected due to their ability to deliver highly viscous drugs in a small volume (<2.25 mL). If electromechanical platforms are considered, reusability may be necessary to address cost and disposal challenges.

### Reusable Devices for Frequent Dosing and Compliance Monitoring

The growing focus on sustainability and a desire to incorporate electronic/connectivity features may also facilitate a partial shift towards reusable devices in the future. This trend is more likely to take hold with drugs that require frequent dosing (e.g. weekly and daily), where waste from disposable devices is high and a need to ensure regular dosing adherence is key, such as with BETASERON (interferon beta-1b) BETACONNECT (Bayer, Leverkusen, Germany). For less frequently dosed drugs, for which there is a major trend, the case for reusable devices is not as strong – cost per dose for a reusable device would be relatively high, and the waste difference between one large reusable device with electronics versus a handful of single-use devices is not as stark. It should also be acknowledged that there are strategies to minimise the environmental impact of disposable, including within the supply chain.

### Enhanced Ease of Use

While autoinjector devices are generally acknowledged to be easy to use, room still exists for them to be improved further. The need is perhaps greatest for new, injection-naïve users,[8] and it is likely that users who inject infrequently will also require more support. Training programmes, enabled by connectivity, online guides and tools, will continue to close the gap, but device enhancements could also play a role.

One example is preventing "wet-injections", where a user removes the device from the skin too early before the full dose is delivered. The impact of wet-injections is amplified with less-frequent dosing, as a significant period (perhaps months) of treatment may be missed. In some cases, the device is removed early due to patient misunderstanding, and the introduction of digital apps and connected devices that facilitate better time counting (in training and in real-time) can help, as would true end of dose indicators. It is possible that the user may accidentally remove the device prematurely from the skin, or even deliberately if discomfort is experienced, and the chances of this increase with the longer injection times necessitated by viscous drugs, as such, additional innovations may be required.

### Connectivity Enabling Disease Management

Connected devices and related software offer the potential to enhance disease management through data collection and providing real-time insight to patients, as well as enabling connection to support services from providers and gathering real-world data for subsequent analysis. Most progress in this regard has been

| Needs | Current Solution Examples | Future Innovation Examples |
|---|---|---|
| Reliability/PFS Compatibility | • Improved device/PFS designs<br>• Improved siliconisation<br>• Polymeric PFSs | • Enhanced designs for next-generation devices/containers |
| Human Factors/ Usability | • Multiple user feedback/ indicators<br>• Simple two-step devices<br>• Enhanced customer training | • True end-of-dose indicator<br>• Connected training devices<br>• Wet injection prevention |
| High Dose Volume | • 2.25 mL hand-held autoinjectors<br>• 3.5 mL wearables | • Handheld >2.25 mL (e.g. with longer hold time)<br>• Wearables > 3.5–25 mL |
| High-Viscosity Formulations | • Wider bore/thin-wall needles<br>• Enhanced springs | • Electromechanical<br>• Alternate power sources<br>• Longer hold time<br>• Polymeric PFSs |
| Faster, Lower-Risk Device Development | • Platform devices – fixed dose, with limited customisation | • Platform devices – variable or fixed dosing, with wider range of customisation |
| Disease Management | • Compliance monitoring | • Multiple sensors/monitoring<br>• Integrated interventions |
| Sustainability | • Disposal management systems | • New materials/reusable devices<br>• Supply chain efficiency |

Table 1: Summary of autoinjector achievements and potential future innovations.

made in diabetes, with integrated insulin pens already on the market to alleviate the complexity of disease management. Medication is another focus area. Companies that offer an integrated solution for diabetes are setting a template for other disease states to follow in due course, with connected injection devices playing an important role. As a result, many device manufacturers are developing connected versions of their autoinjectors, and it is expected that these will be important next-generation products.

### All-Encompassing Platforms

Today, relatively few autoinjectors are developed that are not ultimately part of a platform. However, the predefined specification ranges are often relatively narrow, meaning autoinjector companies may still offer a wide array of device platforms to cover all potentialities, and a pharma company may well need several platforms to cover their portfolio needs.

The industry is slowly moving towards more comprehensive platforms. Moving forward, this trend is expected to continue, with single platforms able to accommodate a wider range of drugs by offering:

- Delivery of a broad range of viscosities (up to 3000 cP). This helps with standardisation of manufacturing infrastructure, while providing flexibility (drug viscosities and/or needle gauge can change during development) and accommodating user-driven issues ("non-viscous" drugs can present as "viscous" if the drug is injected too soon after removal from refrigeration).
- Wide range of customisable injection speeds.
- Variable- and fixed-dose options.
- Cartridge-based options.
- Full-range of dosing volumes right down to the microlitre level. This is useful for paediatric applications that often require smaller volumes, as well as for dose ranging during clinical trials.

In conclusion, the ever-evolving biologics landscape is creating the need for more innovation, and the future will likely see the needle-based autoinjector category continue to evolve significantly (Table 1).

*Acknowledgements to Jayshree Srinivasan for her research and to Mathias Romacker for his insights that supported the creation of this article.*

## ABOUT THE COMPANY

Congruence Medical Solutions' purpose is to enhance the potential of injectable drugs that have emerging and hard-to-address delivery needs. Congruence does this by designing, developing and supplying innovative, versatile drug delivery device platforms in partnership with multiple pharmaceutical and biotechnology customers who trust the company's domain expertise and responsive, innovative approach. Congruence's growing portfolio addresses compelling problems, including microlitre dosing, viscous drug delivery, multi-dosing, variable dosing and minimising drug waste.

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## ABOUT THE AUTHORS

**Richard Whelton**, MBA, MBiochem, leads business strategy and marketing at Congruence Medical Solutions. He has nearly two decades of experience in medical technology, devices and life sciences. He is passionate about improving human health through innovative products and strategies. Over his career, he has held multiple roles in strategy, innovation and marketing, including a decade at Becton Dickinson & Co, where he worked on the development and commercialisation of a variety of drug delivery products, including self-injection devices. Mr Whelton holds an MBA from The Wharton School at the University of Pennsylvania (US) and a Master's Degree in Biochemistry from the University of Oxford (UK).

**Philip Green**, PhD, has extensive experience in the commercialisation of drug delivery products with a specific focus on combination injectable devices and IV/SC switching. From 2009 to 2018 at Merck, Dr Green was responsible for commercial device strategies around subcutaneous biosimilars and oncology products. Previously, he worked for BD, where he was responsible for advanced drug delivery partnerships, including microneedles and wearable injectors. Prior to this he held multiple drug delivery development roles with Zyma and L'Oreal. Dr Green received his BSc in Chemistry from Bristol University (UK), his PhD in Pharmaceutical Chemistry from the Welsh School of Pharmacy, Cardiff (UK) and undertook his postdoctoral research at the University of California, San Francisco (US).

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# OVERCOMING THE CHALLENGES OF ULTRA-LARGE-VOLUME SUBCUTANEOUS INFUSIONS

**Here, Rob Limouze, Director of Product Management at KORU Medical Systems, looks at the obstacles facing ultra-large-volume subcutaneous infusion drug delivery and highlights how the KORU Freedom infusion system meets these challenges.**

When given the choice, patients consistently prefer subcutaneous (SC) over intravenous (IV) drug delivery.[1,2,3] Use of the SC route has expanded recently through devices that can deliver up to 5 mL, more than the 2.5–3.0 mL limit of autoinjectors. Innovation in ultra-large-volume SC drugs (ULV SC) – those with volumes between 5 and 50 mL and beyond – is increasing rapidly.

There are unique challenges to realising the promise of ULV SC drugs. These have been identified over a decade of serving tens of thousands of immunology patients with SC immunoglobulin (SCIg), at volumes ranging from 5 to 200 mL (without hyaluronidase) and up to 600 mL (with hyaluronidase). Ten ULV SC drugs have been approved since 2010, most recently Empaveli® (Apellis Pharmaceuticals, MA, US) (pegcetacoplan) for paroxysmal nocturnal haemoglobinuria in 2021. Of the drugs using an injector, the KORU Freedom system has been specifically cleared for use with all but one and has been used in pivotal studies supporting the drug's approval (Figure 1).

## DEVELOPMENT AND COMMERCIAL SUCCESS DESPITE THE CHALLENGES OF ULV SC

ULV SC drug absorption differs from that of smaller volume injections. Infusion site back pressure can be higher at larger volumes and flow rates. Additionally, the impact of temperature on viscosity can have a clinically significant impact on delivery time when volumes are larger. A study

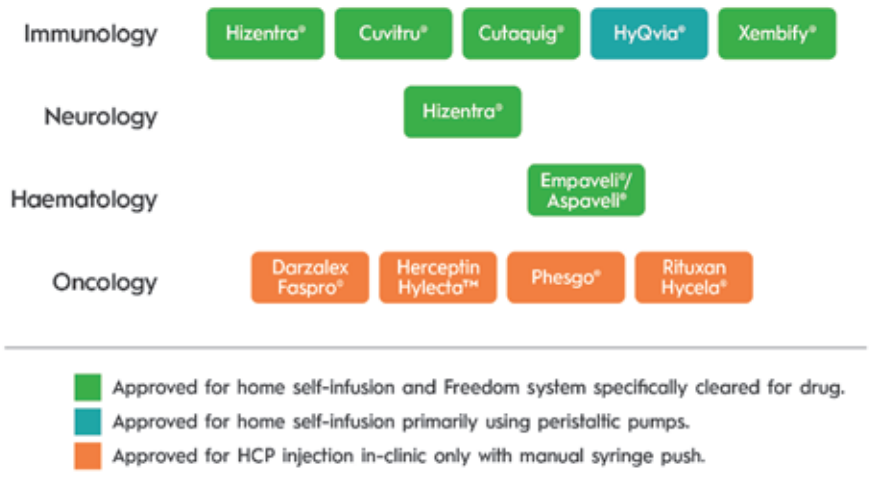


Figure 1: Drugs approved for SC injection of 5 mL or greater volume since 2005.

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"KORU Freedom uses a constant pressure system that allows the flow rate to adapt to back pressure at the injection site for an optimal patient experience."

of 17 immunoglobulin patients where the infusion rate slowed in response to site back pressure showed an average flow rate compensation of 20%. It also demonstrated that patients experienced variability in absorption from one infusion to the next (Table 1 & Figure 2).

At large volumes, many believe that maintaining a fixed flow rate regardless of infusion site back pressure can lead to patient discomfort. KORU Freedom uses a constant pressure system that allows the flow rate to adapt to back pressure at the injection site for an optimal patient experience.

A related challenge is accommodating the "bleb" that forms as the SC space fills with medication. The geometry and variability of bleb shape and size makes it challenging to secure a rigid patch injector throughout an entire infusion. The tethered design of the KORU Freedom infusion system accommodates variability in bleb shape and size while allowing patients to select easily between multiple infusions sites, such as legs, arms or abdomen, to accommodate lifestyle and patient preference.

The use of hyaluronidase can mitigate the above challenges by improving the rate of drug absorption by temporarily degrading hyaluronic acid and opening the SC space. However, its use creates new requirements. The flow rates made possible with hyaluronidase can exceed the back pressure tolerated by electronic systems and, depending on drug infusion requirements, customisation of system components may be needed to achieve desired treatment times.

| | |
|---|---|
| Total Number of Patients | 17 |
| Total Number of Infusions | 34 |
| Average Dose (mL) | 70.9 |
| Average Predicted Flow rate per Site (mL/Hr) | 16.8 |
| Average Measured Flow rate per Site (mL/Hr) | 13.4 |
| Average Decrease in Flow rate per Site | 20% |

Table 1: Change in flow rate to adapt to injection site back pressure. (Source: KORU and third-party data on file.)

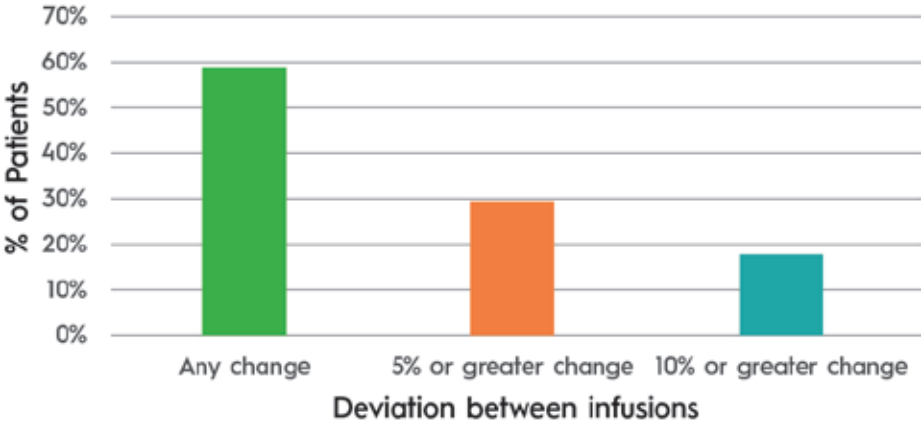


Figure 2: Patients experiencing differing flow rates between infusions 1 and 2. (Source: KORU and third-party data on file.)

"The modular design of the KORU Freedom system allows for rapid customisation and entry into the clinic while meeting drug delivery requirements."

The modular design of the KORU Freedom system allows for rapid customisation and entry into the clinic while meeting drug delivery requirements. Entry into Phase I–II studies can be accomplished with minimal development, allowing for device optimisation for Phase III without creating development delays or requiring pharmaceutical developers to fork the development path into a multiple-device strategy.

ULV SC drugs require patients to be trained in person by nurses before being certified for self-administration. Providing this education works differently in each global market. This can create a substantial training burden for drug manufacturers. Working with a partner with a fully developed training capability, as well as a channel to healthcare providers in global markets, can aid in reducing this burden. The KORU Freedom system is used to treat patients globally, with thousands of healthcare providers already experienced with the system.

Most ULV SC drugs are supplied in vials, requiring users to transfer the drug to a secondary container. This process is challenging for users and may not be possible for high-viscosity drugs. The KORU Freedom system has been cleared for use with some prefilled syringes, providing pharmaceutical companies with a means to select from multiple primary containers while eliminating the drug transfer step for patients.

## ABOUT THE AUTHOR

**Rob Limouze** serves as the Director of Product Management for KORU Medical Systems. He has over 19 years of experience introducing and managing product lines in the medical devices market. He obtained a BA in physics from Rutgers University (New Brunswick, NJ, US) and an MBA from Monmouth University (West Long Branch, NJ, US).

## SELECTING A DEVICE PARTNER

While a vendor may provide a delivery device, a device partner offers support spanning drug development and commercialisation. KORU offers proven success in development, clinical research, global registrations, commercialisation and therapy acceptance by tens of thousands of patients. This success rests on the combined efforts of engineering, clinical, commercial, regulatory and manufacturing teams honed by real-world feedback from patients, clinicians and regulators.

## ABOUT THE COMPANY

KORU Medical is a publicly traded medical device company specialising in the design, development, manufacturing and support of SC infusion systems. KORU is an industry leader in ULV drug delivery with more than 30 years of experience. Headquartered in the US with a new, modern facility located in Mahwah (NJ, US), KORU has an expanded reach supporting patient infusions across the globe.

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# ENLARGING THE VOLUME OF AUTOINJECTORS: TRAVERSING INJECTION BOUNDARIES

In this article, Gary Calderwood, Product Manager, Raluca Ganea, PhD, Clinical Affairs Manager, and Gene Rhode Fuensalida Pantig, Senior Scientific Communications Specialist, all of SHL Medical, review how the parenteral space has transformed over the past decade and reports how the company's portfolio of autoinjector technologies has evolved to deliver subcutaneous parenteral drugs of varying formulations, including higher administration volumes.

The medtech industry is at a crossroads, presented with the opportunity to actively participate in and redefine what kind of combination products will emerge and reach the hands of patients in the near future. Prefilled syringe (PFS)-based mechanical autoinjectors have been smoothly integrated in the co-development process between pharma and medtech, enabling patients to self-administer conventional biologics and biosimilars subcutaneously (SC). However, as the R&D formulation pipeline sees volumes and viscosities beyond what it has previously had to deal with, what device technologies does the medtech sector have to offer?

## A REVIEW OF THE RECENT DEFINING MOMENTS IN PARENTERAL DRUG DELIVERY

The current parenteral drug landscape contains 112 autoinjector products (single use, including emergency devices) addressing various chronic diseases. These areas include metabolic, autoimmune, inflammatory and systemic conditions, to name but a few. The latest five-year average for the US FDA's new molecular entities and biologics approvals currently stands at 51 per year. Ten years ago, it was 24 molecules per year. During this time period, notable advancements have been made in formulation science that have facilitated the SC delivery and absorption of biological products, the list of which now includes chemotherapeutic agents – something that has never been seen before.

At this rate of development, there is a possibility to expect more biopharmaceutical developments to shift in the direction of SC administration. Of the many approvals across the decade, there are a few notable ones. For example, a breakthrough therapy for atopic disorders was first approved in the US and EU in 2017 and, within the space of just a few years, this same biologic entered the self-injection space.

This is how, in 2020, SHL found itself as the device developer of one of the world's first PFS-based mechanical autoinjectors in the larger volume range (≥2 mL). At that time, it was not common for a true 2 mL fill autoinjector combination product to be launched on the market – even more so for systemic therapy. This suggests that there is potential to further expand the use of autoinjectors in SC therapy.[1–5]

## EXPLORING AUTOINJECTORS BEYOND 2 ML

In 2018, the SC Drug Delivery and Development Consortium was convened with the goal to identify solutions and raise awareness of the issues and gaps in the high-dose/large-volume drug formulations market. The Consortium aims to fully explore the potential of the SC route of administration. It is notable that, since its

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| Order | Subject | Condensed Problem Statement |
|---|---|---|
| 1 | High-Dose/Volume SC Technology Development | Misguided industry perception of what is possible in the development of large-volume (>2 mL) and high-dose SC device technologies |
| 2 | Bioavailability | Unpredictable and variable bioavailability of biologics |
| 3 | Immunogenicity | Lack of consistency across industry and understanding of untoward SC immunogenicity and the relevant test method to evaluate such a phenomenon |
| 4 | Patient Preference: IV vs SC | Patient preferences are unprioritised and not clearly understood in order to identify optimal trade-offs between IV and SC product design attributes |
| 5 | Clinical Trial Strategy | Unclear understanding of when to initiate SC clinical trials |
| 6 | Payer Preference | Unclear understanding of the value of SC injections beyond the price point |
| 7 | Patient Experience & Discomfort | Need to understand further how the patient experience impacts patient preferences and define quantifiable metrics to assess injection |
| 8 | Patient-Physician Interactions | Unclear understanding of the role of physicians in educating patients about the benefits of SC injections and the impact on overall patient preferences for IV or SC |

**Table 1: Problem statements – condensed for this article – in SC drug delivery developed by the consortium. First reported in the review article titled "Accelerating the development of novel technologies and tools for the subcutaneous delivery of biotherapeutics" published in 2020.[6]**

> "While considerable progress has been made in formulation technology development, it is of equal importance to develop solutions that put the patient experience at the centre of any new delivery system in order to advance parenteral drug delivery."

inception, the Consortium has consisted of leading members of the biopharma and R&D communities. It is therefore recommended that representatives of the medtech industry take part in these discussions and share their thought leadership to further advance the technology within the drug delivery space.

The consortium has developed and reported on eight problem statements that highlight a composite of actionable challenges in SC drug delivery. Ranked in the order of priority, high-dose/volume SC technology development is reported to be the first, followed by bioavailability, immunogenicity and then patient preference (Table 1). The focus of this article is on problem statements 1 and 4.

Considering the steady development of complex biologics, formulation technologies and the identified advantages of treatment self-administration, now is the time for pharma and medtech to explore autoinjectors capable of delivering doses beyond 2 mL. For SHL, it is important to provide a better understanding of current advances in autoinjector technologies in order to shift perceptions of their key role in next-generation SC drug development and delivery.[6]

## A CARTRIDGE-BASED SOLUTION TO ENABLE AUTOINJECTORS BEYOND 2 ML

The overwhelming majority (>98%) of combination products in PFS-based, single-use autoinjectors have an injection volume of 1 mL or less. However, it would be negligent not to consider that current biopharmaceutical trends and pharma pipeline molecules suggest a growing need for higher-capacity drug delivery technologies. This is essential for enabling a better and more comprehensive health and medical landscape. As the healthcare market evolves, device technology development remains central to delivering SC parenteral drugs that require higher administration volumes.[7]

While considerable progress has been made in formulation technology development (such as particle engineering, transiently altering the SC space, etc.), it is of equal importance to develop solutions that put the patient experience at the centre of any new delivery system in order to advance parenteral drug delivery. Patient preference is one of the consortium's top four challenges, which reinforces the value of therapeutic self-administration and the advantages of enabling drug delivery devices, like autoinjectors, particularly those that emphasise ease of use.

Conventionally, autoinjectors are developed around a PFS, which, with its staked needle, can be designed into two- or three-step self-injection devices that do not expose the user to the needle. In comparison, cartridge-based pen injectors traditionally require the user to manually attach the needle to the device before injection. This additional user step may pose a risk of foreign particle contamination and needle-stick injury. In the context of therapeutic self-injections, operational safety is highly important to facilitate medication adherence and improve the patient experience. Considering this, SHL has developed an innovative mechanism called "Needle Isolation Technology" (NIT®) that addresses the challenges associated with cartridge-based injection systems.

Based on a pre-installed needle housed within the cap of the device, NIT technology eliminates the need for users to manually attach the needle. With NIT, users simply unscrew the cap to engage the needle with the cartridge prior to injection, thereby opening the fluid path and allowing the injector to prime automatically. NIT makes it possible for the cartridge to behave like a traditional PFS with a staked needle; the device includes complete needle covering and shielding before and after injection. Additionally, the technology supports complete control of cannula gauge and length to enable target injection time and depth. The removal of an apparent design attribute trade-off between PFS- and cartridge-based autoinjectors has allowed NIT to pave the way for the

possibility of safe and intuitive large-volume/high-dose autoinjectors.

Prior to the establishment of the consortium, the first cartridge-based autoinjector built with NIT was approved by the FDA in 2017. The autoinjector, which is the second-generation device of SHL's pharmaceutical partner's GLP-1 receptor agonist, offers its patients a more convenient injection experience. Since its commercialisation in 2018, the combination product has delivered millions of doses to patients worldwide. Regarding patient experience and safety, the data currently available to SHL demonstrate how the market-proven NIT subassembly has successfully facilitated the safe and effective self-injection experience of patients.[8,9]

## GOING BIG: A TECHNOLOGY TO EXPLORE LARGE-VOLUME AUTOINJECTORS

The inclusion of NIT in an autoinjector opens pathways for increased dose volumes and viscosities, as well as the accommodation of lyophilised drugs, suspensions and other specialty formulations. If limited to PFSs as the primary container, the delivery of high doses will require reformulating the product, in turn raising concerns about stability, particle aggregation and the resultant viscosity.

Recently, treatments in the oncology area have been exploring the transition from the intravenous (IV) to the SC route of administration through enzyme-assisted drug formulations, further opening the possibility of cartridge-based autoinjector combination product development. When considering the treatment burden on the patient, data available to SHL suggest that there is a preference towards delivering a drug product using a single device, rather than multiple. SHL performed comparative literature studies to produce this reasoning.

Additionally, the development of primary containers with volumes greater than 2 mL and the infrastructural maturity of the associated fill/finish technology opens pathways for the appropriate large-volume device technology. To enable patient self-administration in circumstances where a PFS-based autoinjector seems infeasible for single-device injection, SHL has developed the Maggie® device technology.[10–12]

The Maggie device, built with NIT, was initially developed with a standard 3 mL cartridge. It was designed to address the technology gap between PFS-based autoinjectors and on-body patch pumps, effectively expanding the potential delivered dose volumes of autoinjectors to 3 mL. The architectural design of the device and its NIT subassembly allows the needle to be permanently hidden, from the moment when the patient unscrews the device cap up until the device is disposed of. This is intended to alleviate preconceived patient concerns associated with needle-based injections.

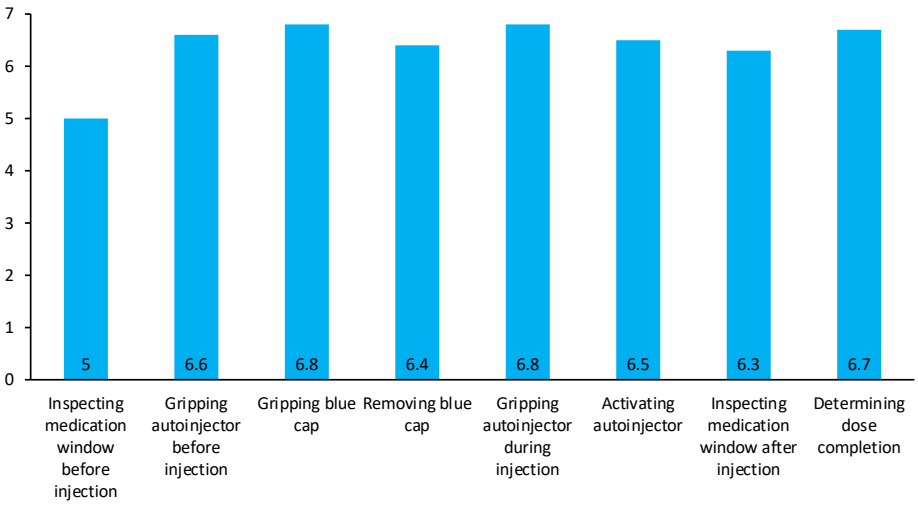


Figure 1: Statistical summary of a Maggie human factors study conducted in 2019. After using the autoinjector, nearly all participants highly regarded Maggie for its ease of operation, indicating a very user-friendly device. Evaluations were made on a scale where 7 is highest and 1 is lowest.[14]


Figure 2: Basic handling instructions for Maggie 5.0 – a two-step autoinjector and the newest addition to the Maggie family of devices.

In 2019, a human factors study was performed by SHL and its research partner to understand the operational usability of the Maggie device. Using a standard protocol, device-experienced and device-naïve participants were given a Maggie autoinjector to use and were then asked to rate the ease or difficulty of operation (where 7 is highest and 1 is lowest). Nearly all participants reported a high regard for Maggie when it came to its ease of operation, indicating a very user-friendly device (Figure 1). Furthermore, this study has enabled SHL to collect user feedback regarding the device's strengths and opportunities for improvement, and has found that no significant design improvement is needed for the device to successfully function. The study highlighted the intricate design engineering work that SHL has invested in to address the technological gaps in the drug delivery sector.[13]

With a strong future outlook, SHL further challenged the notion behind the limits of SC autoinjectors. SHL notes that explorations between medtech and pharma are currently lacking due to existing perceptions of what is possible in the development of large-volume SC devices. With the right technical research and collaboration in the combination product development process, autoinjectors should be seen for their expanded large-volume/high-dosing utility – formally closing


Figure 3: Designed to address the needs of varying molecules, SHL's NIT® family of devices includes autoinjectors for larger-volume, lyophilised and other specialty formulations.

the technology gap between PFS-based autoinjectors and on-body patch pumps. In response to this need, SHL recently launched Maggie 5 mL – the larger-volume variety within the Maggie family of devices. This larger-volume version leverages the lessons gathered from its predecessor and retains the two-step injection handling sequence (Figure 2).

Currently available scientific research indicates that biological therapeutics are shifting from traditional IV administration towards SC administration to reduce costs, time of delivery and adverse systemic effects. The ultimate goal is to increase patient quality of life and treatment adherence. Preliminary available information indicates that the SC tissue can be limited in its ability to handle fast injections of large volumes, resulting in varying degrees of leakage (sometimes called "wet injections"), site reaction and patient discomfort. Although there might be some limitations, SC delivery of large volumes seems to be feasible and tolerable based on currently available research.[15–17]

At present, several technologies have been proposed to overcome some of the mentioned limitations and these are able to minimise intermolecular interactions to reduce the viscosity of high-concentration formulations, to form fluid suspensions or to modify the SC space to facilitate the delivery of a larger volume of fluid, such as transient permeation.[12]

SHL has also undertaken preliminary usability work on the feasibility of longer holding times for autoinjectors. In terms of holding stability over simulated injection times of up to 60 seconds, the study showed no statistically significant change in relative positioning, orientation or needle cover engagement of the device with the injection site. The composite of these elements serves as SHL's guiding principle to explore cartridge-based autoinjectors – through SHL product offerings that are in various stages of development – with its pharma partners even further (Figure 3).

## PARALLEL DEVELOPMENTS AND FUTURE OUTLOOK

As SHL advances the technological feasibility of large-volume drug delivery, there remains a focus on continuing to enable conventional device needs across various disease areas. The Molly® autoinjector device technology continues to meet with regulatory approval and commercial success, made possible by a modular manufacturing set-up that allows SHL to manage multiple simultaneous device projects, streamline processes and enable faster development timelines. Recently, the modular Molly platform has been supporting the high production forecast demand for a combination product approved in 2021, which has far exceeded SHL's previous levels of device delivery to the market. This is a true testament to Molly's scalability and SHL's responsiveness to the ever-changing annual production needs of a combination product.

True to its modular product design, expanding the Molly's design attributes to improve device performance is an active pursuit – SHL has seen technical progress in the delivery of higher-viscosity drugs (≥ 25 cP), while also maintaining the same device geometry. The Molly autoinjector is now compatible with 8 mm needle PFSs, offsetting injection constraints in


Figure 4: Enabled by platform modularity, the Molly autoinjector technology is always evolving and allows for various customisations according to industrial design, branding and commercialisation strategy, formulation and patient requirements.

> "True to its modular product design, expanding the Molly's design attributes to improve device performance is an active pursuit – SHL has seen technical progress in the delivery of higher-viscosity drugs, while also maintaining the same device geometry."

PFS-based mechanical autoinjectors. This increased freedom for injectable drug delivery is also supported by wider pre-set viewing window options that are optimised for different injection volumes (Figure 4). SHL has redefined the idea behind conventional autoinjectors through platform modularity, and the Molly autoinjector technology continues to evolve to address the ever-changing market needs.

For SHL, the key advantage to having a design and manufacturing infrastructure built upon platform concepts is that such an asset investment philosophy can be leveraged for its Maggie technology offering. The Maggie device family is intended to be a large-volume autoinjector platform that addresses customer requirements on priming and drug delivery volumes, as well as injection time, cannula size and injection depth. Just as the modular Molly is the platform of choice for more than a dozen global pharma companies, the goal for the Maggie family of devices is to become the industry platform of choice to enable patients' independence in disease areas in large-volume/high-dosing therapy as yet unseen in the self-injection space.

## ABOUT THE COMPANY

SHL is a solutions provider in the design, development and manufacturing

## ABOUT THE AUTHORS

**Gary Calderwood** is a Product Manager at SHL, leading efforts on the development and lifecycle management of the company's device technologies, from concept through to production. In his role, he specialises in bridging the gap between the technical, strategic and commercial needs of SHL's specialty autoinjectors portfolio. Prior to his current role, Mr Calderwood was a Senior Design Engineer at SHL, where he led and assisted in the exploration and development of several autoinjector devices within the company's expanding product portfolio. Mr Calderwood possesses a higher degree in Medical Design Compliance in addition to a Bachelor of Science in Product Design. He has more than a decade of professional experience in a broad range of design-related roles, with a focus on product development.

**Raluca Ganea**, PhD, is SHL's Clinical Affairs Manager, working together with the global product management team. In this role, she leads activities to support the development and lifecycle management of drug delivery devices, including the planning and execution of clinical trials and studies, as well as performing clinical assessments and research activities. She has more than 10 years of experience in the medical device, biotechnology and bioengineering sectors. She holds an MSc in Biomedical Engineering from the Technical University in Iasi (Romania) and a PhD in Biotechnology and Bioengineering from the Ecole Polytechnique Fédérale de Lausanne (Switzerland).

**Gene Rhode Fuensalida Pantig** is a resident molecular biologist and pharmacist at SHL, most recently taking on the role of Senior Scientific Communications Specialist. In this new role, he leads the establishment of a scientific affairs working group. Prior to joining SHL, he worked for three years as a researcher in the Institute of Molecular Biology at Academia Sinica, Taiwan's national academy. He is trained in classic molecular biology techniques, having worked with Dr Sue Lin-Chao – whose mentor is Dr Stanley Norman Cohen, developer of genetic engineering methods still used today in the field of biologics.

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of advanced drug delivery devices, such as autoinjectors and pen injectors. The company also provides final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe. With locations in Switzerland, Taiwan, Sweden and the US, SHL has successfully built a strong international team of experts that develops breakthrough drug delivery solutions for pharma and biotech customers. These include advanced reusable and disposable injection systems that can accommodate large volume and high-viscosity formulations – and connected device technologies for next-generation healthcare.

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# REACHING A NEW ZENITH IN PROTECTING LARGER-VOLUME SENSITIVE MOLECULES, FROM FILLING TO SELF-ADMINISTRATION

**In this article Victoria Morgan, Director, Segment Marketing, Global Biologics, and Eric Kurtz, Senior Specialist, Technical Product Development, both of West Pharmaceutical Services, discuss how the company's Daikyo Crystal Zenith™ insert needle prefilled syringe system meets the needs presented by the healthcare sector's shift to home-based care and the increasing prevalence of biologics in the pharmaceutical pipeline.**

In recent years, the healthcare sector has witnessed a sustained shift of treatment location from hospitals to the home, accelerated by the practical difficulties imposed by the covid-19 pandemic. However, even prior to 2020, there were strong market forces at play driving the growth of the self-administration market – patient demand for greater convenience, double-digit growth in specialty and biologic drugs and the value of autoinjectors becoming increasingly recognised across multiple therapy areas.

For some pharma and biotech partners, this opportunity has perhaps been somewhat suppressed by compatibility issues with the available glass primary packaging options, most notably that some sensitive biologic drug formulations become unstable when exposed to silicone oil. Siliconised glass syringes can also pose a risk to the supply chain and the patient due to challenges around aggregation, contamination and breakage.

This article charts the progress of an alternative polymer-based portfolio of vials, syringes and cartridges that have been designed to overcome the challenges posed by glass container systems. It also introduces the latest evolution – a 2.25 mL insert needle syringe system designed to deliver higher volumes. In support, this article presents the results of a customer case study where the polymer-based platform was shown to quickly and safely overcome the challenges posed by the glass alternative.

## THE DEMAND FOR HOME-BASED HEALTH

Over the years, much has been written about the shifting focus of healthcare provision and the building of momentum behind home-based health and self-care. The ability for patients to take greater control of their conditions within their own home satisfies many challenges currently

> "Even before the pandemic, patients – particularly older patients – indicated their support for at-home drug administration, with research pointing to an overall preference for avoiding medical facilities and taking their medication at home."

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Figure 1: Daikyo® Crystal Zenith® insert needle syringe system.

facing the traditional model of clinic-based care. It not only provides patients with greater autonomy and convenience, but also frees up the valuable time of healthcare professionals (HCPs). It can also help reduce the overall cost to payers – a critical consideration in the context of the increasing pressure that an ageing society is placing on healthcare systems.

Even before the pandemic, patients – particularly older patients – indicated their support for at-home drug administration, with research pointing to an overall preference for avoiding medical facilities and taking their medication at home.[1] The influence of covid-19 only served to cement this feeling among patients, at the same time as HCPs sought to maintain limits on unnecessary face-to-face engagement in the interests of treatment efficiency and reducing the spread of infection.

Separate studies have shown that the broader area of self-care has the potential to improve outcomes where patients are equipped with the means to self-manage conditions. This is true both in the sense of improving their knowledge of their symptoms and treatments, and in empowering them to self-administer their medicine, advised by an HCP where it is appropriate.[2] Typical applications here are for the management of chronic conditions, such as diabetes, or those used to alleviate acute situations, such as anaphylactic shock. Sustained success in these areas has resulted in the emergence of a well-established market for autoinjectors, delivering therapies at a frequency and volume that is readily acceptable and manageable for patients.

Against this backdrop, innovators in the pharmaceutical and biotechnology sectors have continued to explore new areas where autoinjectors have potential, aiming to support increasing cohorts of patients with the ability to effectively self-administer their medication. One such example is the expansion of the potential drug volume delivered via autoinjectors from the typical dose of 1 mL up to 2.25 mL and even 5 mL.

> "Potential barriers remain for some biologic formulations where the material used for their primary packaging is glass."

## THE NEEDS OF BIOLOGICS

This development has been driven by various factors, one of which is the growth in demand for biologic formulations, which often require higher volumes to deliver the desired effect. Another is the emergence of results from human factors studies that have demonstrated patient tolerance for injection durations of up to 15 seconds, a notable increase from the previously accepted threshold of 10 seconds. The combination of these two factors opens the door to self-administration of a wider range of biologic therapies via subcutaneous injection for applications that would previously have required multiple injections or intravenous delivery within a clinical setting.

These developments hold significant promise for further advances in the field of self-administered care. However, potential barriers remain for some biologic formulations where the material used for their primary packaging is glass. Here, the siliconisation process coats the glass barrel within the prefilled syringe (PFS) container system with silicone oil so that the desired gliding forces are achieved when the plunger is deployed. While the presence of silicone oil is not typically a cause for concern, in the case of some sensitive biologics it can be the catalyst behind protein aggregation. These elements can lead to diminished efficacy and safety in the delivered dose.[3]

## DAIKYO CRYSTAL ZENITH®

For biotech companies, the question in these circumstances is how to protect the integrity of a larger-volume, highly sensitive, and highly valuable biologic formulation in a non-glass-based container without compromising the cleanliness and robustness required of the primary packaging.

An alternative to siliconised glass can be found in the Daikyo Crystal Zenith® (CZ) component portfolio from West, which includes a 2.25 mL insert needle (IN) PFS system (Figure 1). CZ is a cyclic-olefin polymer that presents a sterile containment system for silicone oil-sensitive drug formulations. The elastomeric plunger used in the CZ PFS system is coated with an inert FluroTec® barrier film, which reduces the risk of leachables from the elastomer and prevents absorption of the formulation. By supporting syringe functionality, the film also avoids the need for additional silicone oil to be used, dramatically reducing exposure to the key source of protein aggregation. Indeed, studies conducted by West on a randomised selection of syringe samples detected no silicone oil down to 1 ppm extracted from the assembled CZ PFS.

"The results found the drug to be stable within the CZ system, which outperformed glass and alternative polymer-based systems for sub-visible particles."

In further evidence of CZ's credentials for safeguarding formulation integrity, the precision injection-moulding process used to engineer CZ polymer syringes facilitates a 4-log reduction in endotoxin levels while also enabling needles to be attached free of tungsten or glue, which are additional possible sources of drug contamination.

Break-test data recorded during tests carried out by West also demonstrate how CZ mitigates against the risk of breakage. This is not only an important consideration in relation to the fill-finish process, where breakages result in costly downtime, but also in transportation environments and for the activation of the autoinjector itself, where higher forces can be required to deliver large-volume or high-viscosity injections.

## REAL-WORLD CASE STUDY

In the case of one pharmaceutical customer, the benefits of the materials science incorporated within CZ helped resolve an acute packaging challenge that caused costly delays to the development schedule for a drug used within an autoinjector application. Here, the customer employed a platform approach to packaging, with the formulation development team opting to contain a new biologic within a previously used large-volume glass syringe system.

In analytical tests to assess the stability of the formulation, the results provided a clear indication of the drug's sensitivity to the silicone present within the "default" glass containment option. This was the cause of poor stability over time, with silicone particles and protein aggregation both present within the drug product after a period in storage.

Having lost critical time early in drug development, the customer was prompted to seek out an alternative primary containment solution that would avoid the risk of protein aggregation through exposure to unacceptable levels of silicone oil. The solution also had to demonstrate physical properties that answered the demands of an autoinjector use-case, which incorporated not only container closure integrity (CCI) and breakage resistance, but also the ability to operate within specific tolerances for break loose, extrusion and gliding forces, injection force and rigid needle shield removal force.

Having identified the potential of the CZ 2.25 mL IN PFS system, the customer conducted a series of tests to verify the performance of the system in accordance with these demands. The results found the drug to be stable within the CZ system, which outperformed glass and alternative polymer-based systems for sub-visible particles. The CZ system also conformed to United States Pharmacopeia <1207> for CCI testing; the forces registered were within the defined tolerance range, and no syringe breakage was exhibited.

This case study highlights the potential for materials such as CZ to be deployed in biologic applications where there are potential silicone interaction risks that can negatively influence development schedules, increase costs and delay time-to-market. At a more fundamental level, it underlines that, while the continued innovation in biologics is opening up new treatment pathways for patients, the complex nature of these formulations, in terms of volume and physicochemical properties, requires continued innovation in containment solutions to ensure the delivered dose will achieve the desired effect.

## CONCLUSION

As has been discussed, there is evidence that the paradigm of the relationship between patients and HCPs is continuing to shift. This does not diminish the essential advice, guidance and education provided by trained HCPs, but it does mean that devices such as autoinjectors must continue to evolve to meet the highest levels in performance, drug integrity and safety if, more frequently, the person administering the medication is expected to be the patient and the point of delivery increasingly closer to home.



## ABOUT THE COMPANY

West Pharmaceutical Services is a leading provider of innovative, high-quality injectable solutions and services. As a trusted partner to established and emerging drug developers, West helps ensure the safe, effective containment and delivery of life-saving and life-enhancing medicines for patients. With approximately 10,000 team members across 50 sites worldwide, West helps support its customers by delivering over 45 billion components and devices each year.

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## ABOUT THE AUTHORS

**Victoria Morgan** is Director, Segment Marketing, Global Biologics, at West, a provider of pharmaceutical delivery and packaging systems. Ms Morgan has over 25 years of sales and marketing experience in both big pharma and pharmaceutical supply, and she currently has responsibility for West's global biologics strategy development and implementation.

**Eric Kurtz** is a Senior Specialist for Technical Product Development at West. Mr Kurtz has 15 years of experience across several technology and engineering oriented industries and specialises in product management and new product development.

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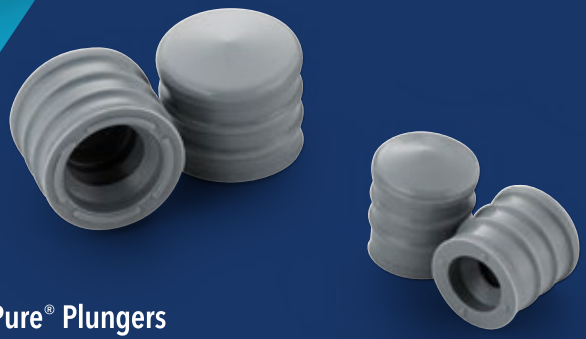

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Nemera
we put patients first

# A HIGH-QUALITY AND ROBUST SAFETY SYSTEM FOR HIGH-VOLUME BIOLOGICS AT HOME

**In this article, Audrey Chandra, Category Project Manager, and Cécile Gross, Global Category Manager, Parenteral, both at Nemera, discuss the company's development of a new product for the safe delivery of high-volume biologics at home.**

Needles have been used to inject drug treatments for a long time, via intradermal, subcutaneous or intramuscular routes. Thanks to prefilled syringes (PFSs), a number of new drugs are now being administered in medical settings. These include different types of molecules – for example, anti-thrombotic agents, such as heparin. Vaccines and other small molecules are also commonly administered subcutaneously (SC) by healthcare professionals. However, recent developments in drug research and production have made available bigger molecules. Biological drugs have become available in PFSs and are predominantly used to treat complex chronic conditions.

> "Home-care administration brings many benefits, lowering the cost of treatment for all stakeholders and increasing adherence to regimens."

The trend towards self-administration comes from two directions at the same time: from pharmaceutical companies that offer these biological drugs for chronic conditions in PFSs – and patients themselves.

Intravenous (IV) treatments involve patients going to healthcare facilities to receive their injection, as handling PFSs or IV administration would be too tricky and dangerous for novice users at home. The risk of needlestick injuries and the wrong use of the device are considered too high, leading to compromised patient safety. Both cases therefore require patients to travel to clinics or hospitals on a regular basis, leading to frequent hospital chair time for patients, also contributing to the burden on hospitals. Therefore, pharmaceutical companies are striving to move injectable drugs from IV to SC, hence avoiding hospital chair time for patients or long and inconvenient hospitalisation.

In parallel, and following the covid-19 pandemic, patients have ceased to visit their healthcare professionals and got used to teleconsultations. Some patients even became reluctant to go for their regular medical visit at the hospital. They preferred to manage their drug regimen with reassurance at home, without having to worry about being exposed to the virus.

Home-care administration brings many benefits, lowering the cost of treatment for all stakeholders and increasing adherence to regimens. Self-administration in a home-care setting becomes more and more common, leading to increased risk of use errors and sharp injuries to be expanding concerns for patients' safety. With this in mind, protecting users from sharps injuries whilst optimising the injection experience has become a must. Patients or caregivers need reliable, robust and easy-to-use devices to administer their treatment on a regular basis at home, independently and with optimised convenience.

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## SAFETY SYSTEM FOR BIOLOGICAL SELF-ADMINISTRATION

How did Nemera enter this market? It first offered a safety system with a Luer lock, but the availability of PFSs with a staked needle has made it possible to offer the first Safe'n'Sound® in 1 mL. Compatible with several kinds of glass PFS following ISO standards, it is also compatible with the PLAJEX® polymer PFS from Terumo (Tokyo, Japan).

In order to add the benefits of a platform approach, the device has been conceived as flexible. Available in different kinds of flange types, it can offer customisation with "soft-touch" material to improve grip, as well as an overcap to ease the rigid needle shield removal. Colour customisation for a safer drug or dose identification is also available.

Features also include a large thumb pad for ease of use, clear visibility for easy drug inspection and a rounded shape for an increased labelling surface. As for product performance, robustness has been the focus of the entire design. As a result, the full body in polycarbonate and the plunger rod in polypropylene with a large thumb pad and large finger flanges enable one-handed injection, no bending of any parts and good resistance in drop tests.

Safe'n'Sound® has been fully validated through user studies and is already commercially available with market references in Europe and the US. To facilitate its partners' choice of assembly tools, Nemera has also bound partnerships with industrial providers that have gained full knowledge of the product characteristics and can be recommended.

Figure 1: The Nemera Safe'n'Sound® 2.25 mL safety system.

## SAFE'N'SOUND® 2.25 ML: A CUSTOMISABLE PLATFORM

Biological drugs are very often needed in high concentration. This can be driven by the nature of the molecule, the composition of the final drug and the effort to decrease the frequency of treatment for the patient. Their viscosity increases according to the power law of the antibody concentration. Thus, to be injected, these molecules need to be diluted, which leads to higher injection volumes and lower (but still high) viscosity. As a result, larger-dose drug deliveries are a growing segment, with volume shifting towards 2 mL.

Taking this market need into account and leveraging its experience with the 1 mL version, Nemera developed a 2.25 mL device, safeguarding the device robustness as well as the platform approach (Figure 1).

Increasing the volume to inject has not compromised the ergonomic design, which makes the Safe'n'Sound® 2.25 mL intended for naïve users, including patients with dexterity issues, as well as operable by experienced users and healthcare professionals alike.

## FOCUS ON PHYSICAL IMPAIRMENT

In immunology, for example, where biologics and biosimilars are often used to treat chronic diseases, patients often have dexterity issues due to symptoms triggered by the pathology itself, age or comorbidities. These chronic conditions include, but are not limited to, rheumatoid arthritis, psoriatic arthritis and multiple sclerosis. To help such patients manage the removal of the needle cap, Nemera has developed an overcap. This rigid needle shield remover allows an intuitive gesture for quick and safe removal, thanks to its ergonomic design. Users' inputs have been integrated in the development process as early as possible to identify the key elements to take into account.

> "Differentiation for pharma partners and drug identification for patients are crucial elements that can be handled through colour coding."

Differentiation for pharma partners and drug identification for patients are crucial elements that can be handled through colour coding. Thanks to its broad injection capabilities, Nemera is able to offer this customisation option as well as soft-touch material customisation with biomaterial injection.

## FULLY AUTOMATED MANUFACTURING CAPABILITY

Nemera chose to invest in a new industrial line to address market needs. The choice to increase its footprint in Europe was guided by its desire to better serve European customers from a sustainability and transportation standpoint. From an industrial point of view, the plant benefits from the company's long experience in managing parenteral projects and not starting from scratch. As for product quality, the goal was to implement a line capable of producing a "glass-like" quality product, requested by several regulatory pathways and by high-value biologics. Leveraging from the current line, the direction has been optimisation, especially in process and quality control.

As a result, this new line is equipped with new sets of moulds and high-end machines (Figures 1, 2 and 3), which will be industrially ready by 2024. Nemera's efforts for continuous improvement as well as capacity expansion are embodied in this new state-of-the-art industrial line to produce high-quality devices with automated

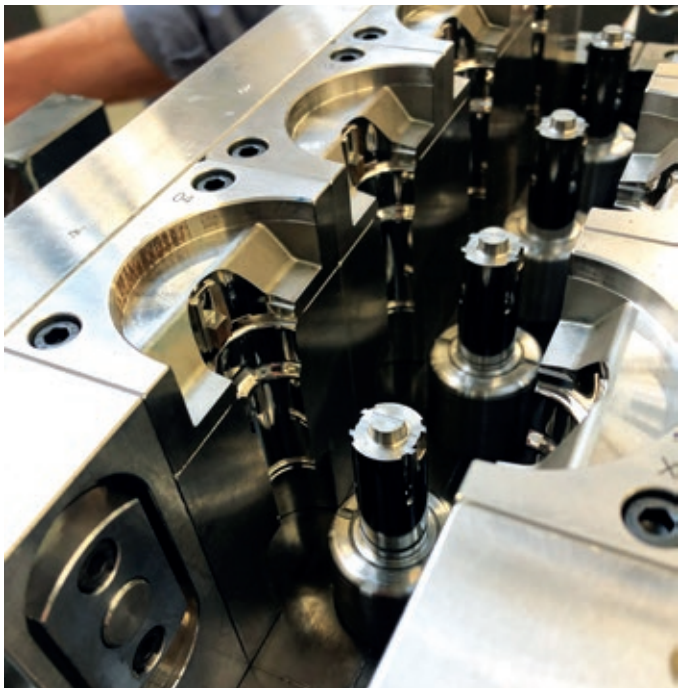

Figure 2: High-quality industrial line mould for glass-like safety devices.


Figure 3: State-of-the-art industrial line assembly.

Figure 4: Automated industrial line packing machine.

processes, tight visual control, especially on critical areas, as well as labelling and automated storage. These will limit human handling and therefore particle contamination, eliminate scuffs and scratches and focus on assembly to ensure final locking and safety mechanism activation.

The 100% visual inspection and dimensional control will be performed twice on all outputs: after the injection process of the sub-components as well as before the assembly of the sub-components to constitute a complete device. During the whole process, the sub-components will be packed in a tote to facilitate transfer between the injection machines to the assembly ones, and the assembled devices in a thermoformed tray, bulk being out of the question.

## A FULL RANGE OF SERVICES

Through capabilities in design research, human factors engineering, user experience design, engineering, laboratory services and regulatory support, Nemera is uniquely positioned to offer all the support that customers require, leveraging its Insight Innovation Center's consulting expertise. Its service programme includes:

- Laboratory and analytical services to support characterisation and compatibility of drug products, syringe candidates and devices such as Safe'n'Sound® to optimise their integration.
- Help defining user groups/populations and early-use-related risk-analysis activities to define the human factors and usability programme necessary for a client's regulatory/filing strategy and identified clinical risks.
- Developing instructions for use, value-added packaging, connectivity add-ons to support patient engagement/adherence and integration of training devices into the patient services model.
- Conducting formative and summative usability testing globally for all aspects of the device and supporting assets in alignment with the human factors programme definition through human factors engineering report documentation for use in regulatory submissions.
- Programme management excellence to ensure all elements of the programme are integrated to drive efficiency and mitigate any programme risks proactively.

## TRAINING TOOLS

Nemera collaborates with Noble (FL, US) to incorporate Safe'n'Sound® patient onboarding kits to allow patients to repeatedly practise the self-administration process (Figure 5). This partnership allows Noble to support Nemera's launch of the new premium add-on passive safety device, by incorporating a robust training platform programme in tandem with the drug delivery device. The training solution is designed to replicate the Safe'n'Sound® 1 and 2.25 mL in form and function, which will allow for better assistance educating patients on the proper use of the device.

This capability combined with Nemera's device platforms and manufacturing excellence helps customers achieve the outcome of

> "Ensuring patient safety and fostering patients' adherence to therapies are at the heart of everything Nemera does."


Figure 5: Nemera-Noble collaboration.

a successful regulatory submission and commercial launch of safe, effective and differentiated combination products while mitigating the risks associated with multiple partners who may not have expertise and experience in all the aspects critical for success.

Ensuring patient safety and fostering patients' adherence to therapies are at the heart of everything Nemera does. Its ultimate goal is to bring superior value to patients and customers.

## ABOUT THE COMPANY

As a world-leading drug delivery device solutions provider, Nemera's purpose of putting patients first enables it to design and manufacture devices that maximise treatment efficacy. It is a holistic partner and helps its customers succeed in the sprint to market of their combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, it works with its customers as colleagues. Together, they go the extra mile to fulfil their mission.

*Safe'n'Sound® is a registered trademark of Nemera La Verpillière. PLAJEX is a registered trademark of Terumo Kabushiki Kaisha (Terumo Corporation).*

## ABOUT THE AUTHORS

**Audrey Chandra** is the Category Project Manager at Nemera. She graduated from the Faculty of Medicine Universitas Atma Jaya, Indonesia and pursued her master's degree in Strategy and Business Development at Toulouse School of Management, France. Ms Chandra is in charge of the Dermal Category at Nemera, as well as providing strategic support for various other targeted marketing projects. She also works on diverse content management, along with communication activities co-ordination.

**Cécile Gross** is Global Category Manager at Nemera, focusing on parenteral devices. She oversees the product portfolio strategy, development and lifecycle for safety system, pen injector and on-body injector platforms. Ms Gross has more than two decades of experience in the medical device industry, marketing B2B technological products and implementing product lifecycle management for various kinds of devices. She graduated in International Business and completed her initial training with a master's degree in Marketing and Management in the Healthcare Industry at the IMIS Institute (Lyon, France).

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# PRODUCT SHOWCASE: Aktiv Pharma's ARAI Autoinjector Platform

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"Aktiv had one major, counterintuitive advantage – at the time, the company did not have an autoinjector, or any experience of developing one, and was therefore not constrained by established paradigms."


Figure 1: ARAI – Aktiv's advanced emergency autoinjector platform. Six ARAI Gen-1 products are currently being advanced to NDA submission.

In 2013, the US Department of Defense (DoD) issued a request for proposals to develop a glass-free autoinjector. In practice, glass-free was just one of a rigorous set of the DoD's requirements, which also included improved usability, robustness, drug stability and reliability. In essence, what the DoD was after was a next-generation autoinjector that would improve on the shortcomings of the autoinjectors available to them at the time. Importantly, the DoD was looking for a platform that would be amendable to a range of applications and drug formats.

The desire for such a platform approach has been a staple of the autoinjector industry for many years, and the progress made in this direction has filled many pages in past issues of ONdrugDelivery magazine. In this regard, Aktiv had one major, counterintuitive advantage – at the time, the company did not have an autoinjector, or any experience of developing one, and was therefore not constrained by established paradigms. Aktiv approached the development as a whiteboard exercise – the company listened and took notes on all the requirements and goals that were presented. It then put its innovation engine to work and built the ARAI autoinjector from scratch.

This small first step led to a long-lasting partnership between Aktiv and the US government. To date, the company has secured over US$70 million (£64 million) in government funding to develop the ARAI platform (Figure 1) and is anticipating

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Broomfield, CO 80021
United States

**aktivpharmagroup.com**

| Product Name | Configuration |
|---|---|
| Pralidoxime chloride (2-PAM) | Single compartment 2 mL |
| Scopolamine | Single compartment 1.2 mL |
| Tranexamic acid (TXA) | 1,000 mg in 2 mL; 2,000 mg in 4 mL |
| Atropine | Single compartment 0.7 mL |
| Dual-injection atropine/2-PAM | Two single-compartment containers: 0.7 and 2 mL |
| Atropine reconstitution | Single container, dual-compartment |

Table 1: Aktiv's autoinjector pipeline consists of a variety of configurations, all made using the same basic components and manufacturing lines.

the total value of its US government contracts to reach up to $300 million by the end of 2022, which will support the continued advancement of its portfolio of six emergency autoinjector products to commercialisation. This is currently the strongest portfolio of US government-oriented autoinjector products (Table 1), and Aktiv is planning to add several other high-value consumer-market products to its pipeline in the coming years, both independently and in partnership with other pharmaceutical companies.

Internal studies have shown that ARAI has superior reliability and robustness, and is simple and intuitive to operate, even for novice users. Its unique features lend itself to the platform approach – ARAI is designed to allow a dose volume range from <1 to 5 mL, an option for injection of separately stored drug constituents through drug-specific needles into separate depots to eliminate adverse interactions between the drugs, and an option for automatic reconstitution of the dose just prior to injection. All these configurations use the same basic device components and share the same manufacturing equipment, with the major change between configurations limited to the size and form of the primary container, which is achieved by a disciplined separation of functions that minimises dependencies between the subsystems of the autoinjector.

Figure 2: ARCH – the glass-free, flexible primary drug container used in ARAI.

"Unlike other autoinjectors, the ARAI autoinjector relies on Aktiv's proprietary glass-free flexible primary container made from high-barrier films, in a form of blister package named ARCH."

Unlike other autoinjectors, the ARAI autoinjector relies on Aktiv's proprietary glass-free flexible primary container made from high-barrier films, in a form of blister package named ARCH (Figure 2). The ARCH blister package can be made in a range of volumes and can have a single compartment or a plurality of adjacent compartments, which can be merged by peeling a frangible seal separating them, without the need for any moving parts. Aktiv is collaboratively working with the US FDA on the regulatory approach to ARCH via the Emerging Technology Program.

The ARAI autoinjector is activated by a power-pack containing pressurised $CO_2$. Upon activation of the autoinjector, the released gas deploys the needle and, when the needle reaches the target depth, the pressure compresses the ARCH primary container and delivers the dose. After a pre-determined dwell time that ensures complete delivery of the dose, the needle is retracted to a safe and concealed position. There are no mechanical connections between the power-pack and the primary container or the needle-activation mechanism.

The rise in gas pressure in the device drives all device functions, meaning that developing an ARAI product with a new dose volume only requires a new ARCH container and no changes to any other parts. Similarly, since there are no mechanical linkages, the needle gauge, needle length and injection depth are configurable with minimal changes to the device assembly. The injection pressure can also be fine-tuned to accommodate a range of viscosities. The initial pressure of up to 65 bar is adjusted through an arrangement of a valve and bleed holes that operate independently from other functions of the device.

ARAI is not limited to Aktiv's proprietary ARCH primary container and can also accept regular glass or moulded plastic cartridges, blow-fill-seal cartridges or even plastic or aluminium tubes. A patented approach creates pressure equilibrium between the inside of a rigid primary drug container and its surroundings, eliminating stresses on the container's walls during injection and preventing damage at elevated pressures. Form factors are also very configurable – since there are no mechanical connections between the subsystems, the form factor of the device is not constrained to a pen shape and can be easily changed to other formats, such as a wearable injector (Table 2).

"Since there are no mechanical connections between the subsystems, the form factor of the device is not constrained to a pen shape and can be easily changed to other formats, such as a wearable injector."

| Attribute | Options |
|---|---|
| Injection parameters | • Injection time: 0.2 s or longer<br>• Needle dwell time: up to 30 s<br>• Needle gauge:<br>– demonstrated 18–25G<br>– intramuscular or subcutaneous<br>• Back pressure configurable for low and high viscosities |
| Payload | • Volume: <1 mL up to 5 mL<br>• Single-compartment, dual-compartment mixing/reconstitution, dual-container simultaneous injections |
| Primary container | • Glass or plastic cartridge<br>• Any collapsible container: blister, blow-fill-seal, tube, pouch, injection moulded |
| Form factors | • Pen-shaped<br>• Wearable<br>• Others |

Table 2: The ARAI autoinjector architecture supports a wide range of injection parameters, payloads, primary containers and form factors.

This strict separation of functions also lends itself to the superior reliability of ARAI. Aktiv has recently demonstrated that ARAI exceeds the 99.999% successful activation rate required by the recent FDA draft guidance. During the development of the ARAI autoinjector, particular attention was paid to defining critical functions in a manner that allows the platform's advantages to be fully realised. This was done by producing reliability specifications for each function, which then allows for new devices to be developed with confidence that they will also meet the overall reliability requirements.

Even the feedback of the user interface was designed not to alter device reliability. Unlike other autoinjectors, where audible or other feedback cues require additional subsystems that can potentially reduce reliability, ARAI's tactile, audible and visual feedback is generated by the critical device functions. This kind of platform flexibility and reliability is nearly impossible to achieve with spring-based autoinjectors, which are burdened by high sensitivity to dimensional tolerances and subsystem interdependencies.

In addition to ARAI, Aktiv is developing PenPal (Figure 3), a connectivity-enabled autoinjector for the consumer market that embodies all the advantages of ARAI in form factors that are more suitable for chronic conditions. Aktiv is also partnering with a leading biopharmaceutical company to develop a glass-free container closure system for biologics that eliminates drug contact with problematic materials associated with glass, such as silicone and rubber, improves usability and logistics and reduces drug wastage and environmental impact.

## ABOUT THE COMPANY

Aktiv is a rapidly growing specialty pharmaceutical company developing, manufacturing and commercialising sterile injectable products in a portfolio of proprietary, value-added, glass-free, prefilled delivery systems. Aktiv is establishing itself as a vertically integrated contract design and manufacturing organisation with a unique combination of product competencies that specifically target biopharmaceuticals. The company's facilities in Colorado (US) include device; chemistry, manufacturing and controls; and manufacturing equipment development labs, as well as assembly cleanrooms and sterile fill-finish suites operated under cGMP. Aktiv's team of about 70 employees is anticipated to double in 2023, and triple to over 200 in 2024. The company's portfolio of glass-free container closure systems and delivery systems includes substitutes for glass vials, prefilled syringes, reconstitution syringes, intravenous closed transfer systems, intranasal delivery systems, wearable injectors and autoinjectors. The company's culture emphasises diversity, equity, inclusivity and collaborative leadership across the entire organisation.


Figure 3: Aktiv's PenPal platform, currently under development, combines the advantages of ARAI with essential features for consumer applications.

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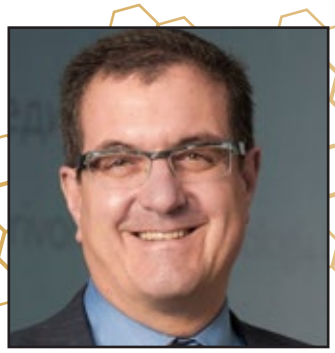

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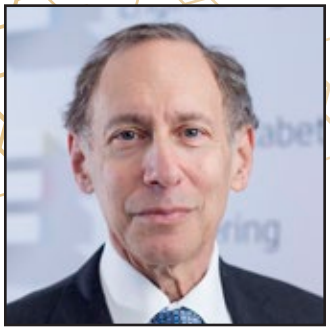

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# simatec

# UNLIMITED POSSIBILITIES BY USING A GAS-PRODUCING DRY CELL

In this article, Marc Beutler, Innovation Manager, and Matthias Meier, Research and Development Engineer, both of simatec, discuss the myriad advantages of using the company's gas-producing dry cell as a drive system for injectable drug delivery devices, as compared with spring-based and electromechanical drives.

Existing forms of therapy are increasingly switching to at-home care. This means that new challenges for drug delivery and supply chains are emerging. High-volume delivery systems with remote monitoring also need new approaches to continue to ensure quality performance, patient safety and end-user benefits. The simatec drive revolutionises existing delivery systems, making them more convenient, lightweight, power independent and silent (Figure 1).

For almost 40 years, simatec, based in Wangen an der Aare in Switzerland, has been engineering products and solutions for industry. Innovation and customer focus are two factors of the company's success, and its existing successful technologies can now also be transferred to the medical industry. In particular, simatec is developing a new type of drive that is ideal for applications with prefilled injection systems, cartridges or other container closure systems.

> "simatec is developing a new type of drive that is ideal for applications with prefilled injection systems, cartridges or other container closure systems."

Through the "design thinking" method, simatec is aiming to provide even wider support for innovations and place its customers' needs more firmly at the heart of all considerations. Design thinking is based on the basic principles of team,


Figure 1: Simatec is developing a new type of drive that is ideal for applications with prefilled injection systems, cartridges or other container closure systems.

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space and process. The English industrial designer Tim Brown defines it as follows: "Design thinking is based on the assumption that problems can be solved better when people from different professions, working together in an environment that inspires creativity, develop a problem together, consider people's needs and motivations and then create concepts that are tested more than once."

There are six steps that describe the design thinking process:

- Empathy/Understanding
- Observing
- Defining a point of view
- Finding ideas
- Prototyping
- Testing
- Getting feedback from potential users.

simatec uses agile and iterative creative processes, as well as plenty of interviews, to gather the ideas and wishes of possible future customers. The company is aiming to create new, intelligent solutions and products, customised exactly to the requirements of its customers, and thereby create new business areas.

## FOCUS ON PATIENTS

A number of interviews with doctors, pharmacists, homecare staff and patients have demonstrated an unmet need for affordable and portable dispensing systems that are "simple and smart" to use. Additionally, the tendency to use smaller drive systems is not only born out of a desire to increase comfort, but also a great demand in the areas of paediatrics or at-home treatment for patients with chronic conditions.

While there is currently a demand for some more advanced applications and features in drug delivery devices, such as digital support, there is also a major emphasis on patient centricity and user friendliness that emphasises simple, easy-to-use devices. However, many start-ups in the medical sector are focusing heavily on digital products and services. Which one of these trends will ultimately succeed remains to be determined and, for the present, the topic of digitisation is likely to remain an ongoing concern. As such, simatec is committed to solutions that are modular and meet the specific needs of its customers.

> "Compared with existing products, such as elastomer pumps or spring-operated systems, simatec's drive offers improved accuracy and reliability."

Compared with existing products, such as elastomer pumps or spring-operated systems, simatec's drive offers improved accuracy and reliability. However, when compared with electromechanical systems, its low cost and convenience are the most significant advantages. The fact that simatec's gas-producing dry cell operates in silence was initially taken for granted by simatec's specialists. However, for users, this is a massive improvement in comfort during drug delivery in many situations.

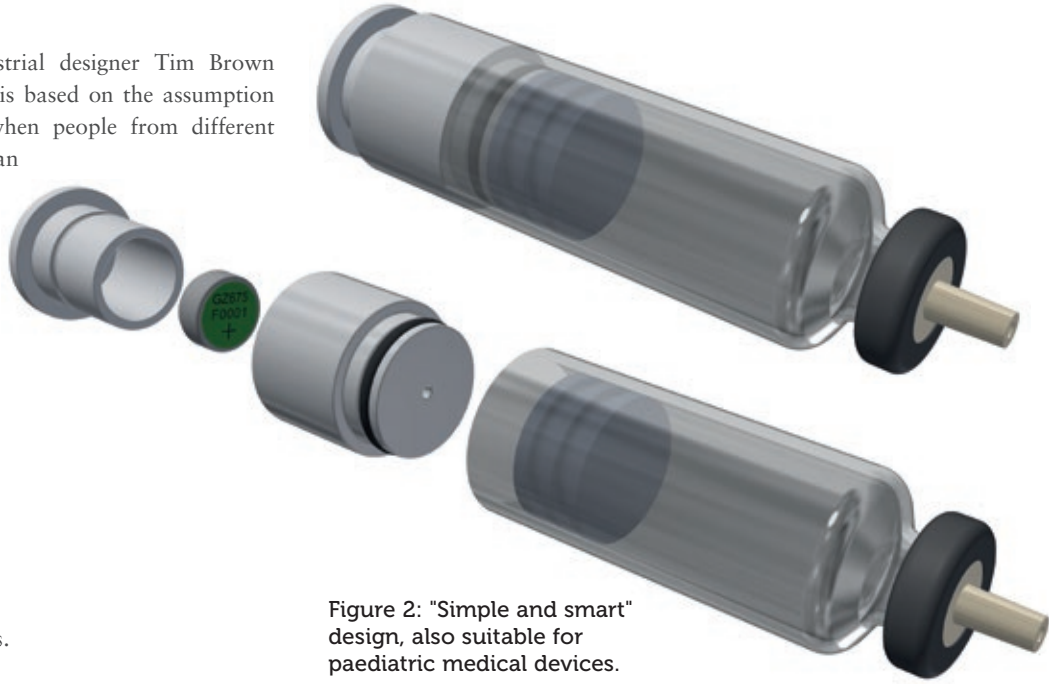

Figure 2: "Simple and smart" design, also suitable for paediatric medical devices.

## ADVANTAGES OF GAS-PRODUCING DRY CELL

By working together with its customers as partners, simatec is inspired to help implement its gas-producing dry cell into innovative devices that not only meet, but exceed, today's requirements. simatec encourages all potential partners to approach the company with any enquiries – simatec is the specialist for drives powered by the gas-producing dry cell.

### Fewer Components, Lower Cost, Increased Sustainability

The simplicity of the gas-producing dry cell drive is not only valuable in terms of purchasing and assembly costs, but also in terms of sustainability. Lowering the component requirement of a drug delivery device means that it consumes fewer resources, which is directly reflected in an improved sustainability profile (Figure 2).

### Very Straightforward Operation

The gas-producing dry cell looks very similar to a standard button cell battery. To activate it, the circuit between the positive and negative pole is closed via a defined electrical resistor. Hydrogen gas is generated in proportion to the flowing electric current. Using a modifiable resistor, the precise rate of gas production can be adjusted at any time via a simple control loop. Start-stop operation can also be implemented (Figure 3).

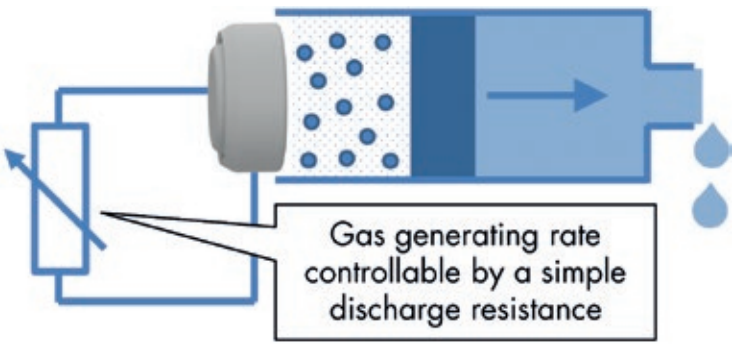


Figure 3: The gassing rate is directly proportional to the electrical current flowing through the gassing cell.

### Excellent Functionality with High Viscosity or Fine Needles

The gas-producing dry cell is excellent for small but accurate dispensing rates. For example, a single cell can generate gas at a rate of up to 10 mL/h at standard atmospheric pressure; with a required overpressure of 1 bar in front of the needle, the gas-producing dry cell can achieve a rate of 5 mL/h. This speed can be multiplied by connecting several single cells in series.

The system can generate pressures of up to 25 bar if required, making it ideal for applications where more force is needed to dispense the medium due to higher viscosity or a small needle diameter. It is even possible to handle paste-like materials.

### Wide Application Temperature Range

The gas-producing dry cell can be used at temperatures between -20°C and +55°C, covers a very wide range of applications and is ideal for drugs that require cold chain storage. Its functionality is unaffected by long-term storage. This has been proven in an industrial environment for years.

Figure 4: The gas-producing dry cell looks like a standard button cell battery. The size is smaller than a fingertip.

### Free of Air Bubbles in the Drug

Dispensing drugs by displacement has a significant benefit over systems that use vacuum: no vacuum is generated, which prevents the formation of air bubbles.

### High Level of Safety and Toxicologically Harmless

The molecular hydrogen produced by the gas-producing dry cell is highly pure. Hydrogen gas is toxicologically harmless to the human body in small quantities. Products with the gas-producing dry cell can be approved in all areas where explosion-proof protection is required due to the low electrical output. With a size of Ø11.6 mm by 5.5 mm, the gas-producing dry cell is capable of producing up to 140 mL of pure hydrogen (1 atm at room temperature). Compared with other systems, the high power-density it achieves is unique (Figure 4).

## ABOUT THE COMPANY

simatec ag is an independent, internationally operating Swiss family business that has been managed in the second generation by Mischa N. Wyssmann since 2005. Since its foundation in 1983, the company has been engineering and manufacturing innovative products for the maintenance of rolling bearings. To date, the subsidiaries simatec Inc in Charlotte (NC, US) and simatec GmbH in Pforzheim (Germany) have started their operations. simatec ag is also involved in joint ventures in other countries.

## ABOUT THE AUTHORS

**Marc Beutler** has a degree in mechanical engineering from the Bern University of Applied Sciences (Switzerland) and an interest in innovation and project management. He joined the simaX innovation team in February 2022 to find new business areas related to the gas-producing dry cell, with a specific focus on medical applications. He is responsible for evaluating the therapeutic fields that best fit the existing technology, always considering patient needs.

**Matthias Meier** studied mechanical engineering at the ETH in Zurich (Switzerland) and graduated in 2005. After four years at Maxon Motor AG (Sachseln, Switzerland) and five years in a small handicraft business, he is now pursuing his passion for the development of technical products at simatec. Since February 2022, he has been part of the simaX innovation team and is now responsible for the co-ordination and execution of the validation tests related to this project. His wide technical experience, acquired over his eight years at simatec, is of great value in this regard for himself and the team.

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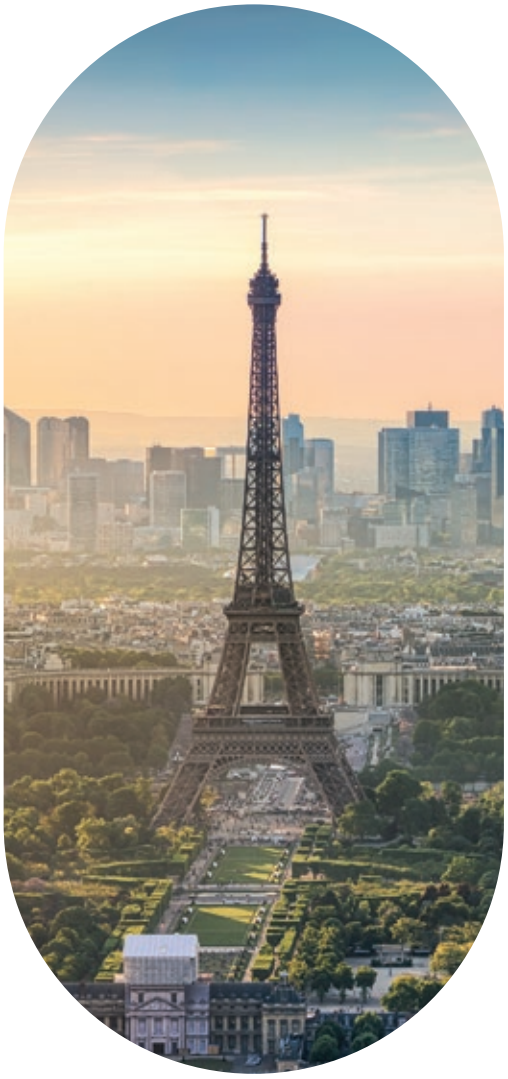

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# DESIGN STRATEGY AND CONSIDERATIONS FOR COMPRESSED GAS-POWERED DEVICE APPLICATIONS

In this article, Jack Auld, Co-Founder and Chief Executive Officer of Altaviz, discusses the potential of compressed gas as a power source for drug delivery devices, and explains how Altaviz can empower drug developers with the expertise to make full use of this exciting technology.

## INNOVATIVE ENABLING TECHNOLOGY REQUIRES APPLICATION DESIGN EXPERTISE

Drug delivery device development and manufacturing organisations serve a biopharma customer base whose hallmark is high-diligence, data-based decision making. While this approach reduces risks in delivering life-saving and life-sustaining drugs, it has also led to a slow pace of change and innovation. However, new gas-powered technologies can provide flexibility to tailor the performance in ways that have not been available with traditional technologies.

The vast majority of autoinjector designs on the market today are similar to the first devices developed in the 1970s. These designs are powered by compression springs and have inherent limitations, including:

- Noise and vibration from the moving mass of the spring
- High-volume/viscosity drugs exceeding the limits of existing spring-based systems
- Syringe breakage from the impact of the spring release
- Stress and creep on housing materials
- Force reduction over time due to stress relaxation of the spring
- Manufacturing challenges of detangling and managing large springs
- Requalifying manufacturing lines for simple changes like viscosity or delivery times.

The autoinjector market is expected to grow over the coming years,[1] especially considering the increase in higher-viscosity biologics, which are not good candidates for spring-loaded delivery technologies, currently making their way through the pharmaceutical pipeline. Innovation and performance enhancements in compressed-gas-powered autoinjector technology are made possible by Picocyl's (CO, US) medical-grade compressed gas cylinders (Pico-Cylinders).[2] This article will explore design considerations for gas-powered autoinjectors made with these cylinders (Box 1).

> "Today, gas-cylinder-powered applications across the drug delivery segment include autoinjectors, on-body injectors, specialty oral dosages and nasal delivery."

## ARE MEDICAL-GRADE GAS CYLINDERS READY FOR DRUG DELIVERY DEVICES?

Today, gas cylinder-powered applications across the drug delivery segment include autoinjectors,[3] on-body injectors,[4] specialty oral dosages[5,6] and nasal delivery. A summary of Altaviz-developed platforms based on Pico-Cylinder technology is shown in Figure 1.

Enabled by a design team with proven medical device and gas-powered delivery domain expertise, Pico-Cylinders have

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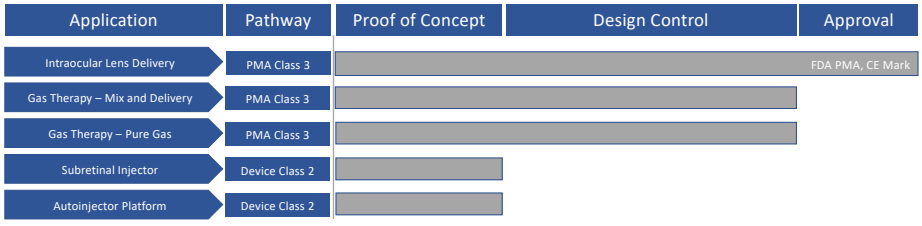
## BOX 1: DESIGN STRATEGY AND CONSIDERATIONS FOR COMPRESSED GAS-POWERED DEVICE APPLICATIONS

**Select a Team to Reduce Risk**
A team that can demonstrate past success, is experienced with gas-powered applications and has device and therapy knowledge can help significantly de-risk a project.

**Establish a Design Strategy**
It is important to make an early decision on whether to use a platform or a bespoke device, make use of proven accelerator subsystems and build confidence with early data.

**Leverage Inherent User Experience Benefits**
Gas-powered devices offer key benefits over traditional spring-powered devices, including silent, low-vibration power; the ability to engineer the delivery time; and the ability to engineer the force profile from activation to the end of delivery.

**Adopt a Systems Thinking Approach**
Be sure to consider the product requirements for the patient and use environment; the cylinder size, gas and gas pressure and isolation; and the plunger drive, system volume and Pico-Cylinder deployment and activation options using a systems thinking mindset.




Notes:
- IOL (Class 2) – both FDA approved and CE marked
- Gas Mix & Delivery (PMA Class 3)
- Pure Gas Delivery (PMA Class 3) – CE marked; PMA near submission
- Subretinal Injector – Preclinical Human Factors
- Autoinjector Platform Device – Pre-Design Verification Testing

Figure 1: Altaviz platforms based on Pico-Cylinder technology.

been used in precision applications since 2012. One example is a cataract surgery delivery device that was commercialised in 2017. To date, millions of intraocular lenses (IOLs) have been safely delivered across 64 countries via this innovative self-powered device, which offers unparalleled control for surgeons during implant delivery. Integrating the Pico-Cylinder into the IOL delivery device has allowed the IOL manufacturer to have the best-in-class delivery device in the cataract market.

## GETTING PAST A COMMON CONCERN: GAS PRESSURE ISOLATION AND SAFETY

Safety questions should always be at the forefront when changing from an established technology. A common safety question is: "How is the gas isolated from the prefilled syringe to prevent any potential exposure that would contaminate the drug?" Figure 2 presents a schematic diagram of a drug delivery device that shows how the gas-powered plunger rod is the only part of the system in contact with the stopper. The gas, fully contained within the Pico-Cylinder and the system volume, does not make contact with the drug, stopper or patient and is isolated by the atmospheric barrier.

A second common question is: "Are the gases safe in terms of exposure and the environment?" The most commonly used gases are carbon dioxide ($CO_2$), argon (Ar) and nitrogen ($N_2$), all of which are found in the atmosphere and are environmentally friendly.

A third common question is: "Is pressurised gas safer than springs in a medical device?" In a gas-powered delivery system, the pressure is fully contained within the gas cylinder until point of use and, upon gas deployment, the gas first expands into a "system volume" before any pressure is applied to the plunger rod. As a result, the internal components only see pressures lower than the cylinder pressure and only at the time of use.

Furthermore, the system volume chamber pressure steadily increases from atmospheric pressure up to the point friction is overcome, initiating plunger rod movement, which allows soft loading of the system components, including the primary drug container, thus reducing the chance of breakage. In contrast, a delivery system powered by a spring endures the full preloaded force of the compressed spring over the full shelf life of the device, leading to plastic creep in the housings and stress relaxation in the springs. When activated, a spring in the spring-loaded system rapidly accelerates and as much as a third of the spring's mass acts like a hammer on the device's internal system components, leading to syringe breakage and potentially startling users from the noise and feel of the impact.

A fourth common question is: "Are gas cylinders safe and reliable?" Pico-Cylinders are designed with compliance to the BS EN 16509:2014 standard for transportable, non-refillable gas cylinders, ensuring a safe,

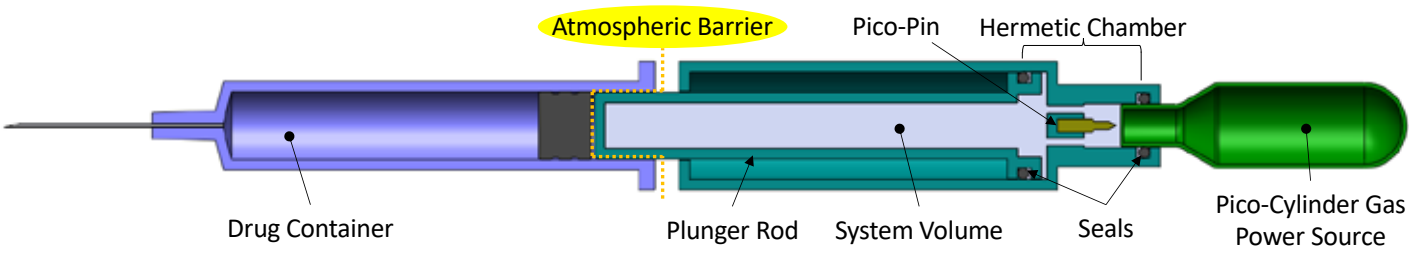



Figure 2: Gas pressure isolation from primary drug container.

robust transportable design with burst pressures in excess of 500 bar. Because the gases are hermetically sealed in full metal containers that are 100% tested for leak integrity following temperature cycling above 120°C, shelf-life durations of over five years are common and achievable.

## LEVERAGE INHERENT USER EXPERIENCE BENEFITS

The enhanced flexibility offered by compressed gases in generating syringe pressure, tailored to the application via systems engineering of the system volume, opener pin and cylinder pressure, can also extend to offering enhanced user experience factors, such as reduced noise, vibration and injection time compared with conventional spring-based systems. The noise and vibration of a gas-powered system is limited to the opening of the cylinder and the movement of the plunger, compared with the high moving mass and impact forces common to spring-based systems. A demonstration video of a gas-powered platform autoinjector can be found on Altaviz's website.

## ESTABLISH DESIGN STRATEGY

Among the first decisions to be made when considering a delivery device for a new drug product is whether to design a bespoke, drug-specific device or start with a platform device that has broader application potential. If opting for the platform path, an early decision is necessary to enable defining the platform performance range, features and customisations. Ideally, a platform's functionality provides a maximum range of drug volume and viscosity capability, minimum cost and time to customise for each application, and a minimum effort to manage autoinjector variants once in commercial production.

This flexibility can be built into a platform that takes advantage of the Pico-Cylinder's high-energy density. As shown in Figure 3, a 1 mL Pico-Cylinder filled with Ar at 270 bar can deliver a wide range of volumes and viscosities. The intention here is not to suggest what volumes are suitable for a specific drug or within a patient's tolerability range, but to demonstrate the very broad operating window for a compressed-gas-powered autoinjector, even before considering the ability to change gas pressure easily to tailor the delivery times for specific applications.


Figure 3: Volume and viscosity window for 1 mL Pico-Cylinder at 270 bar.

> "The key advantage of using gas power is the design flexibility to tailor and increase the performance of a delivery device in ways that were previously unattainable."

## SYSTEM DESIGN

The key advantage of using gas power is the design flexibility to tailor and increase the performance of a delivery device in ways that were previously unattainable. Successful implementation requires a thorough understanding and implementation of the product requirements into the device and then optimisation of cylinder requirements to maximise performance (Figure 4). The fastest and most efficient path to product execution is to leverage the expertise and technologies of an experienced team to create early designs that demonstrate the device's performance.

Whether developing a bespoke delivery device or a broad platform, best practices include first identifying target usage requirements for the specific drug or range of drugs. Parameters, including operating temperature range, drug viscosity, delivery volume and time, should be established to assist in identifying the optimal device subsystems. Each of these design parameters may leverage the available application accelerator subsystems to decrease design

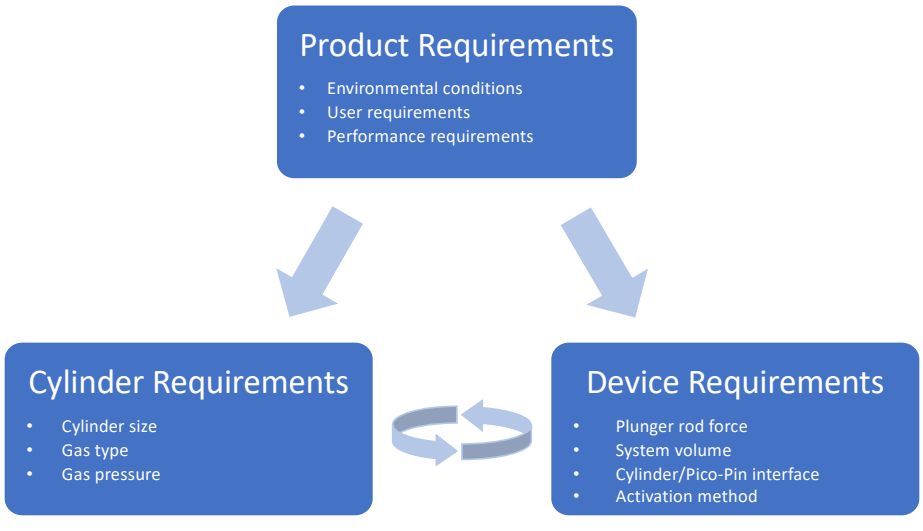



Figure 4: Product, cylinder and device requirements in a Pico-Cylinder driven system.


Figure 5: Dual-phase gases provide a constant pressure at a set temperature resulting in a constant force profile.


Figure 6: Force drop over stroke due to increase in internal volume as plunger deploys.

risk, project timeline and development cost by building upon prior learnings. These subsystems include standard options for:

- Cylinder size, gas selection and cylinder cap configuration
- Opener pins (Pico-Pins) and valves for selected applications
- Activation mechanisms, such as push to skin, thumb button or side/lever action.

## Cylinder Size and Gas Selection

Standard cylinder sizes are 0.7 and 1.0 mL, which are suitable for most applications. Custom sizes can also be made to fit specific applications when required.

In terms of gas selection, the primary consideration is the use environment. When devices are intended for use in a temperature-controlled environment, such as an operating room, dual-phase gases (liquid and vapour) may be preferable due to their ability to provide a constant pressure throughout a long delivery stroke up to the expansion limit of the gas. This allows for a constant delivery force throughout the entire stroke, as illustrated in Figure 5.

Conversely, some devices, such as autoinjectors, may be used across a wide temperature range from low temperatures (shortly after being stored in a refrigerator) to high temperatures (after being stored in automobiles or backpacks). For these applications, a single-phase (vapour only) gas may be preferable because its pressure varies as a function of the absolute temperature (°K), as defined by Gay-Lussac's Law:

$$\frac{P_1}{T_1} = \frac{P_2}{T_2}$$

For the use case of an autoinjector operating in the range of 0°C–40°C (273°K–313°K), the pressure of argon will fluctuate by only 15% compared with dual-phase $CO_2$ or HFC 134, where the pressure would increase by 185% and 247% respectively. Vapour phase gases, therefore, are the best choice for autoinjectors or devices where the patient self-administers across a wide temperature range.

Similar to spring powered delivery devices, vapour phase gas devices will demonstrate a reduction in delivery force as the plunger deploys (Figure 6). This is due to an expansion in internal volume resulting in a reduction in system pressure as governed by Boyle's Law:

$$P_{Initial} \, x \, V_{Initial} = P_{Final} \, x \, V_{Final}$$

The expansion ratio is simply the proportion that the internal volume increases over the stroke of the device, as defined by the equation:

$$Expansion\ Ratio, \% = \frac{\left(System\ Volume_{Final} - System\ Volume_{Initial}\right)}{System\ Volume_{Initial}} x\ 100$$

With optimised expansion ratios, the system will deliver near-constant force over the entire injection stroke, as shown in Figure 7. This leads to a consistent drug delivery rate and faster delivery time for a given peak flow rate. As a result, the patient will experience a more consistent delivery and shorter injection times.

Unlike springs, the force drop characteristics can be tailored for an application by designing to a target expansion ratio. As an example, the expansion ratio may be minimised by incorporating additional system volume to provide a more consistent force profile (Figure 8).

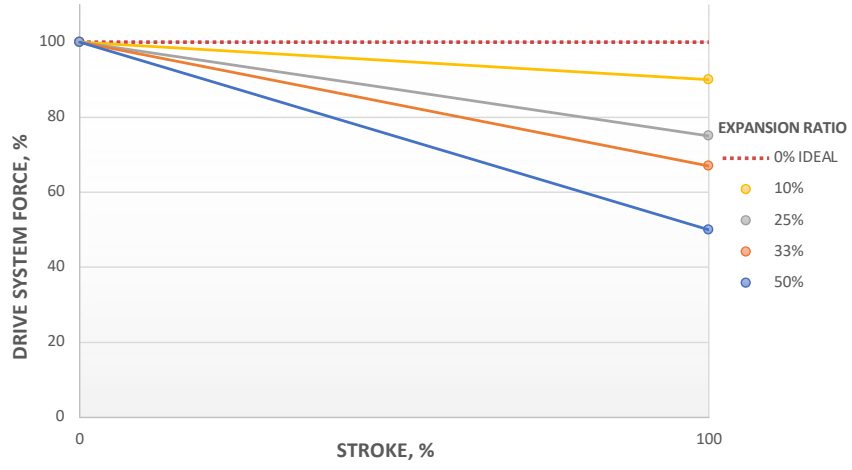



Figure 7: Delivery force profile as function of expansion ratio.

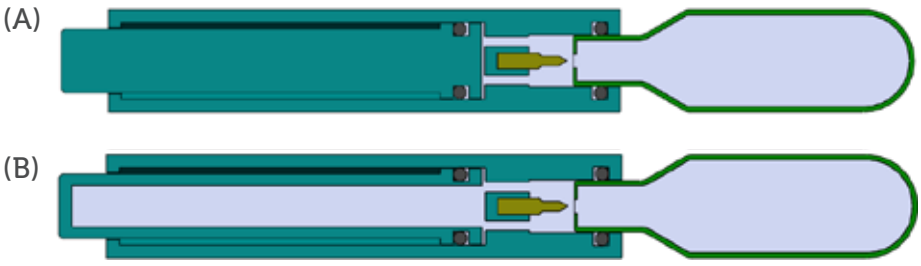



Figure 8: A more consistent force profile can be achieved by incorporating additional system volume (B) compared to a traditional layout (A).

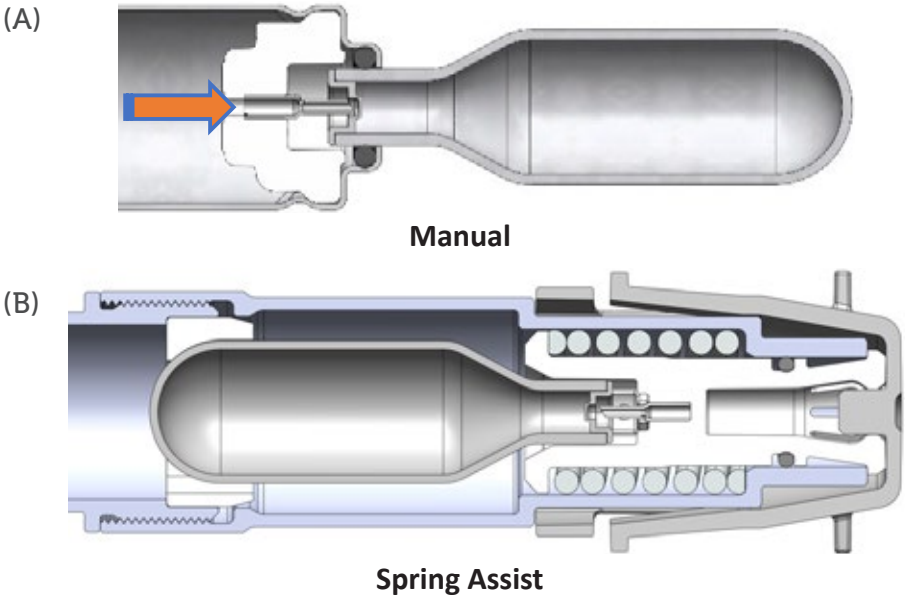



Figure 9: Two Pico-Cylinder deployment concepts.

> "To ensure the overall function and reliability of the device, Pico-Cylinders are validated with off-the-shelf Pico-Pins that interface with the cylinder's unique breakaway septum to provide the consistent, low-force opening that is the hallmark of this system."

### Pico-Cylinder Deployment

To ensure the overall function and reliability of the device, Pico-Cylinders are validated with off-the-shelf Pico-Pins that interface with the cylinder's unique breakaway septum to provide the consistent, low-force opening that is the hallmark of this system. Figure 9 illustrates the interface between the Pico-Cylinder and Pico-Pin in two potential deployment concepts.

The interface between the Pico-Cylinder deployment and end-user activation mechanism may be tailored to the use case and patient needs. In the IOL inserter example, the manual activation method was used by incorporating a lever to move the Pico-Pin into the Pico-Cylinder to activate the device (Figure 9a).

In the case of other autoinjector systems, the common two-step activation method (remove cap and press to skin) has been employed with a spring-assist mechanism (Figure 9b) to deploy the gas from the Pico-Cylinder. Alternatively, the same mechanism may be activated with a push button or side lever.

## BUILD CONFIDENCE AND REDUCE RISK VIA EARLY DATA GENERATION

Recognising the need for rapid feasibility data, Altaviz has developed a test system capable of using client-provided drug or Altaviz's silicone oil formulations up to 100,000 cP along with a variety of component inputs and system settings, as summarised in Table 1. The test system is portable to enable use at a client site. This test system provides graphical data (Figure 10) that summarises syringe force and plunger position over time, graphed within seconds of each test sample. It enables ease of experimentation and enables clients to compare options with minimal hassle.

## SUMMARY

Compressed gases are a proven power source used across a range of precision healthcare applications. They provide a power option for differentiated, next-

| Test Systems Inputs | |
|---|---|
| **Components** | **Parameters** |
| • Prefilled syringes<br>– 1 mL long<br>– 2.25 mL<br>• Simulated drug formulation<br>– Up to 100,000 cP<br>• 0.7 mL gas cylinder<br>– Pressures up to 275 bar<br>• Plunger rod<br>– 3–8 mm diameter<br>• Production Pico-Pin | • Dose selection<br>– 1 mL long: 0.5, 0.75, 1.0 mL<br>– 2.25 mL: 1.0, 1.5, 2.0, 2.5 mL<br>• System volume<br>– 3–6 cc |
| **Data Collection and Reporting** | |
| **Collection** | **Reporting** |
| • Plunger position<br>• Drive system pressure<br>• Syringe force | • CSV data<br>• Graphical data output versus time/position |

Table 1: Test system parameters and outputs.

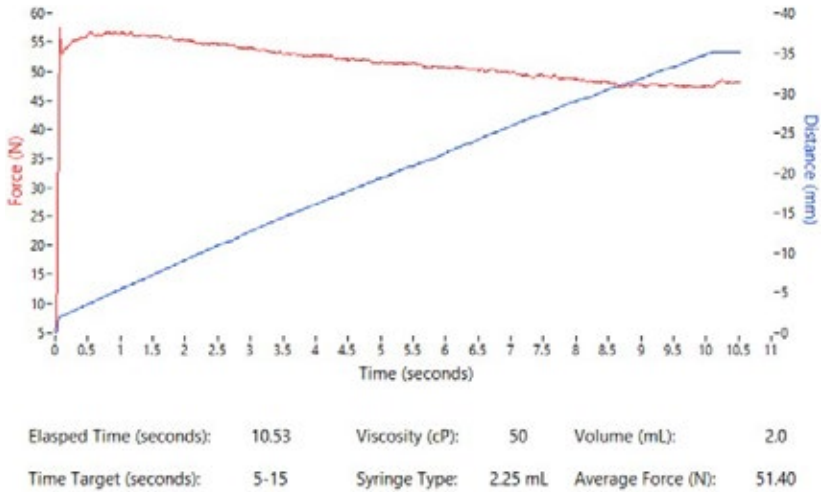



Figure 10: Altaviz test system graphical output showing position data and force profile.

generation drug delivery devices. A platform with broad capability and flexibility can be effectively designed around a single cylinder size with the assistance of gas-power experts. These gas-powered systems can solve many problems or address limitations of legacy designs. Leveraging the design expertise and technology of teams experienced with gas-powered systems will mitigate risk and accelerate the time to market to get innovative products into end-users' hands.

## ABOUT THE COMPANY

Altaviz develops and manufactures platform technologies and products for the pharmaceutical, biotechnology, medical device, and other specialised healthcare segments requiring high performance and innovation in an ISO 13485 environment.

As experts in next generation, gas-powered devices, Altaviz applies its technical and therapeutic area knowledge to provide innovative device solutions that solve complex problems and enhance patient care while meeting ISO 11608 and ISO 14791 standards. Altaviz' clients may engage to leverage existing platforms and application accelerators or develop custom solutions.

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## ABOUT THE AUTHOR

**Jack Auld** is Co-Founder and Chief Executive Officer of Altaviz, a company founded to conceptualise, design, develop and commercialise innovative delivery platforms and solutions for next-generation drugs, implants and specialised applications. Mr Auld has over 20 years of experience in ophthalmic device and drug delivery, with 52 US and 114 international patents. Mr Auld's passion is leading smart people to creatively solve real-world problems, creating better outcomes and experiences for patients. Prior to founding Altaviz, he worked with ophthalmic surgeons to translate those needs into state-of-the-art hand-held devices. For the past 10 years, his focus has been on expanding applications for gas-powered devices, including intraocular lens inserters, subretinal delivery systems for gene therapies and parenteral drug delivery devices, including autoinjectors.

# Technology Showcase: Investigation into the Feasibility of a 2 mL Needle-Free Injector

Portal Instruments

Figure 1: Prime needle-free device.

The current paradigm of injectable drug delivery has stagnated since the early 2000s. Despite recent innovations, such as the European launch of the first electromechanical reusable and connected autoinjector (UCB's CIMZIA [certolizumab pegol] ava Connect® in early 2021), almost all new biologic drugs are launched with specific and undifferentiated self-injection options – a spring-based mechanical autoinjector or a prefilled syringe (PFS), often with attached safety device. This now-common set of options only serves two classes of patients well.

The autoinjector appeals to patients who wish to avoid seeing a needle and can patiently wait for an injection to complete – albeit with sometimes ambiguous cues. The PFS works well for patients who are not needle-phobic and prefer the control over the injection speed. Outside these two classes of patient, each device technology represents a compromise: patients may have to accept a medication with reluctance; need someone else to administer it for them; or need to seek out non-injectable therapies that may require more frequent dosing, dietary restrictions or a greater risk of serious adverse events (note the recent warnings and use restrictions placed on oral janus kinase inhibitors by the US FDA).[1] The lack of enthusiasm that arises from having only suboptimal device options may increase the risk of poor adherence and poor persistence on therapy.

Additionally, the trend towards larger-volume injections for patients makes these devices even less user-friendly and thus reduces their appeal. This trend is a byproduct of the need for increased doses for either efficacy reasons or as a way to make dosing less frequent. Typical biologic concentrations are ≤200 mg/mL; as dose needs increase, there is a trade-off between volume and concentration, which leads to either a drug volume or viscosity that results in drug-delivery solutions that either take more time or force to inject. With the trend towards larger-volume injections for patients – 2 mL autoinjectors with similar use characteristics have recently been approved, and there are further studies clinically investigating 2 mL devices – it seems the burden on patients will not lighten anytime soon.

Makers of oral medications in certain classes seem aware of the opportunity created by a suboptimal patient experience and are working to highlight it in their marketing. Pfizer's branding of Xeljanz® (tofacitinib) as "Unjection™" is the most visible example of this.

Given this context, there is a significant opportunity to transform the patient experience with a reusable and connected needle-free injector. Having already demonstrated in Portal Instruments' PRECISE II saline self-injection study that the company's Prime needle-free drug delivery platform (Figure 1) is preferred over a PFS by more than 8:1 (78% versus 9%) amongst healthy volunteers and is reported to inject with lower levels of self-reported pain, the company sought to further explore the platform's potential with a 2 mL injection. In this study, PIONEER, Portal Instruments explored the feasibility of a 2 mL needle-free injection, the first using a handheld needle-free injection device. The PIONEER study demonstrated similarity in patient-reported outcomes, including perceived pain and user preference, between two 1 mL needle-free injections and a single 2 mL needle-free injection. This demonstrated feasibility of 2 mL needle-free injections and its comparability with two 1 mL doses is exciting for the possibilities it brings to patients.[2,3]

First, Portal Instruments' technology allows for very rapid injection with a decrease in pain perception (Figure 2). A 2 mL injection of a biologic drug may require the patient to press an autoinjector, such as the AJOVY® device (Otsuka Pharmaceutical, Tokyo, Japan), against their skin for 30 seconds. However, Portal Instruments' platform can inject the same volume in 600 ms, making for a 50-times faster injection. This leads to potential advantages in user

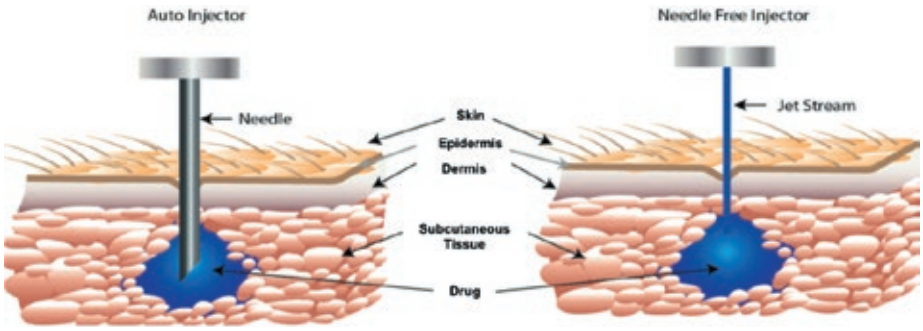


Figure 2: A high-pressure, narrow jet pierces through the epidermis, delivering drug into the subcutaneous space.

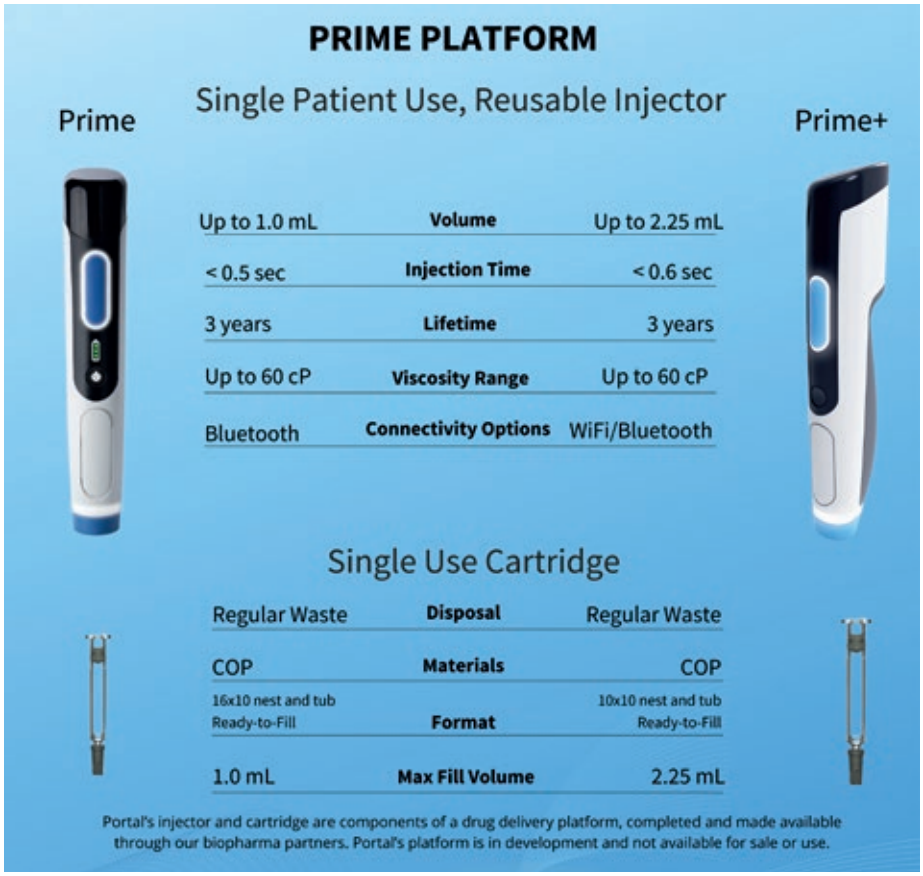


Figure 3: Portal is part of a solution designed to offer next-generation, connected needle-free drug delivery.

preference and reduced risk of user error (e.g. premature lifting of the device during long autoinjector delivery times, resulting in medication loss), with such a significantly faster injection time (Figure 3).

Next, the needle-free nature of Portal Instruments' device may remove a significant barrier to acceptance and adoption of injectable therapies for users who are afraid of needles, which is reportedly 25% of the population.[4] Many users, even if they lack needle anxiety, may be reluctant to bring an injectable medication into their home, fearing accidental use by or injury to children or others with whom they reside.

Lastly, the environmental impact of needle-based injections is significant and largely unquantified. A reusable system, such as Portal Instruments' needle-free injector, which produces less waste in total and eliminates biohazardous waste, would inherently be a better choice for pharmaceutical companies looking to decrease their environmental impact. Altogether, removing disposable needle based devices, which are classified as biohazardous waste, from the world will result in both direct monetary and other societal benefits.

As a fortunate secondary effect, the electromechanical nature of Portal Instruments' system includes integrated connected health and digital capabilities, which could be used to drive patient adherence and persistence with therapy. Medication non-adherence is a significant drag on the positive and potentially life-changing benefits of all therapies, injectables included.

*Note: All trademarks and company names are the property of their respective owners.*

## ABOUT THE COMPANY

Portal Instruments aims to transform medicine by enabling patients to self-inject their biological drugs with a revolutionary needle-free device. This innovative drug delivery system is designed to replace autoinjectors and early studies show it is overwhelmingly preferred by patients. Issued from MIT Research and connected to the cloud, the Portal Instruments' device allows biopharmaceutical companies to differentiate their therapies with a patient-centric drug-delivery solution.

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# INTERVIEW

In this interview, Arnaud Guillet of Biocorp talks with ONdrugDelivery about connectivity in the injectables space, sharing some of the insights Biocorp has gained from its decade of experience in developing connected drug delivery devices. Mr Guillet shares his thoughts on the current state of connected drug delivery, the challenges of demonstrating the value of these technologies, and what's next for Biocorp as a company.

## ARNAUD GUILLET, VICE-PRESIDENT, BUSINESS DEVELOPMENT, BIOCORP

Arnaud Guillet is Vice-President, Business Development at Biocorp, in charge of finding partnerships and licence 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 he has additional past experience in the pharmaceutical industry with Sanofi (Paris, France) and the insurance industry with AXA (Paris, France). He graduated from HEC Paris (France), a major European business school.

**Q Regular readers of ONdrugDelivery will be familiar with Biocorp but, for those who aren't, please could you give an overview of the company?**

A Biocorp's speciality is developing connectivity solutions that are useable across a range of drug delivery devices. For example, in the injectables space, our most famous product is the Mallya smart cap, version one of which is now on the market. With Mallya, we're currently doing specialised developments with big players, such as Sanofi, Novo Nordisk and Merck KGaA. Another Biocorp product your readers may be familiar with is Injay, our smart prefilled syringe (PFS) solution, both for naked PFSs and PFSs equipped with safety systems (Figure 1).

Figure 1: Injay, Biocorp's simple add-on connectivity solution for PFSs.

In fact, Biocorp was one of the first players to really investigate connectivity in the drug delivery space; we started the journey around 10 years ago. That's how we launched the first connected device in the space – the Datapen (Figure 2), which is a motor-driven pen injector with Bluetooth Low Energy (BLE) connectivity. Datapen is still a platform that we are developing, although with more of a focus on the motor-driven aspect over the BLE connectivity part because markets are looking for very cost-effective solutions.

Figure 2: Datapen, Biocorp's reusable connected pen injector.

> "Another factor is the digital ecosystem, which adds significant complexity because connected systems need to communicate with each other."

Based on this experience, we quickly expanded into add-on solutions – there is a strong appetite for simple solutions. From the pharma and industrial standpoints, simplicity really is the critical factor. Seeing this, we quickly pivoted our development efforts to add-on solutions over fully integrated delivery devices, launching Mallya in 2014–15. And we've been developing the platform ever since.

**Q Let's broaden the scope – what's your take on the current status of connectivity technologies in the delivery space as a whole?**

A I would say that connectivity is currently most strongly influenced by a couple of internal and external factors. Starting with the internal factors, you've got device usability. When you're looking at adding connectivity to a drug delivery device, it's a complex problem – you're adding electronics to an otherwise purely mechanical device, you're adding extra functionality that needs testing and verification, you're adding complexity for the patient who needs to use the device to deliver their medication. As you can imagine, switching from a very simple and purely mechanical device to an electronic device is anything but trivial.

Another factor is the digital ecosystem, which adds significant complexity because connected systems need to communicate with each other. By default, they just don't – if they're not using the same application programming interface (API), they're not speaking in the same language. Figuring out how to get connected devices to interface with everything they need to has been a very big challenge.

Then, thinking more externally, you need to consider how you communicate with healthcare providers (HCPs). This is

key, because a huge part of the value of a connected device is its ability to deliver real device usage data to HCPs, who can then use it to engage further with their patients. A major consideration for anyone working in connected drug delivery devices is how to deliver the information gathered by the device to an HCP in a way that isn't an additional burden for them. If HCPs see this technology as additional work for them, it's never going to reach its full potential.

There is also the regulatory burden to consider. This is still a novel technology, and drug delivery is a risk-averse industry, so it has taken time and effort for regulators to understand connectivity and find where it fits in the regulatory model. When we first started to introduce connected products to regulators, we had to answer a lot of questions; "What are these devices?", "Is an add-on considered part of the main device?", "Are these combination products?". In practice, there are three things to deal with for an add-on in this regard: the combination policy, the hardware and the software. Clear guidelines and regulatory pathways would be very helpful for seeing more successful developments in the connectivity space.

Naturally, this is all very complex by itself, but then you need to consider how it fits into the digital and pharmaceutical ecosystems. For example, you have data protection and data management to handle, which come with their own set of considerations, challenges and additional regulations. In tandem, there's the question of how a connected product fits into the target market and, in particular, how it fits into that market's reimbursement programmes. The lack of clear, value-based models for connected drug delivery devices has been an issue because adding connectivity creates an extra cost; where this leaves patients out of pocket, it acts as a major bias against adopting the technology.

Where we see some positive signs are where the biases imposed by these factors have been lifted. In this regard, covid-19 has had a notable influence here from a regulatory standpoint because, in the face of the pandemic, regulators understood that it was time to accelerate progress in digital health. We've seen them re-clarify the best way to proceed with these technologies and validate some applications on a provisional basis so that they can generate some real-world evidence and build their case. It's really helped with reimbursement on certain applications, which is encouraging progress.

I also think that we've seen a positive trend in device usability. The miniaturisation of electronic components has enabled us to develop devices that are slimmer, closer to traditional delivery devices and have improved interoperability. Take the diabetes space as an example, it's spectacular how you can now interface the data from your glucometers with mobile applications, artificial intelligence titration software and the data from a system like Mallya all together in a single place with a simple API interfacing tool. This development has been really helpful for driving up adoption.

**Q How do you see different markets and healthcare systems factoring into the adoption of connectivity? For example, is there a difference between how the fully state-owned UK NHS and the US private insurance-based model have responded to connected drug delivery devices?**

A That's an interesting aspect to consider. In my view, while they are very different systems, both are well situated to adopt connected devices; the big difference is that it's not going to be the same discussion. With the US, it's going to be all about healthcare expenditure – the consideration is really based on the value and the cost effectiveness. Whereas, for the European markets, adoption will be much more driven by public opinion, so there we need to demonstrate what connectivity can do for patients.

That said, it ultimately all comes down to the same process – demonstrate the efficacy of the product, build your case, prove that you're actually saving costs, boost patient engagement and show the value of the technology in the long run. You need to put money on the table, make sure you have sufficient time and collect sufficient statistically meaningful data. Having all of that in place will be key to seeing adoption in both markets.

Once everything is in place, it's then a matter of who to have the key discussions with. In the US, it'll likely be health plan providers, whereas it'll be more state-driven in the UK, Germany and France. Germany in particular is an interesting case because of the Digital Health Apps (DiGA) Initiative, which will, based on limited evidence, clear an application on a provisional basis to give you some time to reimburse and prove that the product will actually yield some benefits for the healthcare system. It's a good example of an original approach that could help foster connected technology.

Another factor in the US is the new current procedural terminology (CPT) codes for reimbursement and telemonitoring, which will enable us to engage HCPs more effectively about adopting connected devices because there will be a system for them to be paid for the time they spend on the software portal and dealing with the data fed back to them by the devices, rather than this simply being an additional burden.

In Europe, the way to significant adoption will really centre on building a body of clinical evidence. However, the European healthcare ecosystem is much more fragmented, so I think it will take longer to see widespread adoption, but it will ultimately reach a higher proportion of the population. There's a cumulative aspect to it; every step we take forwards, the other areas can see success, which will make them more inclined to adopt connectivity themselves – it builds and snowballs as positive feedback.

**Q Which therapeutic areas do you think are likely to lead the way in terms of adoption of connectivity?**

A Diabetes is the stand-out case. It's very complex – you have to use a number of data points from your glucometer. As a patient, you don't necessarily know exactly how to interpret these data, so you need a doctor or an AI to interpret them and tell you what to do and how much to inject. This is an obvious case where digitalisation can greatly simplify the process and improve patient quality of life.

All this makes diabetes a good laboratory for connected devices, plus it's an indication

"It ultimately all comes down to the same process – demonstrate the efficacy of the product, build your case, prove that you're actually saving costs, boost patient engagement and show the value of the technology in the long run."

Figure 3: Mallya, Biocorp's smart cap.

where you can clearly demonstrate the impact on relapses and hospitalisations, which in turn shows the impact on the healthcare costs, society and patient wellbeing. Additionally, the adoption rate amongst diabetes patients is already quite high in terms of connectivity; I think part of that is a demographic factor – Type 1 diabetes patients are typically younger, and it's Type 1 patients that are the trendsetters when it comes to connectivity.

Another category leading the way on connectivity is cardiovascular disease. Here, it's not the utility of tools that will drive adoption, like with diabetes, but rather the risk associated with the disease. If a cardiovascular patient doesn't stay in control of their disease, it can lead to very costly hospitalisations and serious healthcare complications. So, in the cardiovascular space, there's real value in using connectivity to make sure that patients are managing their disease properly.

In a similar way, the respiratory sector is an interesting case. While it's well known that poorly managed respiratory conditions, asthma and COPD in particular, are a massive burden on healthcare systems and life threatening for patients, it's an enormous challenge to engage patients because the serious complications only come much later – sometimes patients don't take their medicine for years before it happens. Connectivity is a potential solution to this challenge, so there's a lot of potential in the sector.

> "The next logical step to tackle this non-adherence is to look into monitoring how patients are taking their prescribed medications and how they can improve patient adherence so that the drugs are as effective as under the clinical conditions."

Then there's the developing market for biologics around indications such as multiple sclerosis, rheumatoid arthritis, Crohn's disease and others that are delivered using PFSs and autoinjectors. This is an area we're very interested in, because the biologics involved are very expensive and administered relatively infrequently, often only once every one or two weeks. Additionally, there is not necessarily a direct symptomatic incentive for patients to take them because they don't experience a clear outcome from taking their medicine but, if they don't, the consequences are severe. Therefore, I think that some payers will realise that, while they are reimbursing very expensive medicines based on the clinical results, in practice there are many hospitalisations as before. The next logical step to tackle this non-adherence is to look into monitoring how patients are taking their prescribed medications and how they can improve patient adherence so that the drugs are as effective as under the clinical conditions.

**Q We've touched on interoperability and the digital ecosystem a few times up to this point, could you expand on Biocorp's approach to this aspect of connected drug delivery?**

A Absolutely. On its own, a connected device can monitor treatment adherence but not manage it. The treatment management part comes from the software and the service you're accompanying it with, and there are some key considerations for how you implement it. How do you interpret the data that you receive? Do you use AI to process it automatically and expect patients to be autonomous or do you involve HCPs? How do you engage both parties? To succeed, it's critical to map out the stakeholders and the patient journey.

The importance of thoroughly understanding the individual behind the patient is something we recently discovered. We want to invest more into behavioural science because, in many cases, while you'll naturally need to tailor a digital solution to the target indication disease, patient non-adherence comes down to sociological, psychological or cultural issues that lead the patient to not take their medicine – it goes beyond just the complexity of understanding and using their device. This is why, on top of tailoring a solution for the disease, we need to provide answers for specific individuals to prevent non-adherence, so this is a key area of focus for us.

To this end, we want to invest in modern software that is not only able to give us full insight into the treatment, but also able to profile the individual user and fit them into different categories. So, when the software identifies a non-adherent patient, it will be able to determine that patient's particular profile and tell what issue is relevant, and the application will tailor its response to make sure that the patient, with their specific needs, is addressed as an individual. For example, if you tend to forget your medicine, we'll send you reminders; but if you don't, and you don't want to be bothered by them, we'll address you in a different way. It's really just tailoring the context and understanding the individual, so that we can engender sustainable engagement with the patient.

**Q How is Biocorp gathering data and demonstrating the benefits of connectivity in terms of improving adherence and disease outcomes?**

A Currently, we are building a lot of clinical trials for Mallya (Figure 3), as well as discussing and launching a lot of initiatives in this regard. For example, we are participating in a major European initiative called Trials@Home to prove the benefits of using Mallya together with connected glucometers and digital solutions to perform decentralised trials. The goal is to really demonstrate the feasibility, benefits and efficacy of these tools.

Beyond that, we are building some clinical studies to demonstrate the value of Mallya, both as part of the broader digital ecosystem, but also the intrinsic value of Mallya itself as just a smart cap. This is actually an excellent example of a key

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challenge we're facing across all connected device development – how do you isolate the contribution of a single device or piece of technology so that you can build a case for it?

Basically, there are two options. Either you build an entire digital ecosystem by yourself and build your case for the whole thing as a singular entity. This approach has some major drawbacks in that it's not that flexible – you can't integrate it with anyone else's technology – and it's very expensive. The second option is to find a way to demonstrate the benefits of your device as part of the much broader digital ecosystem. The challenge here is how do you design your clinical trial methodology? You need to find a way to isolate the value of your technology specifically, so you have to have a group that is just Mallya and another that is Mallya plus ecosystem and nothing on top of that. That way, you can examine the device factor in isolation.

It's a real challenge. We've found some solutions to circumvent the issue but it's an ongoing process. We're planning to launch this initiative from next year, first at a European level to demonstrate proof of concept. Hopefully we can leverage the results of these trials in many European countries for further development, and also expand towards the rest of the world.

**Q For Biocorp specifically, what's coming next for the company over the coming months and into 2023?**

A First and foremost, maturing our product portfolio will be an important aspect of the coming months. We have already launched Mallya V1 on the market, but there are also specific customised versions of Mallya for Sanofi and Novo Nordisk, so we'll be maturing them and bringing them to market. As part of this, we're looking to increase our manufacturing capabilities, including optimisation and automation, so that we are ready to meet any increased demand in a cost-effective manner. Accompanying that, we are also looking to increase our software development capacity, both so that we can boost our interoperability so that our devices can better interface with the other players in the market and also so that we can develop our own mobile app to work with our devices.

On the sustainability front, we're planning to conduct a major review to ensure that we are able to meet the demands of the market and potential partners. This is a fast-moving area, so it's important to stay on top of it. For Biocorp, our products use plastic, they use electronics, so we need to optimise our sustainability profile. Fortunately, because we focus on add-on solutions, we tend to develop reusable solutions, which are naturally more environmentally sustainable. However, if we go disposable, it's important that we do so in a manner with minimal environment impact, such as near-field communication (NFC) technology.

On the product side, we announced a new device at Pharmapak – Sween, an automatic needle insertion device to help patients who have needle phobia (Figure 4). We intend to bring this device to market on our own, targeting the end of 2023. We expect this device to see good traction because it's tackling a critical issue and is in line with our traditional expertise in injection modelling and drug delivery submissions.


Figure 4: Sween, Biocorp's injection assistant for patients with needle phobia.

## ABOUT THE COMPANY

Recognised for its expertise in the development and manufacture of medical devices and delivery systems, Biocorp has acquired a leading position in the connected medical device market, thanks to Mallya. This intelligent sensor for insulin injection pens allows reliable monitoring of injected doses and thus offers better compliance in the treatment of diabetics. Available for sale since 2020, Mallya spearheads Biocorp's product portfolio of innovative connected solutions.

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# IT'S TIME TO LEVEL UP LYO – INTRODUCING A SWIFT SHIFT IN DUAL-CHAMBER AUTOINJECTOR TECHNOLOGY

**Here, Brent Buchine, PhD, Chief Executive Officer at Windgap Medical, discusses the need for automated, easy-to-use reconstitution devices, especially in lyophilised medications, and introduces the company's technology platforms, which rise to the challenge.**

In the pharmaceutical industry, the rapid rise of injectables has been impossible to ignore. These drug products offer an alternative to oral medications, and are changing the landscape of the pharmaceutical industry. The growing prevalence of chronic diseases, a focus on developing cost-effective treatments and drug shortages continue to drive market growth.[1] According to Precedence Research, the global injectable drug delivery market reached US$561 billion (£483 billion) in 2021 and is expected to surpass $1,224 billion by 2030.

Increasingly prevalent in the injectables space are lyophilised and powdered medications:

- The manufacture of lyophilised drugs has grown in both the pharmaceutical and biopharmaceutical sectors by around 13.5% per year over the last five years.[2]
- Of the top 100 drugs, 16% are lyophilised, according to BCC Research.[3]
- Due to the rapid growth in biologics, the percentage in this category is even higher, at 35% lyophilised, also according to BCC Research.
- Markets and Markets reports in their 2020 global forecast that more than half of injectable drugs will soon require lyophilisation,[4] creating new challenges and opportunities for drug delivery.

> "More than half of injectable drugs will soon require lyophilisation, creating new challenges and opportunities for drug delivery."

## WITH RISING USE COMES MORE CHALLENGES – ESPECIALLY WITH DIFFICULT-TO-MIX DRUGS

The growth with lyophilised injections is driven by several factors, each with its own challenges.

First is a rise in the use of lyophilisation as a preservation technique for biological products and drugs in the pharmaceutical industry.[5] Lyophilised products have a much longer shelf life and thermal stability than products in liquid form.[6] This is especially helpful for inherently shelf-unstable biologics – drug products on the cutting-edge of biomedical research. It also reduces the need for cold-chain management during shipping. Biologics, while one of the most

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effective means to treat several previously untreatable illnesses and conditions, are currently difficult to formulate and administer; their large molecular size often creates a highly viscous dose that can be easily degraded.

The use of depot injections is another factor driving an increased prevalence for powdered medications. Depot injections use extended-release medication formulations to enable long-acting drug dosing. A single depot injection could reduce a once-daily regimen down to bi-weekly, monthly or longer intervals. While designed to improve patient compliance and outcomes, depot formulations often have unique mixing challenges. They must be stored separately and then "suspended" in a liquid vehicle just prior to administration, a process that can also be difficult due to high viscosity and large-volume dosage requirements.

It is also increasingly common for companies to develop lyophilised formulations to get through their clinical trials and then reformulate a more user-friendly liquid version of the product for commercial sale. This process adds time and risk to their development programme as they test different drug delivery methods versus taking the lyophilised product all the way through approval to market.

When a lyophilised drug does make it into a patient's treatment plan, the most common delivery solution for powdered and lyophilised medications continues to be a kit with two vials, multiple needles and a syringe.[7] This approach requires several complicated steps to draw fluid from the diluent vial, dispense it into the powder container, shake or swirl vigorously, manually observe dissolution, attach a new needle, manually draw the combined ingredients and then inject. The process requires a substantial amount of time and medical training – although even with training, complicated procedures introduce or increase the possibility of human error and environmental impact, which can result in an incorrect dose, a reduction in a drug's effectiveness or worse.

Current dual-chamber bypass cartridge technologies offer little improvement. While the two vials are integrated into a single cartridge containing both drug and diluent, drug delivery can be orientation-dependent and still reliant on vigorous shaking to ensure a full reconstituted dose. In addition, dual-chamber autoinjector manufacturing is often more complex, and the end-user patient experience is lacking – both of which leave a strong desire for something better.

Drug developers looking for devices must ensure they meet a diverse set of requirements, from balancing patient needs and compliance to the mixing complexities of effective drug delivery and a rapid path to market.

> "Windgap addresses the critical challenges of delivering difficult-to-mix drugs with two dual-chamber reconstitution autoinjector platforms – its compact ANDIPen® and an LVDC autoinjector."

## INJECTING SIMPLICITY INTO COMPLEX DRUG DELIVERY DEVICES

One company in particular aims to simplify, automate and accelerate the drug delivery process for both pharmaceutical companies and the patients who depend on them.

Windgap Medical addresses the critical challenges of delivering difficult-to-mix drugs with two dual-chamber reconstitution autoinjector platforms – its compact ANDIPen® and a large-volume, dual chamber (LVDC) autoinjector. Each of these two wet/dry dual-chamber autoinjector platforms automates rehydration and administration, simplifies the reconstitution steps and allows the user to administer a dose in seconds.

One of the primary drivers of Windgap's technologies is its focus on human factors engineering, which considers patient capabilities, limitations and lifestyle characteristics to develop products that bypass common delivery and manufacturing issues, all of which protect the medication, the patient and the outcome.

### ANDIPen: Twice the Shelf-life, Half the Size

Windgap's ANDIPen addresses significant yet unmet user needs within a competitive market by increasing portability, temperature stability, ease of use and shelf life for the medications it administers. The ANDIPen reduces the number of steps to two simple user operations: twist and inject (Figure 1).

- **Cap twist and removal** – A simple cap twist connects the diluent and powder chambers through a rotational valve. This simultaneously aligns two fluid channels to create a fluid pathway while releasing a spring that drives the diluent to interact with the powdered drug. This automatically rehydrates the correct dose and exposes the needle-shield-fired trigger. The interconnected chambers move inside the autoinjector to maximise the surface area and interaction between the two parts, speeding up dissolution.


Figure 1: The ANDIPen reduces the number of steps to two simple user operations: twist and inject. *Windgap Medical's products are not commercially available or currently approved anywhere around the globe.*

- **Injection** – Depressing the needle shield initiates the automatic needle insertion into the skin and delivers the reconstituted medication. After device injection and removal, the needle shield extends to provide needle safety.

All of this occurs in just a few seconds – no shaking or swirling required. The ANDIPen platform can accommodate volumes of 0.3 mL or less, with a viscosity of up to 1 cP, with custom needle lengths and gauges for either subcutaneous or intramuscular delivery. The ANDIPen offers powerful and rapid device-controlled automixing capabilities within its volume and viscosity range – and is small enough to provide a patient with peace of mind in their pocket.

## LVDC: Difficult-to-Mix Drugs at the Press of a Button, No Shaking Required

Capitalising on the success of its ANDIPen drug-delivery platform and with funding from the US National Institutes of Health, Windgap began developing an LVDC device to quickly and completely mix lyophilised drugs with viscosities up to and greater than 1000 cP and deliver dose volumes of up to 5 mL – opening the door for additional treatment areas in biologics, large molecule and lyophilise-compatible medications.

The novelty of this device comes from its innovative primary drug container (PDC) configuration. Windgap's PDC architecture uses two standard, off-the-shelf, single-chamber cartridges nested side by side and connected with Windgap's novel proprietary mixing and delivery needle hub. The side-by-side nesting of the cartridges enables a short and more compact autoinjector using ISO standard cartridges that are compatible with industry-standard filling methods for powder and liquid products (Figure 2). The PDC architecture is simple and scalable, as well as able to accommodate a variety of cartridges size (1, 2.25, 3, 5 mL, etc.).

When reconstitution is initiated, septum-piercing needles puncture both cartridges simultaneously. This dual puncture creates a closed fluidic connection between the two sides, transferring the liquid from its initial cartridge to the powdered drug cartridge for mixing. A single button press cycles fluid from one cartridge to the other. When the button is released, the fluid returns back to the original cartridge.

A stored gas energy source within the autoinjector governs the number of mixing cycles, using a regulated gas pressure to control the mixing/delivery force via a mixing valve. This technology can be adjusted to fit the number of cycle requirements, mixing pressure and delivery pressure to meet the drug and user needs.

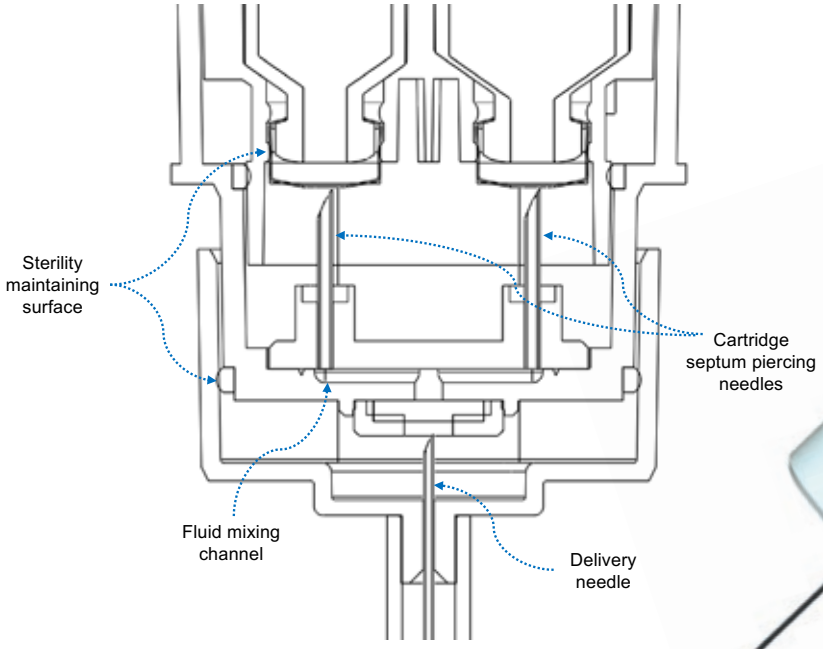


Figure 2: Left: Cut-away schematic of the mixing and delivery hub of the PDC. Right: Windgap's side-by-side PDC with mixing and delivery hub.

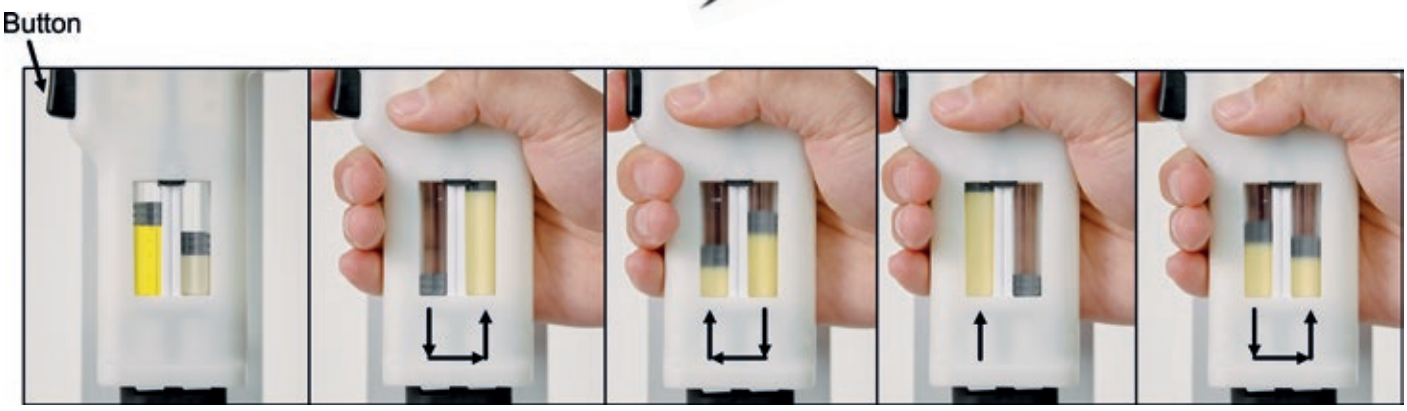


Figure 3: Demonstration of Windgap's reciprocating autoinjector mixing a cyanide antidote drug product currently under development. Arrows indicate alternating fluid flow in the PDC between cartridges.

> "These proven platforms put Windgap in a prime position for collaboration with the pharmaceutical industry by simplifying drug delivery devices for any therapeutic application."

Like Windgap's ANDIPen device, the LVDC is orientation-independent, so it can be used at any angle, in any environment. The cartridge size, mixing needle diameter, fluidic channel length and fluidic channel diameter are all customisable to serve a wide range of medications, including – and especially – difficult-to-mix drug products (Figure 3).

### This Method of Reciprocating Mixing has Several Key Advantages

Internal studies have shown that this method of reciprocated mixing has decreased the mixing time for difficult-to-mix drugs from hours to seconds, increasing the rate of dissolution by an astounding 98% compared with conventional shaking and swirling methods.

Improved human factors and a reduction in mixing complexity reduces the potential for errors by the user. Drug delivery products that would normally be administered in the clinic can be self-administered by the patient in the comfort of their own home.

**Both of these proven platforms put Windgap in a prime position for collaboration with the pharmaceutical industry by simplifying drug delivery devices for any therapeutic application.**

Windgap's platforms drive early-phase innovation and speed to market while minimising and managing risk by taking a powdered product from clinical development all the way to commercial production, often faster and at a lower cost than developing a stable liquid formulation midway through R&D.

## CONCLUSION

As the injectables market continues to skyrocket, the demand for simple, automated and easy-to-use reconstitution devices will continue to rise, especially with regard to lyophilised medications. Both of Windgap's platforms have been designed to be compliant with emergency-use reliability requirements. The company's technology platforms continue to rise to the challenge, with a team of experts ready to collaborate on innovative pharmaceutical solutions built with patients in mind.

Windgap's first device programme has been globally licensed to, and is being commercialised by, ALK Abelló, a Danish pharmaceutical company located in Hørsholm. This programme uses Windgap's ANDIPen for the delivery of reconstituted adrenaline (epinephrine).

## ABOUT THE COMPANY

Windgap Medical offers autoinjector platforms that simplify, automate and accelerate the delivery of difficult-to-mix drugs, freeing patients, families and potential treatments from the limitations of current medical delivery technology. With an innovative design, development and manufacturing process, Windgap's "instant solutions" create a new frontier of pharmaceuticals for partners seeking to harness its wet-dry drug delivery technology and an increased speed to market. Its first product is for the administration of adrenaline for anaphylaxis, with additional products under development in a variety of markets. Windgap Medical is an emerging, privately held pharmaceutical company in the Greater Boston area.

*Windgap Medical's products are not commercially available or currently approved anywhere around the globe.*

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## ABOUT THE AUTHOR


**Brent Buchine**, PhD, has worked in advanced R&D and innovation for over 20 years. In addition to being a serial entrepreneur, he has authored multiple peer-reviewed publications, received over 150 citations and filed dozens of patents based on his inventions. As Chief Executive Officer of Windgap Medical, he oversees corporate strategy, business development and an assertive drug development pipeline across several treatment areas.


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# SILICONE-OIL-FREE, COATING-FREE, TUNGSTEN-FREE PREFILLABLE SYRINGES

In this article, Taras Bredel, Business Development Director at Injecto, and Bernd Zeiss, Head of Global Pharmaceutical Support at Gerresheimer Bünde, present the studies, development, performance and benefits of the Injecto lubrigone$_3$ plunger stopper combined with the Gerresheimer RTF® glass syringe – a silicone-oil-free, coating-free, tungsten-free, low-particle prefilled syringe solution for sensitive drug products.

The prefilled syringe (PFS) market is expected to grow from €6.6 billion (£5.7 billion) in 2021 to €13.1 billion by 2028 at a compound annual growth rate of 10.7%.[1] In 2019, there were more than 8,800 injectable drug products in the pharmaceutical pipeline, of which more than 2,500 were protein-based large molecules.[2]

> "Existing marketed drug products can benefit from an improved product offering by renewing or broadening their delivery format options."

Developing large-molecule drug products is a complex process, demanding careful planning for the primary packaging and the referred risks over the lifetime of the product. Likewise, existing marketed drug products can benefit from an improved product offering by renewing or broadening their delivery format options.

Increasingly, PFSs are being selected as a delivery format for liquid injectables due to their many significant advantages, including patient safety through the reduced risk of pathogen exposure, dose accuracy, cost benefits (such as product storage and time needed for administration) and the ease of self-administration. Glass is by far the most common material for PFSs due to its many advantages. However, studies indicate that protein loss is significantly increased with siliconised glass syringes compared with silicone-oil-free syringes and that silicone oil increases the surface adsorption capacity of proteins, resulting in insoluble aggregates and the loss of monomers.

Furthermore, studies indicate that the amount of insoluble aggregates can be correlated to the level of silicone oil. Aggregation may occur when proteins bind to the surface of the silicone oil, creating heterogeneous nucleation sites in which the proteins undergo an irreversible change in conformation. When the oligomeric state of the proteins is adversely affected by this cyclic behaviour, the therapeutic effect is degraded and the potential for immunogenic response grows.[3-7]

According to Martin Gonzalez, PhD, Senior Group Leader, R&D, at Pfizer CentreOne, "Silicone is always a prime suspect in cases of protein aggregation, since it generally interacts with protein and can trigger the aggregation process."[8]

Another known source of protein aggregation comes from the tungsten residuals from the pin used to form the needle bore in glass syringes.[9,10] To mitigate this, Gerresheimer offers silicone-oil-free glass syringes where the bore has been made with a ceramic pin and hence without tungsten residuals.

Stability and efficacy are major liabilities both during a drug product's development and throughout its lifetime – and, although different excipients can be combined with the drug product to accommodate stability, the primary packaging, including the container closure, should be a remedy, not a risk-increasing factor.

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With the increasing number of large-molecule and ophthalmic drug products, complementary primary packaging is paramount. Gerresheimer's glass syringes, combined with Injecto's biocompatible lubrigone$_3$ plunger stoppers, which enable PFSs that are completely free of silicone oil, coating and tungsten, are a key evolution for combining complex drug products with increasingly in-demand ready-to-use delivery formats.

## THE CHALLENGE OF REMOVING SILICONE OIL ON PLUNGER STOPPERS AND IN GLASS CONTAINERS

The ISO 11040-4 regulation stipulates a tolerance span of +/-0.1 mm on the 6.35 mm inner dimension of 1.0 mL (long) glass containers, and the conditioned need for an oversized plunger stopper to ensure container closure normally requires the use of a slip agent, such as liquid or baked-on silicone oil, for rubber plungers to be functional.

A study investigating the removal of silicone oil, performed by Gerresheimer, showed that, after only a short period of storage, rubber plunger stoppers would either get stuck (even when applying forces over 40 N) or the sealing elements would be torn and cause a back flow through the plunger stopper sealing elements. After longer storage, the rubber plunger stopper and glass combination allowed for completion of the administration but required forces over 35 N. A glass syringe and rubber plunger stopper without silicone oil would result in dysfunctional behaviour, as seen in Figure 1.

A similar challenge with increasing forces can be encountered with siliconised syringes and rubber plunger stoppers over time if the liquid silicone oil migrates to form an uneven coating or cause lubrication depletion.[11]

Ageing of siliconisation over time may be an issue affecting long-term storage and long-term functionality. This can be particularly important in autoinjectors, which rely on a constant spring force whereas, during manual injection, a healthcare professional would either recognise higher forces and adapt intentionally or reject the syringe.

## A DEVELOPMENT BREAKTHROUGH

Using complex modelling and comparison of material performance, compression set, friction coefficient, strain and stress characteristics, Injecto identified the profile and design features needed to resolve the storage and delivery problems without lubrication of the container or plunger stopper (Figure 2).

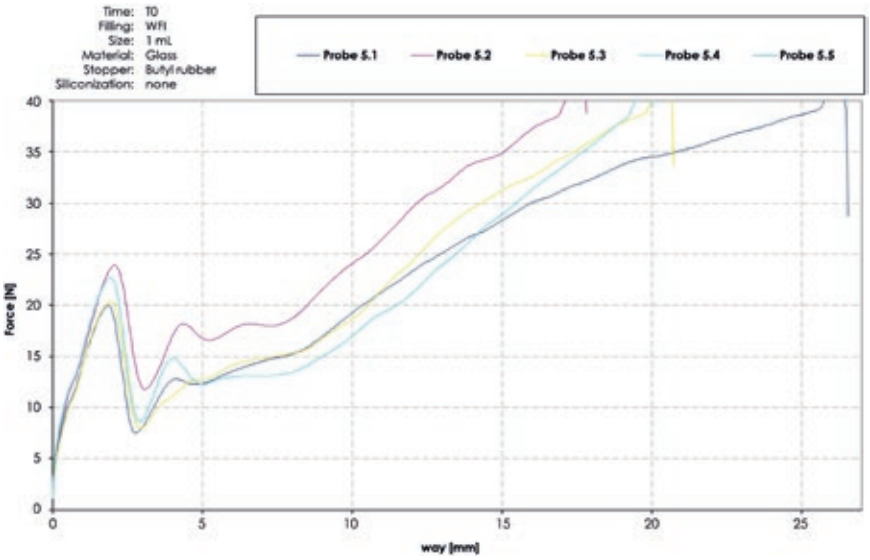


Figure 1: Coated butyl rubber stopper without siliconisation in glass.

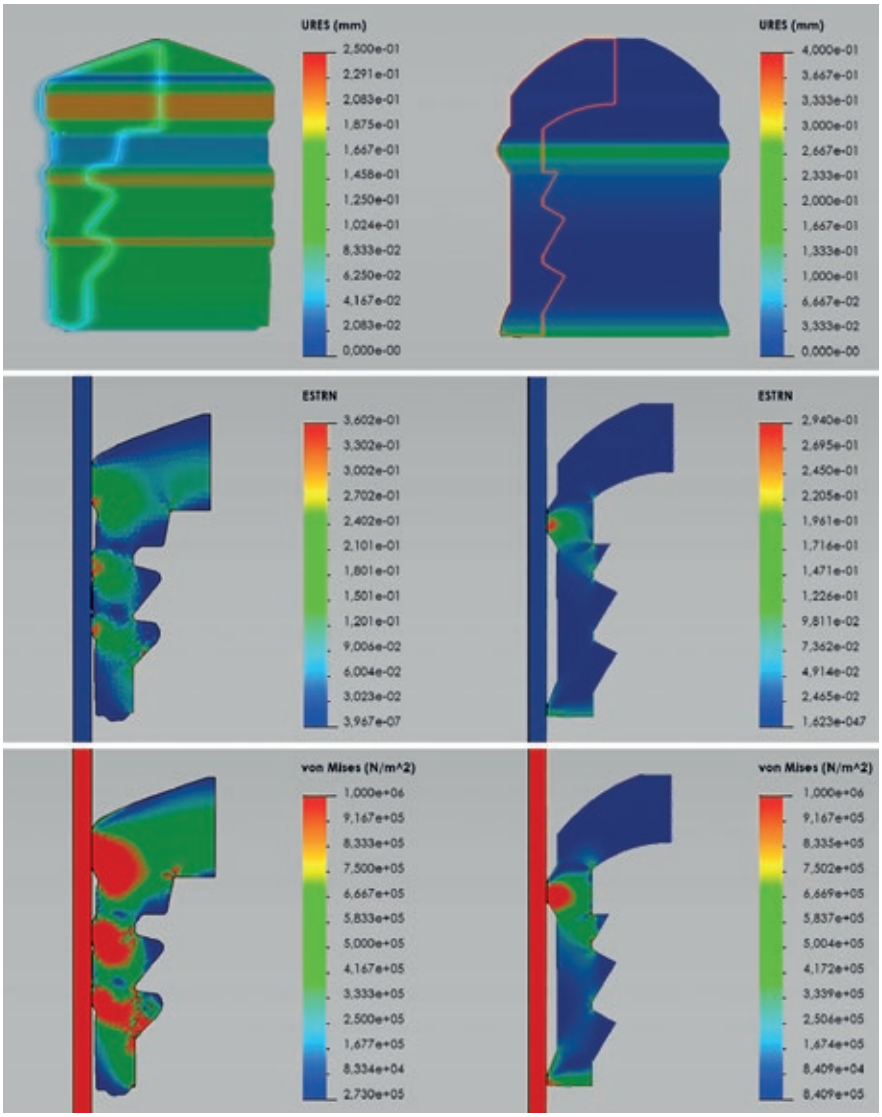


Figure 2: Simulating and comparing strain and stress profiles of unsiliconised lubrigone3 plungers and a coated butyl rubber plunger in glass, in the conversion from dynamic state to motion by combining a nonlinear simulation of hyperelastic using Mooney-Rivlin and a linear elastic deformation using Mohr-Coulomb.
Left: Butyl rubber plunger stopper; Right: lubrigone$_3$ plunger stopper;
Top: Deformation of plunger stopper; Mid: Maximum strain; Bottom: Maximum stress.

Due to the chosen plunger stopper material's shore-A hardness, combined with the compression set, it has been possible to design a sealing element with a steep attack angle towards the container wall. This profile reduces the abutting surface, which, combined with the low friction coefficient between the plunger stopper material and glass, accomplishes the balance between container closure integrity and operating forces. The lubrigone$_3$ plunger stoppers are fully functional with both glass and polymer – cyclic olefin copolymer (COC) and cyclic olefin polymer (COP) – syringes, however there is a slightly higher friction coefficient against polymers compared with glass.

## BALANCING CONTAINER CLOSURE INTEGRITY AND FORCES

To accommodate the full span of the container's inner dimensions, and thereby the larger or smaller outward forces of the plunger's sealing elements against the container inner wall, the lubrigone$_3$ patented inner mass reduction system was developed to reduce excessive outward forces and thereby provide a more uniform force profile (Figure 3). Furthermore, the precision injection moulding production method ensures low plunger stopper tolerances and thereby reduces the overall tolerance stack-up.

As such, the material characteristics, the sealing profile and inner mass reduction system enable removal of the silicone oil and/or lubricous coatings, while ensuring that the lubrigone$_3$ plunger stopper accommodates the full tolerance span of container inner diameters stipulated by ISO 11040-4 and providing consistent container closure and operating forces throughout the entire lifetime of the PFSs.

### Force Profile for 0.5 mL and 1.0 mL (long)

The lubrigone$_3$ plunger stopper has been force tested with random selected Gerresheimer RTF un-siliconised glass syringes (Figure 4).

The 0.5 mL glass syringes had luer adapter and 30Gx½" needles mounted. The syringes were stored under accelerated conditions for three and six months before testing at 100 mm/min for ophthalmic application. The average break loose was 5.0 N and the average glide force was 2.4 N after three months' accelerated storage and, respectively, 5.0 N and 2.3 N after six months' accelerated storage.

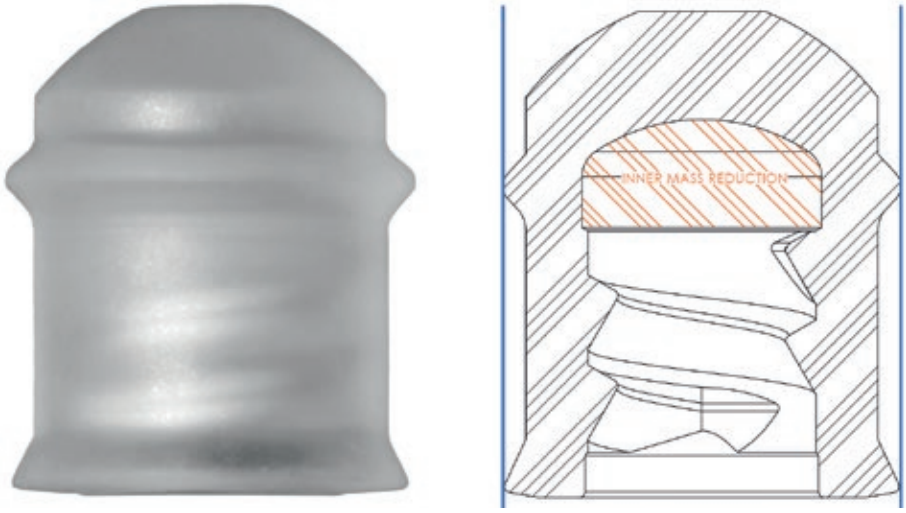


Figure 3: Inner mass reduction.

The 1.0 mL (long) had a 27G TW staked needle. The syringes were stored under accelerated conditions for three and six months before testing at 270 mm/min. The average break-loose force was 7.3 N and the average extrusion force was 4.6 N after three months' accelerated storage and, respectively, 7.1 N and 4.6 N after six months' accelerated storage (Table 1).

### Helium Leak √ PASSED

The lubrigone$_3$ plunger for 1.0 mL (long) has an average 1.03*10-9 Pa m$^3$/s He leak in polymer containers with large inner diameters. With effusive He leak rates of 10-7 Pa m$^3$/s, the probability of microbial ingress approaches zero.

### Blue Dye √ PASSED

32 samples were tested, based on Gerresheimer RTF 1.0 mL (long) glass syringes with staked 27G TW cannulas and lubrigone$_3$ plunger stoppers at different time points. 32 additional samples were tested based on Gerresheimer RTF 1.0 mL (long) COP syringes with luer lock adapter and lubrigone$_3$ plunger stoppers at different time points.

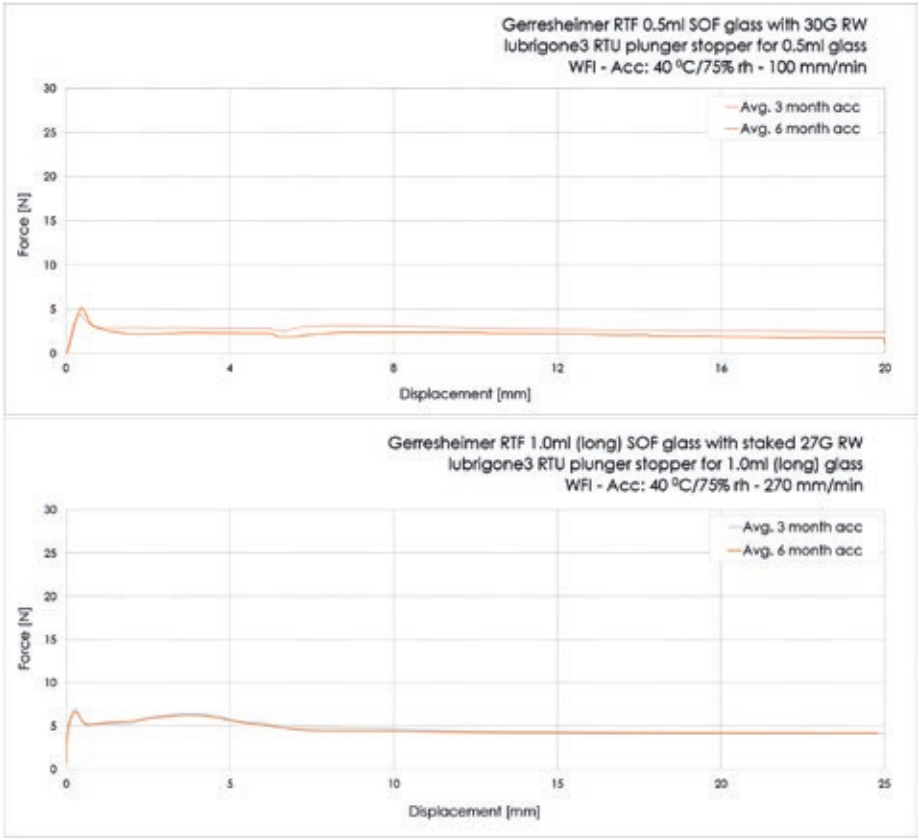


Figure 4: Examples of the break-loose and gliding-force profiles.

| | He leak Speed (Pa m³/s) |
|---|---|
| 1 | 1.2 x $10^{-9}$ |
| 2 | 1.5 x $10^{-9}$ |
| 3 | 1.2 x $10^{-9}$ |
| 4 | 1.3 x $10^{-9}$ |
| 5 | 1.1 x $10^{-9}$ |
| 6 | 9.2 x $10^{-9}$ |
| 7 | 6.5 x $10^{-9}$ |
| 8 | 1.4 x $10^{-9}$ |
| 9 | 1.3 x $10^{-9}$ |
| 10 | 1.0 x $10^{-9}$ |

Table 1: He leak in large inner-diameter COP containers.

## BIOCOMPATIBILITY

There are known cases in which the coatings used to create a barrier between the extractables and the butyl rubber plunger stopper have been damaged. This exposes the drug product to direct contact with the butyl rubber, meaning that some of the leachable compounds in the formulation may potentially cause toxicity.

The lubrigone$_3$ thermoplastic elastomer is a special compounded styrene-ethylene butylene-styrene (SEBS) formulation. This is a biocompatible material with no compounds of concern both in water (pH 2.5–9.5) and water with Tween20, and therefore does not require a coating to inhibit adverse extractables. Consequently, there are no risks associated with the challenges and concerns regarding poly- and perfluoroalkyl substance (PFAS)-based coatings. The material has been thoroughly evaluated and tested against the relevant endpoints of ISO 10993-1:2020 Annex A. The material has been validated as gamma irradiation compliant.

## PARTICLES

In a subvisible particle study with Gerresheimer RTF syringes, the particle count by light obscuration was 2.9 at >10 µm/mL, 0.03 at >25 µm/mL and 0 at >50 µm/mL, which is substantially below a tenth of the particles allowed by USP<789> for ophthalmics (Figure 5). The particulates have also been evaluated by size exclusion chromatography, light scattering, micro-flow imaging and resonant mass measurement, which confirmed the preservation consistency over time with the omission of silicone oil.

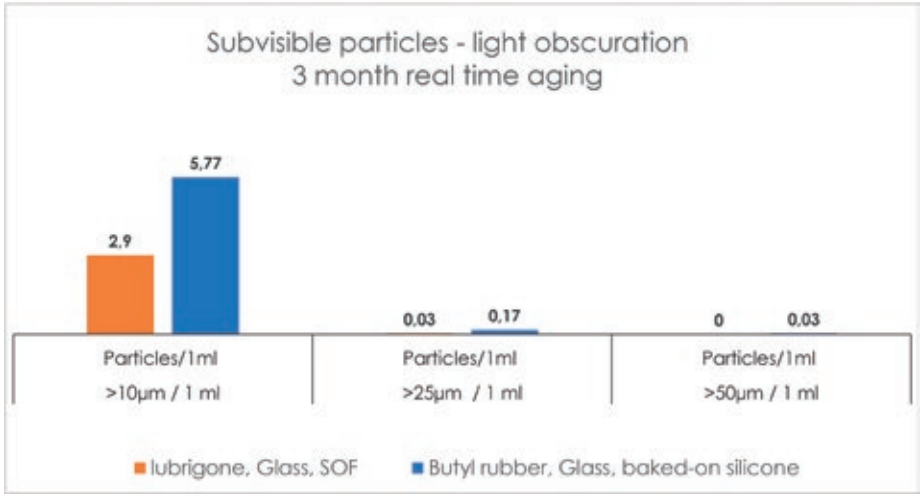


Figure 5: Subvisible particle count in water for injection by light obscuration.

Figure 6: Lubrigone$_3$ plunger stoppers.

> "During injection moulding, only the exact amount of material needed is injected into the mould cavities in each cycle."

### Improved Sustainability

Thermoplastic elastomer plunger stoppers are produced by injection moulding; a highly precise production method that provides many advantages. Firstly, it is a much less resource-intensive production method compared with the compression moulding and vulcanisation associated with processing rubber. The production cycle is typically only a fraction of that for vulcanised rubber. Furthermore, injection moulding is a clean process that outputs sterile parts due to the processing temperature of 170–250°C (338–428°F) and taking place in a Class 7 clean room. There are no hands-on or washing processes involved in the production. The processes for ready-to-use lubrigone$_3$ plunger stoppers are:

1. Injection moulding
2. Packaging
3. Sterilisation.

Secondly, the material waste is minimal. During injection moulding, only the exact amount of material needed is injected into the mould cavities in each cycle. Finally, the lubrigone$_3$ plunger stopper material is 100% recyclable.

## COMMERCIAL SUPPLY

The lubrigone$_3$ plunger stoppers are produced under ISO 13485 in Denmark and are supplied in a ready-to-use state by gamma sterilisation (Figure 6). Furthermore, Injecto is involved in several custom-sized plunger stopper developments for both PFSs and medical devices.

## ABOUT THE COMPANIES

**Injecto** is a Danish company specialising in the development, production and marketing of primary pharmaceutical packaging, with a focus on injection safety and protection of parenteral formulations, aiming for the highest efficacy and prevention of adverse complications. The company's lubrigone

plunger stoppers enable an entirely lubrication-free injection system without the application of ETFE/PTFE coatings or silicone in any form, thereby reducing the risk of primary-packaging-induced protein aggregation and minimising the risk of immunogenic response.

**Gerresheimer** is a major drug delivery device and primary packaging company. Its products include insulin pens, inhalers, prefillable syringes, pharma plastic containers and glass ampoules, vials and cartridges. Gerresheimer Bünde is its centre of excellence for glass prefillable syringes and cartridges.

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## ABOUT THE AUTHORS


**Taras Bredel** has a background as a software engineer within advanced logistic systems, with 20 years of experience in business development, sales and marketing, process strategy and implementation before starting at Injecto. For the last five years, Mr Bredel has been responsible for business development at Injecto and is involved in product development, production co-ordination and regulatory relations.

**Bernd Zeiss** is a biologist by education and graduated from the University of Göttingen, Germany. After several years working as a biostatistician, both in lab automation and in pharma sales, he is now a member of the Gerresheimer business development team. Mr Zeiss works in the Gerresheimer Centre of Excellence for prefillable syringes as Head of Technical Support, Gx® Solutions & Syringe Systems. His main areas of work are technical customer support with regard to syringe systems and investigating possible interactions between syringe components and drug substances.

# INJECTO™

PHARMACEUTICAL PACKAGING

**TUNGSTEN FREE**
The needle bore is made using a ceramic pin to mitigate the risk of tungsten induced protein aggregation

**SILICONE OIL FREE**
The interior of the syringe barrel is completely free of lubrication or coating, thereby reducing the risk of adverse effects by silicone oil induced protein aggregation and unwanted particles in the drug product.

**COATING FREE**
Due to the inert and biocompatible material the plunger stopper has no PFAS-based coating

## lubrigone$_3$™

Combining the lubrigone$_3$ silicone oil free, coating free plunger stoppers with silicone oil free, tungsten free glass syringes provides the highest quality solution for preservation of biopharmaceuticals in prefilled syringes.



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# ADVANCED DELIVERY DEVICE TECHNOLOGY TO SIMPLIFY THE RECONSTITUTION OF LYOPHILISED DRUGS

In this article, Fred Metzmann, PhD, Senior Advisor Portfolio Management, and Chris Muenzer, Vice-President Innovation & Development, both of Haselmeier, present the company's innovative approach to the development of reconstitution devices that allow easy and convenient administration of freeze-dried biologics.

Lyophilisation (freeze drying) is a proven process for increasing the shelf life of vaccines, biologics and other injectables. It allows for room temperature storage of the drug product, which can be beneficial for transportation and distribution, especially in countries that lack sufficient cold chain infrastructure. However, the reconstitution of these products requires several use steps that make them challenging to administer, particularly by patients and caregivers in non-clinical settings.

> "Reconstitution devices based on Haselmeier's reusable and disposable pen platform technology empower patients and caregivers to inject their medication accurately with minimised risk of use errors.."

Reconstitution devices based on Haselmeier's reusable and disposable pen platform technology empower patients and caregivers to inject their medication accurately with minimised risk of use errors. Additionally, these solutions support rapid and sustainable customisation, with the potential to significantly accelerate the development of combination products for customers.

## BIOLOGICS ARE ON THE RISE – INJECTABLES LEAD VALUE SIZE AND GROWTH

The emerging prevalence of chronic diseases leads to a steady rise in the annual number of approvals for various types of biologics including monoclonal antibodies, cell therapies, recombinant proteins, peptides, vaccines and gene therapies. Innovative therapies and innovations in biologics are improving patient outcomes in conditions such as hepatitis C, cancer, autoimmune diseases, metabolic disorders, cardiovascular diseases and orphan diseases.[1,2]

The majority of these biologics are currently administered through intravenous infusion and typically administered in a clinical setting (hospitals/infusion centres). However, subcutaneous injections of biologics are increasingly preferred over intravenous infusions because they reduce the burden on healthcare providers and payers by taking much less time and offering a lower risk of complications (infections, infusion reactions and others).[3,4]

In addition, recent advances in the delivery of traditional biologics include methods to increase the acceptable volume of drug solutions that can be administered subcutaneously.

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"While liquid formulations are typically preferred, lyophilisation is an important alternative for making dry biopharmaceutical formulations achieve a longer shelf life."

Thus, more than half the drugs approved by the US FDA and EMA in the first half of 2021 were injectables, with subcutaneous and intramuscular products accounting for an increasing share.[5,6]

In addition, more than 3,000 biologic therapeutics are currently in clinical trials worldwide, representing a ratio of approximately 50% biologics to small molecules in all Phases I–III.[7]

## LYOPHILISATION TO ENHANCE SHELF LIFE OF BIOLOGICS

Biological drugs are inherently less stable in liquid formulations and tend to lose efficacy due to alterations in their pharmacokinetic and pharmacodynamic properties. This can make it challenging to preserve them for longer periods.

While liquid formulations are typically preferred, lyophilisation is an important alternative for making dry biopharmaceutical formulations achieve a longer shelf life.

Lyophilisation is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapour without passing through a liquid phase. The lyophilisation process can be used to stabilise formulations and therapeutic molecules in a commercially validated manner. In contrast to liquid formulations, the solid obtained by this process has a greater degree of stability and can be stored for longer periods of time at higher temperatures, such as outside of refrigeration.[8]

## NEED FOR RECONSTITUTION SYSTEMS PRIOR TO INJECTION

Before it can be injected, a lyophilised drug must be reformulated into a liquid form by mixing with a suitable diluent. This process of reformulation is known as drug reconstitution, which requires additional preparation steps.

Typically, the drug product is supplied in glass vials with rubber plugs and is mixed or reconstituted with a diluent (usually 5% dextrose solution, normal saline, bacteriostatic water or sterile water for injection) before administration. An incompletely dissolved product can be hazardous to the patient; therefore, reconstitution is a critical performance parameter for lyophilised products.

## CONVENTIONAL RECONSTITUTION PROCESS

Traditionally, the reconstitution process is a multi-step procedure, which can take up to 30 minutes in some cases. The process requires interaction with a reconstitution kit, usually consisting of several pieces of equipment, including but not limited to a medication vial, a diluent vial, a syringe, a reconstitution needle and an injection needle (Figure 1).

The process typically starts with the manual extraction and transfer of the diluent from the first vial to the second vial containing the lyophilised product by using a syringe and transfer needle. After transferring, the contents are mixed until the final mixture is fully reconstituted. The process is usually performed by a trained healthcare provider or caregivers and requires the use of vial adaptors and vial-to-vial systems.

After the drug product has been reconstituted, it must be withdrawn into a syringe and injected. This process can introduce air bubbles into the solution and is dependent on the skill of the user to prepare an accurate dose. One study using 1 mL syringes found that there was "a significant variance in the accuracy, precision and repeatability to prepare a proposed dose".[9]

## GROWTH DRIVERS AND CHALLENGES

The lack of easy-to-use drug reconstitution delivery systems has limited market opportunities in the past. However, with the introduction of novel drug reconstitution systems, the delivery of lyophilised drugs has become convenient. Such systems provide better treatment options for patients and save time and labour for caregivers. With the availability of these systems, lyophilised formulations can be considered a viable alternative to liquid formulations.

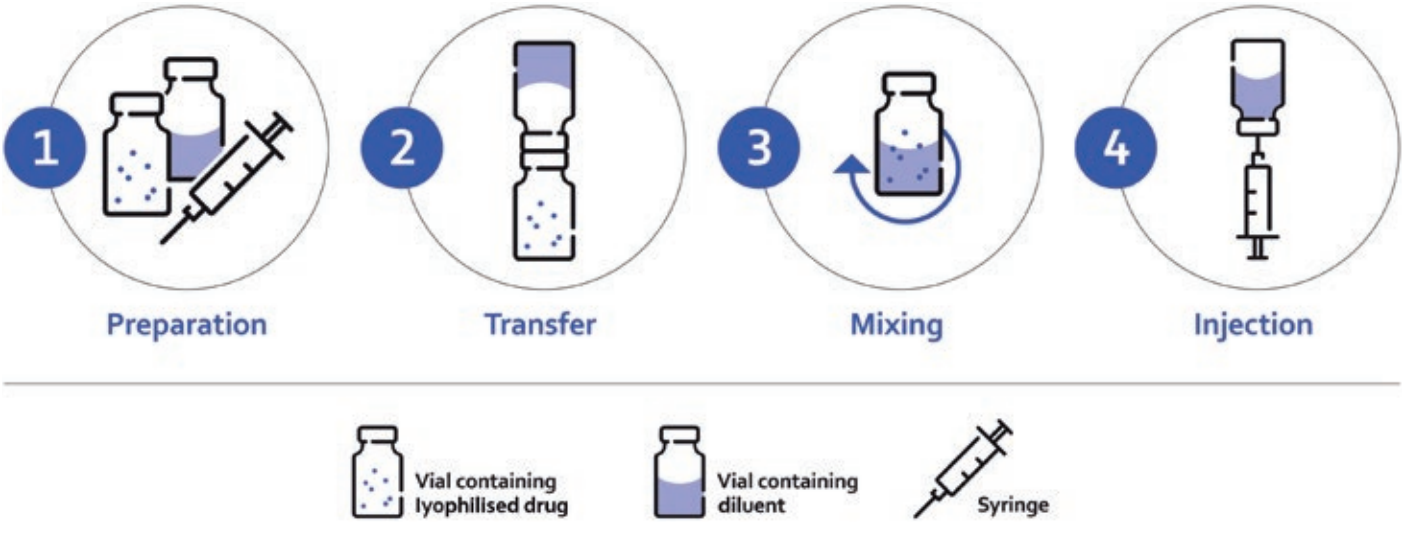



Figure 1: Conventional reconstitution process.

## BOX 1: DUAL-CHAMBER CARTRIDGE SYSTEMS

These container closure systems are designed to enhance the portability, efficiency and optimum delivery of the lyophilised drugs. The components (powder and liquid) are stored safely, can be reconstituted very easily and are then administered safely and conveniently.

Dual-chamber cartridges require the use of injection pens and can combine either liquids with liquids or liquids with medications in powder form. The two chambers are separated by a plunger. Instead of deploying two containers to store the lyophilisate in one and the diluent in another, the dual-chamber cartridges allow mixing and application to be carried out in one operation. The pen system enables higher dosing accuracy and a lower risk of contamination. This translates into higher safety for patients, as literally just the push of a button is needed (Figure 2).

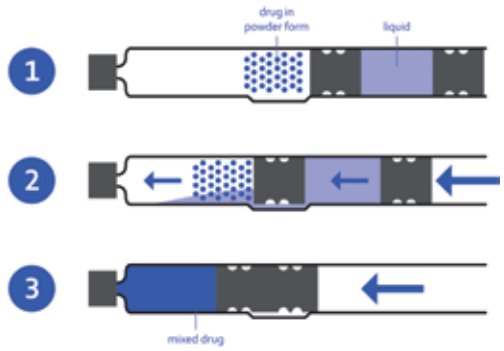



Figure 2: Dual-chamber cartridge.

## PATIENT-CENTRIC DEVELOPMENT

Regulatory requirements are among the biggest challenges facing pharmaceutical companies and device development and manufacturing organisations, especially for products offered as combination products. Global regulatory authorities continue to place great emphasis on ensuring quality and risk mitigation. But they are also paying increasing attention to the development of drug delivery devices that focus on ease of use and patient safety to promote sustained treatment adherence.

For a successful path to approval, essential performance requirements for a therapy's delivery technology must be defined early in the development process. This helps to ensure that the development generates all necessary data required for submitting the application to a regulatory authority.

## HASELMEIER'S SOLUTIONS FOR AN EASIER AND MORE CONVENIENT RECONSTITUTION

An injection system for self-administration combines engineering and design to ensure the safe administration of therapy. This needs to be balanced with a system that removes both the potential physical and emotional barriers to patient adherence to therapy.

With one approved product and several more in development, Haselmeier has experience with multiple solutions that allow easy and convenient administration of freeze-dried biologies (Figure 3). The company's approach is based on proven platform technologies for both disposable and reusable injection pen devices.

These solutions can be separated into two categories based on the primary drug container. For vial-based products, a vial-to-cartridge solution is available. The alternative is to fill drugs into dual-chamber cartridge systems, which allows several other options.

> "With one approved product and several more in development, Haselmeier has experience with multiple solutions that allow easy and convenient administration of freeze-dried biologics."

All these solutions use a precision mechanism to deliver the drug product from a cartridge. The injection pen allows the user to rotate a knob until their exact dose is displayed, which provides a simpler user experience than withdrawing drug from a vial. In addition, the use of this type of mechanism can reduce the variability in the delivered dose.[10]

### Solution A: Vial-to-Cartridge System

For vial-based products, the use of a reusable injection pen, along with a vial-to-cartridge reconstitution system, can simplify the delivery without the need to change the fill-finish process. In this solution, a system like Duoject Medical Systems' (Quebec, Canada) PENPREP EVO™* allows the reconstitution of solid-form drugs in vials with standard diluent-filled cartridges. The final result is a filled cartridge that the user can place into a reusable pen, such as the Haselmeier Re-Vario™ A. The combination of these two marketed technologies reduces the number of use steps, simplifies the transfer process and may have a positive impact on the accuracy of the injection.** In addition, this approach uses established vial lyophilisation infrastructure, which reduces the risk of capacity constraints that can jeopardise time to market.

## DUAL-CHAMBER CARTRIDGE SYSTEMS

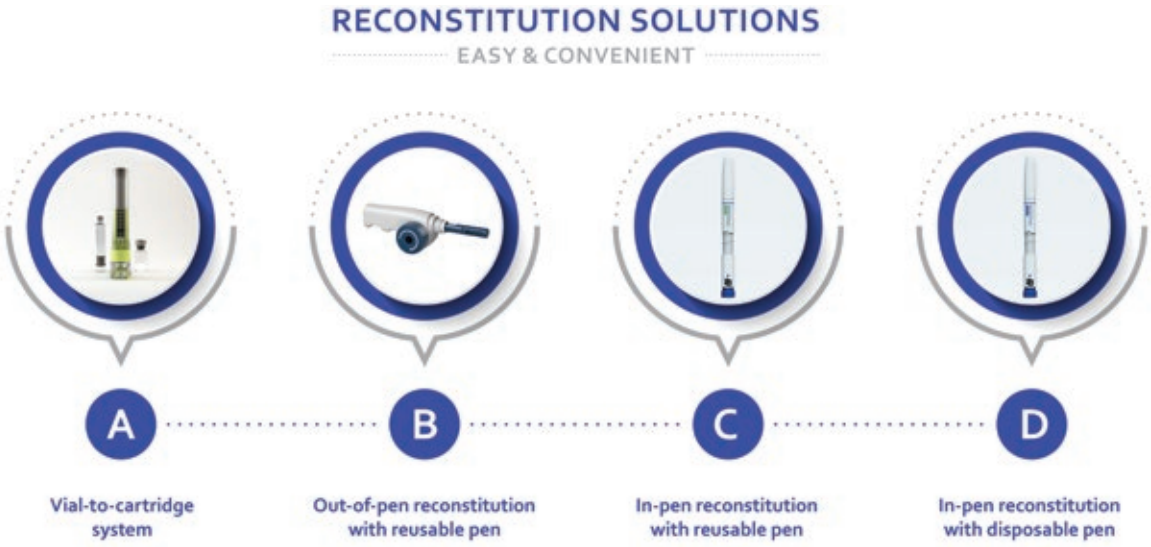
A drug product can be filled into a dual-chamber cartridge system (explained in Box 1). Once the drug is available in this format, Haselmeier has three different solutions:

### Solution B: Out-of-Pen Reconstitution with Reusable Pen

For this solution, the patient is supplied with a separate mixing device used to reconstitute the drug product. Once the mixing step is completed, the cartridge is loaded into the reusable pen and the drug can be easily injected. The advantage of out-of-pen reconstitution is that it simplifies the injection pen itself, but it is at the disadvantage of having another reusable device that the patient needs to manage. The use of in-pen reconstitution technology can reduce this burden.

### Solution C: In-Pen Reconstitution with a Reusable Pen

In this solution, each drug cartridge is supplied with a disposable cartridge holder with a built-in reconstitution mechanism. The patient attaches this cartridge holder to the pen and rotates the mechanism to mix the drug product. Once the mixing step is




| | | | | |
|---|---|---|---|---|
| **Primary Container** | Vial | Dual-Chamber Cartridge | Dual-Chamber Cartridge | Dual-Chamber Cartridge |
| **Pen** | Reusable Re-Vario™ or Re-Vario™ A Pen | Reusable Re-Vario™ or Re-Vario™ A Pen | – Reusable Dose Module<br>– Disposable Cartridge Holder | Disposable Reconstitution Pen |
| **Additional Devices** | Yes (Transfer Device) | Yes (Mixing Device) | No | No |
| **Dose Range** | 0.01 to 0.60 mL | 0.01 to 0.48 mL | 0.01 to 0.48 mL | 0.05 to 0.70 mL |
| **Number of Steps** | 6 Steps:<br>– Attach Vial Transfer<br>– Transfer<br>– Load Cartridge<br>– Attach Needle<br>– Dial<br>– Inject | 6 Steps:<br>– Attach Cartridge to Mixing Device<br>– Mix<br>– Load Cartridge<br>– Attach Needle<br>– Dial<br>– Inject | 5 Steps:<br>– Load Cartridge<br>– Mix<br>– Attach Needle<br>– Dial<br>– Inject | 4 Steps:<br>– Mix<br>– Attach Needle<br>– Dial<br>– Inject |
| **Time to market** | 6 months | 6 months | 12 months | 18 months |
| **Availability** | Marketed | Marketed | Product Concept | Launch 2024 |

Figure 3: Overview of reconstitution systems by Haselmeier. Showed transfer device (solution A) and mixing device (solution B) and all associated intellectual property, including pictures shown, are owned by Duoject Medical Systems Inc.

> "The simplest solution for the patient is to provide a disposable device with an already-integrated drug cartridge."

completed, the drug can be injected with no additional steps. After the cartridge is empty, it is removed along with the cartridge holder and disposed. This solution eliminates the need for a separate mixing device but adds additional cost for the disposable cartridge holder.

### Solution D: Disposable Pen with Integration Reconstitution

The simplest solution for the patient is to provide a disposable device with an already-integrated drug cartridge. With this device, the patient simply completes the mixing step and then injects. After use, the complete pen is disposed. This solution minimises the user steps and the need to manage a reusable device at the expense of reduced sustainability (Figure 4).

## INTELLECTUAL PROPERTY POSITIONING

Part of Haselmeier's intellectual property (IP) strategy is to constantly maximise and expand patent protection for its injection pen technology through continuous innovation and new applications. Haselmeier has already filed several patent applications for its injection pen solutions, covering various innovative technologies and safety features.

## CUSTOMISATION OPTIONS

In addition to the options above, Haselmeier can provide custom solutions to meet the unique needs of any patient population or drug product. The company has experience in developing unique devices that still benefit from its broad IP portfolio. This can range from matching brand colours to custom container closures, to additional features like reuse prevention or needle safety.

In addition, its flexible manufacturing operations for both low-volume manual assembly and high-volume fully automated assembly can fulfil different market requirements.


Figure 4: Examples of Haselmeier's disposable and reusable versions of the In-pen reconstitution solutions.

## ADVANTAGES OF ADVANCED IN-PEN RECONSTITUTION SYSTEMS FROM HASELMEIER

Haselmeier continues to develop innovative drug delivery device technology platforms with the patient in mind. These reconstitution systems offer multiple benefits to patients as well as biopharmaceutical and pharmaceutical companies, enabling them to bring lyophilised therapeutics to the market successfully (Figure 5).

**Penprep Evo is a trademark of Duoject Medical Systems and is not affiliated with Haselmeier.*
***Duoject is neither affiliated with Haselmeier GmbH nor endorses the use of its products.*

### Disclaimer

*The products shown in this article are under development and some of them may not yet have been approved for sale under applicable medical devices regulation. The content provides general information about these products, their fields of application and intended use. Their function, performance and specifications are subject to customer-specific development and may deviate from those shown herein. All information contained herein is directed at medical device manufacturers and pharmaceutical companies. This information shall not constitute a promotion for use in a way which conflicts with any applicable medical device regulations, nor is it directed at patients or intended to replace professional medical advice.*

## ABOUT THE COMPANY

Haselmeier, the drug delivery device business division of medmix, designs, develops and manufactures advanced drug delivery systems, such as pen injection systems and autoinjectors. Patient comfort and customers' needs are always at the heart of the company's practices. With its broad portfolio of technologies and services, Haselmeier delivers user-friendly injection systems that enable patients to self-administer their medication reliably and accurately. Haselmeier is known for its excellent and long-standing track record in providing these innovative drug delivery devices based on its proprietary IP business model. The company collaborates closely with its customers in the pharmaceutical and biopharmaceutical industries. medmix, with its precision injection moulding capabilities and expertise in liquid micro-dosing, plus financial strength and global footprint, helps Haselmeier accelerate innovation in healthcare.

With more than 100 years of expertise in the development and manufacture of drug delivery devices, the global footprint, nearly 250 distinguished and motivated experts, more than 200 patents granted and numerous patents pending, Haselmeier remains committed to developing innovative solutions that support its customers and help improve the health of millions of people worldwide.

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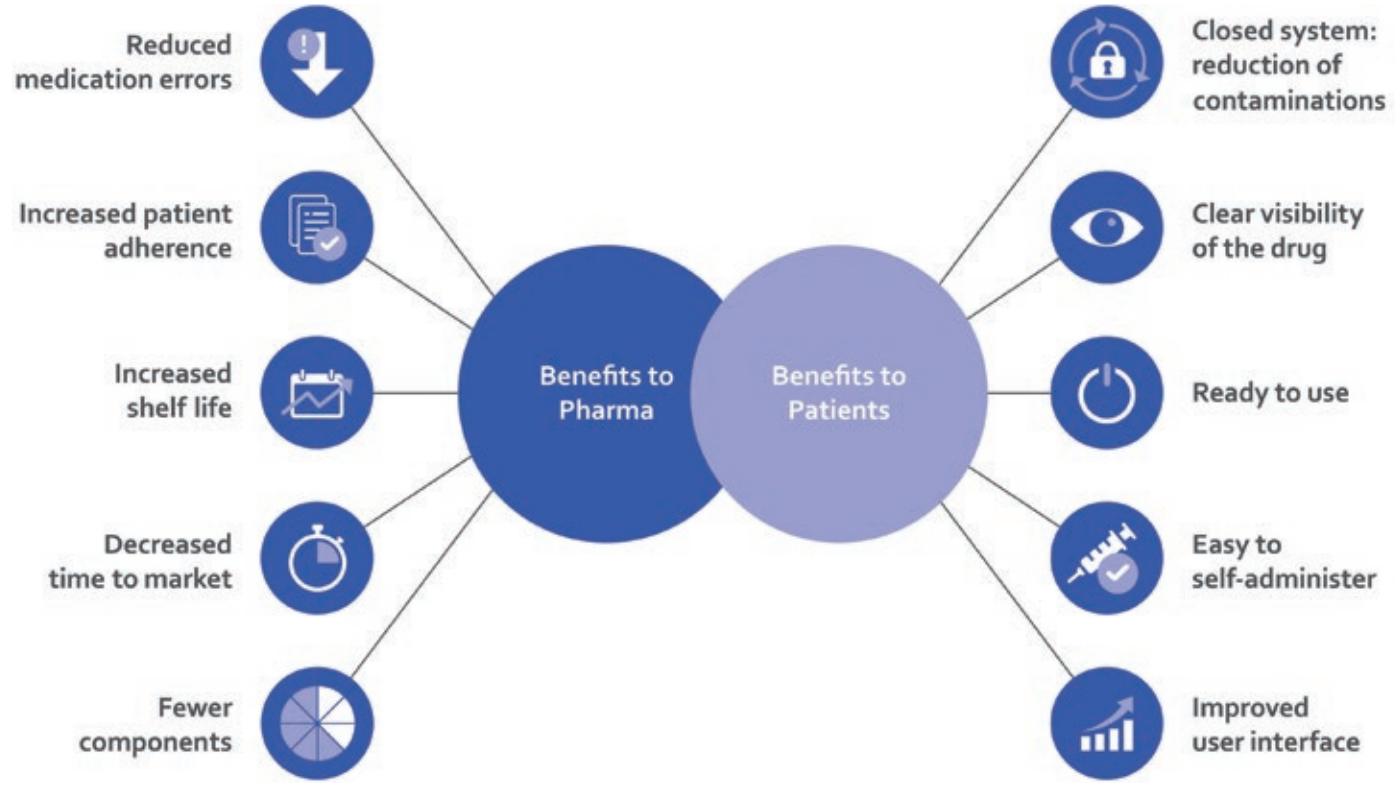


Figure 5: Advantages of advanced in-pen reconstitution systems for pharma companies and patients.

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## ABOUT THE AUTHORS


**Fred Metzmann**, PhD, joined Haselmeier in July 2016 as Vice-President of Sales and Marketing. Previously, he held various leadership positions in the materials and plastics processing industry at Ticona, Celanese, Nypro, Sanner and Medisize. Based on his in-depth knowledge of the drug delivery device and combination product market with more than 25 years of experience in the field, Dr Metzmann was appointed to the strategic role of Director Portfolio & Product Management in 2020 and assumed his current position as Senior Advisor Portfolio Management of Haselmeier, a medmix brand, in 2021. Dr Metzmann graduated in chemistry from Johannes Gutenberg University in Mainz (Germany) and earned his doctorate at the Max Planck Institute for Polymer Research in Mainz.

**Chris Muenzer** is the Vice-President of Innovation and Development at Haselmeier. He leads a team of experts that creates customised drug delivery systems for pharmaceutical and biotechnology companies. He has over 15 years of experience in the pharmaceutical and medical device industry, having worked at Novartis, Roche and the Battelle Memorial Institute. During this time, he has worked at all stages of device development from initial concept and engineering development to clinical trials and launch. Mr Muenzer holds a BSME from Carnegie Mellon University in Pittsburgh (PA, US). He is also the inventor of several patents and a frequent contributor to industry conferences and ISO standards.

Stevanato Group

# REALISING REDUCTIONS IN DEAD VOLUMES WITHIN PREFILLED SYRINGES: A MANUFACTURER'S PERSPECTIVE

**Here, Enrico Barichello, Syringe Product Manager at Stevanato Group, considers the benefits of prefilled syringes, including cost and waste reduction, and looks at the impact and challenges of dead volume within the syringe.**

As the pharmaceutical industry continues to witness the expediential growth in the development of biologics and biotech drugs, so it also uncovers new challenges.

One area for consideration is the effective delivery of the target volume of these drugs to ensure that the patient receives the optimum dose. As a result, there is currently a very strong focus among pharma partners on understanding the levels of wastage associated with the various container types available. This is particularly pertinent in the delivery of ophthalmic medicines, where the drug volumes delivered are especially low.

This article will first consider the key benefits prefilled syringes (PFSs) bring to the entire healthcare ecosystem in comparison with vials, including those of cost and waste reduction. It will then address the challenge of dead volume – a key concern when dealing with more expensive and low-volume drugs. The measures in place today to mitigate wastage will be reviewed and the results of an internal study by Stevanato Group to assess how the morphology of the glass cone impacts dead volume will be presented.

The findings were delivered by the Technology Excellence Centers (TEC) – an analytical and device testing service that supports development journeys from early-stage concepts to launched combination products. The results were then represented in one of the Stevanato Group primary packaging product lines, SG Alba®, which, with an improved dead volume performance, represents a breakthrough solution for biologics.

Precision and efficiency are important factors in any manufacturing process but, in the case of pharma, they are absolutely critical for the production of therapies that offer both the maximum patient benefit and the minimum risk of adverse effects.

> "Precision and efficiency are important factors in any manufacturing process but, in the case of pharma, they are absolutely critical for the production of therapies that offer both the maximum patient benefit and the minimum risk of adverse effects."

## OVERCOMING THE CHALLENGES OF INEFFICIENCY AND WASTE

For certain aspects of the manufacturing process, inefficiency and wastage remain a challenge. Vials, for example, might represent the preferred option for primary packaging as a proportion of the overall market, but they do have some shortcomings in terms of potential drug wastage.

As a container of multiple doses, it is not always possible for the entire contents of a vial to be deployed in full. This leads to situations where residual content must

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"With continued improvements to fill-finish capabilities and production capacity, PFSs have grown in importance as an alternative containment strategy to vials."

be discarded because the drug has not been used in time or stored in appropriate ambient conditions, compromising the efficacy and safety of the dose.

The same cannot be said for PFSs. This injection format simplifies and accelerates administration by presenting healthcare professionals (HCPs) with a prepared dose, avoiding the intermediary stage of filling the syringe from a vial and therefore minimising drug wastage. With continued improvements to fill-finish capabilities and production capacity, PFSs have grown in importance as an alternative containment strategy to vials.

The use of PFSs allows for potentially significant volumes of a drug to be saved over time when the individual instances of drug wastage are multiplied by the number of vials produced at commercial scale. The cost of this waste can be felt particularly keenly in the case of biologics, which represent an increasing share of the landscape and typically carry a high cost-per-dose.

The advantageous combination of high dosing accuracy and low waste, while relevant to all injections, is particularly appealing for therapeutic areas such as ophthalmology. Here, PFSs support the typical profile for parenteral administration, which involves very low and highly specific volumes of valuable, sensitive biologics, with the concern that any variation in the dose will increase the risk of adverse effects.

## MANUFACTURING PROCESSES ENSURE CORRECT DOSE VOLUME

While responsibility for priming the PFS and administering the dose rests with the HCP, successfully delivering an accurate dose in this situation is predicated on highly consistent manufacturing processes that ensure that the volume of drug within the PFS is consistent, precise and accurately reflects the expected dose volume indicated by a marker. Of particular importance is the cone element at the shoulder of the glass syringe, as inconsistencies in the morphology of the cone can result in variations in the internal volume, which has implications for dosing accuracy and drug wastage.

The cone is formed in a process that involves the external surface of the glass tube being heated and cooled multiple times. While the external dimensions of the cone conform to the exact specification set out in a reference technical drawing, and as defined by the ISO 11040-4 quality standard, the internal dimensions of the cone do not necessarily conform to a consistent geometry.

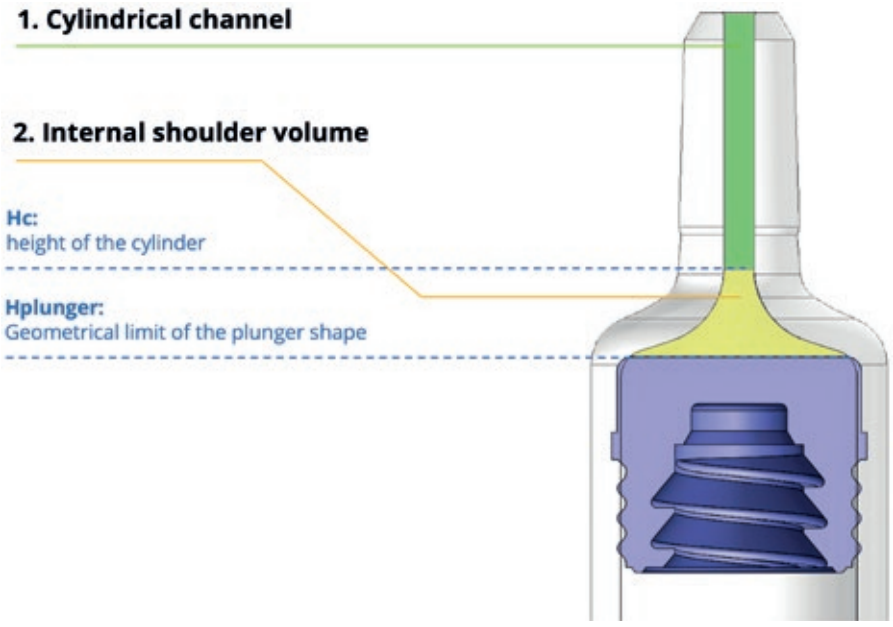


Figure 1: The cone and the shoulder design is a key element to reaching dose accuracy.

The cone's internal dimensions will therefore define the extent of a "dead volume" within the syringe. This is the space that contains the residual drug from a single dose after the plunger stopper reaches its maximum point of travel at the shoulder of the syringe. The greater the dead volume, the higher the level of drug wastage and the greater the level of inconsistency in the delivered dose.

## ANALYSIS OF THE INTERNAL SHAPE OF THE GLASS AND DOSE CONSISTENCY

Stevanato Group, having acknowledged the cost and risk concerns associated with dead volume, set about understanding this issue in greater detail. Employing the capabilities of the TEC, Stevanato's analytical and device testing service, the company undertook two tests to analyse firstly the impact that the internal shape of the glass cone has on the observed dead volume, and secondly the consistency of delivered doses across batches of syringes printed with a dose marker.

The first test involved measuring and modelling the internal profile of the syringe's dead volume, which is made up of the space within both the cone at the shoulder and the cylinder up to the syringe's tip. A total of five 1 mL STD Luer lock syringes with ITC-West 4023 plungers were assessed using a profile projector at a magnitude of 10x and with a sensitivity of 1 µm. For each syringe, the diameter was measured at seven different distances from the tip, and the results were fed into computer-aided design (CAD) software to create 2D and 3D renderings of the average syringe, including data on the internal volume.

The profile projector, which is normally used when processing dimensional controls for bulk products, works by immersing the item to be measured in silicone fluid. Because it has the same refraction rate as air, this allows the item to be observed extremely closely and highly accurate geometric measurements to be taken.

Two of the diameter measurements were critical in calculating the volume of the internal cone: the first – cylinder height diameter (Hc) – is defined as the point furthest from the tip at which the internal channel shape can still be considered a cylinder; the second – plunger height diameter (Hplunger) – reflects the internal diameter of the 4023-plunger stopper's furthest position at the shoulder of the syringe (Figure 1).

> "Adjustment to the PFS design would present an opportunity for a reduction in the dead volume observed within the internal shoulder area."

Equipped with these diameter measurements and the distance from the tip at which they were measured, it was possible to separate the total internal dead volume into two parts – the cylindrical channel and the internal shoulder volume. This analysis revealed that from a total dead volume of 41.11 µL, the internal shoulder volume contributed the significant majority – 32.17 µL (78.3%) – with the remainder – 8.94 µL (21.7%) – being made up of the cylindrical channel (Figure 2).

Close analysis of the cylinder revealed its compliance with the product's reference technical drawing, confirming a diameter of 1.1 mm. The CAD software then provided an opportunity to manipulate the cylinder diameter in a virtual environment and to measure the impact of any change on the cylindric dead volume. This analysis revealed that a 0.5 mm reduction in diameter would result in the cylindrical dead volume being reduced by 79.3% from the original measurement of 8.94 µL down to 1.85 µL.

In terms of the cone area, the test results highlighted how adjustment to the PFS design would present an opportunity for a reduction in the dead volume observed within the internal shoulder area. The dominant limiting factor here is the lack of geometric correlation between the profile of the plunger stopper and the PFS shoulder. Essentially, the tapering of the cone towards the cylinder means that the plunger stopper is limited in the distance it can travel into the shoulder, creating more dead volume.

This finding paved the way for design changes to the internal geometry of the SG Alba® syringe, resulting in a more squared shoulder profile that better corresponds to the plunger stopper profile without compromising on the product's physical strength. In tests, this new design resulted in a reduction in the dead volume of 81.1% compared with the standard shoulder design, with the volume measured to be 6.07 µL, compared with the original volume measurement of 32.17 µL (Figure 3).

The TEC is planning to augment this study by exploring the impact of a variety of factors in greater detail. This includes an assessment of the behaviour of the plunger stopper, including its elastic movement into the dead volume shoulder area during the last phase of drug extrusion, and any potential variance in behaviour resulting from different rubber formulations or coatings. Modelling of the needle hub also has the potential to reveal factors that influence the overall dead volume. This all underlines further the importance of multi-stakeholder collaboration to secure continued reductions in dead volume.

## ANALYSIS OF DOSE PRECISION

In the second of the tests carried out by the TEC, the accuracy of the dose mark printed on the SG Alba® syringe and its influence on dose precision were analysed. This reference point is critical to healthcare professionals in the priming phase, identifying the point to which the plunger should be advanced in the syringe channel prior to injection. Therefore, inconsistency in the dose mark position has the potential to result in the final dose diverging from the desired volume.

The test was designed to evaluate the dose accuracy and dead volume performance of 0.5 mL Luer lock cone syringes serigraphed with a 50 µL dose mark. Samples were drawn from three separate syringe batches to assess the potential for variability.

In the tests, conducted at room temperature, each syringe was manually filled with 150 µL of Milli-Q water using a calibrated pipette. Following a 24-hour storage period, the sample was primed and any air bubbles dislodged before the plunger was gently advanced to the dose mark. The dose was then automatically extruded using a universal tensile machine, which collected the removed liquid. The syringe components, collection components and samples were all weighed pre- and post-test to allow the dose and residual dead volumes to be calculated.

The results recorded the average extruded dose for the three sample batches at 49, 50 and 51 µL, with a standard deviation across the samples of 2–3 µL. They also highlighted that, while there

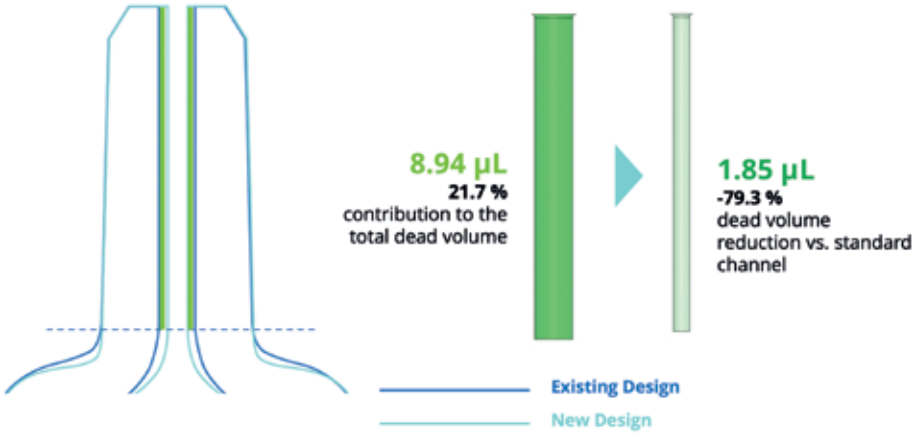


Figure 2: Dead volume reduction by optimising the internal cone design.

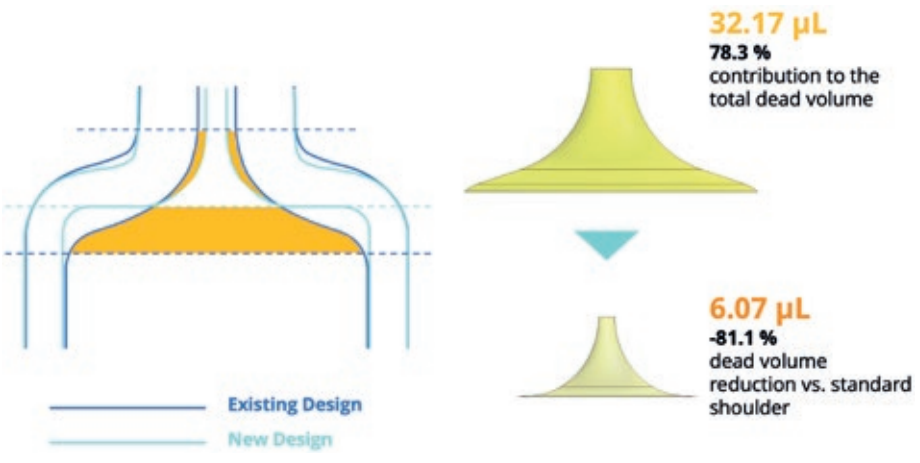


Figure 3: Dead volume reduction by optimising the internal shoulder design.

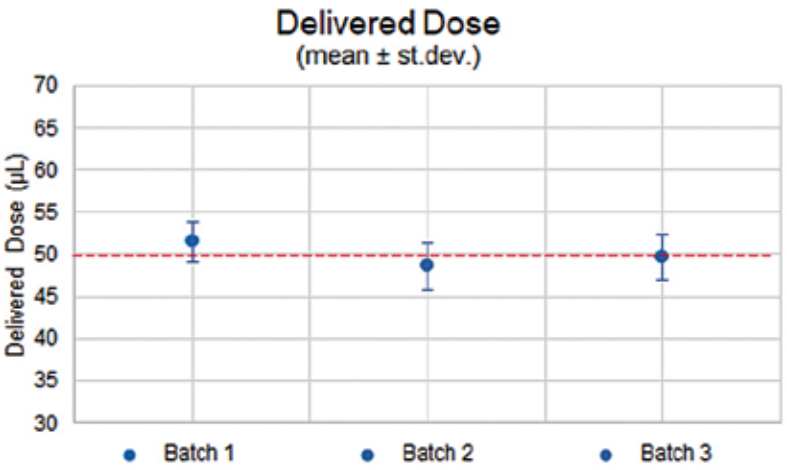


Figure 4: High degree of consistency of the delivered dose across three batches.

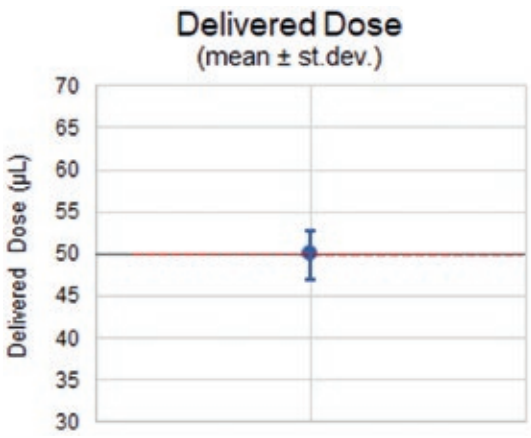


Figure 5: The extruded doses closely aligned to the 50 µL target dose.

was a degree of variability, the extruded doses were closely aligned to the 50 µL target dose. In the case of dead volumes, each sample batch registered an average of 7 µL with a standard deviation of 1 µL, showing the high degree of consistency in dead volume levels across all samples (Figures 4 and 5).

The findings of both tests provide a clear indication of the role of dead volume in PFSs and how product design and manufacturing accuracy are crucial in limiting this element to deliver repeated accurate doses. This is particularly beneficial in ophthalmic applications, where the physical design of the SG Alba® syringe protects against unnecessary wastage of high-value biologics. At the same time, SG Alba® ensures the integrity of these sensitive drugs is protected against silicone migration through the inclusion of a proprietary internal coating, which forms a chemical bond with the glass surface to promote stability.

It is the combination of all these factors that supports the needs of patients requiring low-volume doses administered in precise quantities. To arrive at this point, it is critical to acknowledge, analyse and understand the exact nature of possible variations and inconsistencies so that they can be addressed through continued innovation and improvement.

*SG Alba® is a registered trademark of Stevanato Group and/or its affiliates in one or more jurisdictions.*

## ABOUT THE AUTHOR

**Enrico Barichello** has a background in industrial engineering and a Masters in Management from the University of Padua (Italy), giving him a broad spectrum of skills in technical concepts and complex processes. Mr Barichello joined Stevanato Group in 2017 as a Product Management Specialist for the syringe platform. He defined and co-ordinated all the activities required to bring the products to market, bridging gaps between different company functions and aligning the involved teams. Since January 2021, he has been the product owner – responsible for the roadmap and execution – of the new innovative platform SG Alba®.

## ABOUT THE COMPANY

Founded in 1949, Stevanato Group is a leading global provider of drug containment, drug delivery and diagnostic solutions to the pharmaceutical, biotechnology and life sciences industries. Stevanato delivers an integrated, end-to-end portfolio of products, processes and services that address customer needs across the entire drug life cycle at each of the development, clinical and commercial stages. Stevanato's core capabilities in scientific research and development, its commitment to technical innovation and its engineering excellence are central to its ability to offer value-added solutions to clients.

# Your trusted partner for contract manufacturing services of drug delivery devices

At Stevanato Group, we understand the rigorous requirements to produce components and sub-assemblies for drug delivery systems.
Leading players trust our state-of-the-art manufacturing capabilities and scalable production solutions within the pen injector, auto-injector, wearable, and inhaler markets.

CAMBRIDGE DESIGN PARTNERSHIP

# ISO 11608: WHAT THE NEW STANDARD MEANS FOR NIS MANUFACTURERS

Here, Steve Augustyn, Senior Consultant and Client Manager at Cambridge Design Partnership, looks at ISO 11608 and what it means for needle-based injection device manufacturers.

Over 16 billion injections are given every year. Since ISO 11608-1 was first published in 2000, the series has set the standards for how needle-based injection devices should be designed and verified. This year, the series received its biggest update in a decade. Here is what device manufacturers need to know.

## WHY ISO STANDARDS MATTER

ISO standards set out the definitions, requirements and testing criteria that manufacturers should take into account when creating or redesigning products. ISO standards capture the absolute best practice for the industry, ensuring that devices are both safe and effective, and provide an assurance of quality that healthcare professionals and their patients can rely on.

Adherence to ISO standards is entirely voluntary for companies. However, these standards are still hugely influential – many countries' regulatory bodies expect compliance with the standards, making them de facto mandatory for devices destined for use in those territories. The US FDA, for example, is increasingly using ISO standards as part of its device review and approval process. Therefore, companies designing devices for the US market are highly recommended to demonstrate compliance with recognised standards. In the case of needle-based injection systems (NISs), the FDA directly references the ISO 11608 series in its published guidance for injection devices.

> "The US FDA, for example, is increasingly using ISO standards as part of its device review and approval process."

ISO standards come with the advantage that they are designed to be relevant internationally: they are written in language broad enough to facilitate their application in as many different countries across the globe as possible. They are also informed by regulations within the US and Europe to reduce the compliance burden for device manufacturers operating internationally. The technical committees that develop the standards can comprise members from tens of countries, to ensure they reflect a global outlook and address concerns from across diverse territories.

Due to their global reach and popularity, it is becoming increasingly difficult for device makers to go to market without meeting ISO standards, particularly in territories where competitors and peers are doing so. For NIS manufacturers, adhering to ISO 11608 is critical to doing business worldwide.

## MULTI-STAKEHOLDER STANDARDS SETTING

ISO standards are informed by expert opinion – the technical committees that develop the standards are made up of

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"When a standard is created, it is not at the behest of regulators; instead, it is in response to demand from industry or consumer groups, clearly demonstrating the need for a set of standards to govern products in a particular market."

specialists and professionals from within the industry, as well as subject matter experts from consumer associations, academia, non-governmental organisations and government agencies including the FDA.

Patients and healthcare professionals also play a key role in ISO standard setting. ISO 11608 has been the embodiment of this patient-centric approach: during the writing of 11608-7, the contribution from a blind diabetic member of the group was enormously helpful. The final language in these documents considers the viewpoints of the different stakeholders and the unique perspectives they bring.

When a standard is created, it is not at the behest of regulators; instead, it is in response to demand from industry or consumer groups, clearly demonstrating the need for a set of standards to govern products in a particular market.

ISO standards are periodically reviewed and updated, as in the case of ISO 11608, to ensure they accurately reflect the current market in the face of any new developments, significant trends, or challenges that have occurred since the standard was first published.

## ISO 11608: WHAT IT MEANS FOR NIS

ISO 11608-1 was last updated in 2014, covering systems that deliver discrete volumes of a medicinal product, either through needles or soft cannulas, using intradermal, subcutaneous and/or intramuscular routes. It covers injection devices for single or multiple doses, which are refillable or disposable. It supplements the requirements for prefilled syringes covered in ISO 11040, and specific parts of the standards deal with different aspects of injector design.

A major review of ISO 11608 was published earlier in 2022, driven by advances in NIS technology, including on-body delivery systems (OBDSs) and growing numbers of electromechanical components used in NISs.

For device makers, there are notable benefits. The review aims to ensure the different parts of the standard are better aligned and integrated, as well as reduce duplication and define new concepts and device categories that manufacturers can use as they bring new products to market.

The 11608 series is formed of seven parts:

- General Requirements (11608-1)
- Double-Ended Pen Needles (11608-2)
- Containers and Integrated Fluid Paths (11608-3)
- Systems Containing Electronics (11608-4)
- Automated Functions (11608-5)
- On-Body Delivery Systems (11608-6)
- Accessibility for Persons with Visual Impairment (11608-7).

## ISO 11608-1: THE STANDARD'S PARENT

As the "parent" part of the standard, ISO 11608-1 provides the foundation for the series, establishing the requirements and test methods for all NIS devices within its scope.

As well as adding OBDS requirements, described in more detail below, ISO 11608-1 introduces several new concepts, including "primary function" (a function of the device that allows it to be used safely and effectively) and "functional stability", which expands testing regimens to simulate whole-life testing for reusable devices. There is also more guidance on risk-based design approaches, and ISO 11608-1 adds more specific language to direct the manufacturer to consider the requirements of the medicinal product to be used with the NIS.

## OBDSs AND ISO 11608

The growing interest in OBDSs has been reflected in several parts of the 11608 series, including 11608-1 (General Requirements), 11608-3 (Containers and Integrated Fluid Paths) and 11608-5 (Automated Functions). However, it is 11608-6 that is dedicated exclusively to OBDSs, setting out the requirements for these systems.

OBDSs were created to address several market needs, including extending medicinal products' delivery times; delivering more viscous medicinal products, such as biologics, more easily; and the possibilities of delivering medicinal products after a time delay. These features of OBDSs are useful in facilitating the medication of patients outside traditional healthcare settings.

Unlike infusion pumps, which are concerned with the rate of medicinal products' delivery, the performance of OBDSs is defined by the accuracy with which they deliver a volume of medicinal product – their dose accuracy. And whereas other NISs are designed to be held during the administration of the drug product, either by the patient or by a healthcare professional, OBDSs deliver the medicinal products while attached to the body. That means they can deliver a larger volume of medicinal product than other NISs over a longer time. As a result, OBDSs can typically deliver medicinal products in a way patients may find more tolerable and healthcare providers more appropriate for certain administration use cases.

The unique differences in function and delivery profile that ODBSs offer mean they needed their own equally unique set of requirements and design guidance. 11806-6 gives device manufacturers assistance in creating safer, more efficient products for the growing OBDS market and the reassurance to develop this novel class of system in a way that is likely to satisfy regulators.

## CONTAINERS AND INTEGRATED FLUID PATHS

The increasing impact of OBDSs has also prompted changes elsewhere within ISO 11608. ISO 11608-3, which originally only defined cartridge geometry and performance, has now been expanded to cover NIS containers and integrated fluid paths.

"ISO 11608-3, which originally only defined cartridge geometry and performance, has now been expanded to cover NIS containers and integrated fluid paths."

General requirements for soft cannulas and fluid line connections also now appear in ISO 11608-3 – another change due to increasing popularity of the OBDS device class.

Elsewhere, there are other notable changes for device manufacturers. The requirement for resealing the cartridge has been reduced from 1.5x the intended use to a minimum of 1x the intended life. There are new sampling requirements for particles generated through septum penetration that require the use of 5–100 cartridges, depending on the conditions of use. The requirements on particulates within the fluid path have been revised, and the standard now includes limits for the maximum permitted endotoxin-mediated pyrogenicity.

Meanwhile, the cartridge geometry definition is no longer mandatory and now forms part of an informative annex.

## AUTOMATED FUNCTIONS

ISO 11608-5 supplements the general specifications in ISO 11608-1 by adding requirements for automated dose preparation, dose delivery and needle protection.

Under 11608-5, defining and measuring automated dose delivery time has become a requirement, while needles with automated insertion must meet a modified dose accuracy test to ensure that the dose is delivered at the correct depth.

11608-5 also defines the requirements around fenestrated needles (needles with holes in the side). It explores the implications of both non-perpendicular needle insertion and delivery of the drug product through a flexible cannula.

## DOUBLE-ENDED PEN NEEDLES

Companies working with double-ended pen needles will also need to implement several changes introduced in ISO 11608-2.

The experimental procedure to determine flow rate has been defined more precisely, and the sample sizes have been brought in line with the requirements in ISO 11608-1.

Dose delivery and needle hub removal force are now part of the testing requirements to confirm compatibility between a needle and a specific NIS. The samples needed for functional compatibility have also been reduced while guidance has been introduced on requirements for the inner needle shield.

## HOW TO WORK WITH ISO 11608

Manufacturers have a grace period of three years from the publication of the latest version of ISO 11608 (April 2022), during which they can still verify their designs to the old standards. Once the grace period has expired, manufacturers should verify new device submissions against the latest standards.

Device makers still have some time to consider how the standard will affect them and what changes need to be made to their products or their verification programmes. For those with devices looking to release products beyond the three-year horizon, a gap analysis is needed to ensure adherence to the standard when the device hits the market. For novel devices, more in-depth work may be needed to ensure the product meets the latest version of the standard.

It can be challenging to understand the changes that the ISO 11608 review has brought in, and its implications for device development and verification programmes.

Cambridge Design Partnership (CDP) develops and verifies many needle-based injection systems on behalf of its clients. CDP's clinical trial manufacturing capability gives the company a deep insight into the challenge of moving from design to commercial manufacturing. As one of a handful of British Standards-recognised experts on injection devices, CDP is well placed to advise clients on the implications of these changes in this latest version of ISO 11608.

The benefits of adhering to ISO 11608 are manifold; for some manufacturers, the demands of doing so can be too. For product developers struggling with device performance or needing expert support to meet the ISO 11608 standards, CDP has the expert teams to help overcome these problems.

## ABOUT THE COMPANY

Cambridge Design Partnership is an end-to-end innovation partner, propelling global brands and ambitious start-ups to success. The company builds breakthrough products and services – from insight to ideas, prototypes to production – bringing innovation to life. CDP's teams are multi-disciplinary, uniting scientific rigour, design ingenuity and engineering excellence for consumer, healthcare and industrial clients. People-centred, deeply collaborative, and – above all – expert, CDP is uniquely positioned to shape the future for consumers, patients and industry. Even its ownership model is innovative: CDP is 100% owned by its employees, ensuring an open culture and a total commitment to your project's success.

## ABOUT THE AUTHOR

**Steve Augustyn** is Senior Consultant and Client Manager at Cambridge Design Partnership. He has more than 20 years' experience in the design and development of drug delivery devices, and is also member of the ISO/TC84 – the ISO committee focused on standardisation of devices for administration of medicinal products and catheters.

ON drugDELIVERY

# 2022/23 EDITORIAL CALENDAR

| Publication Month | Issue Topic | Materials Deadline |
|---|---|---|
| Oct/Nov 2022 | Drug Delivery & Environmental Sustainability | Deadline passed |
| November | Pulmonary & Nasal Drug Delivery | Deadline passed |
| December | Connecting Drug Delivery | Nov 10, 2022 |
| January 2023 | Skin Drug Delivery: Dermal, Transdermal & Microneedles | Dec 8, 2022 |
| February | Prefilled Syringes & Injection Devices | Jan 5, 2023 |
| March | Ophthalmic Drug Delivery | Feb 2, 2023 |
| April | Pulmonary & Nasal Drug Delivery | Mar 2, 2023 |
| April/May | Drug Delivery & Environmental Sustainability | Mar 16, 2023 |
| May | Delivering Injectables: Devices & Formulations | Apr 6, 2023 |
| June | Connecting Drug Delivery | May 4, 2023 |
| July | Novel Oral Delivery Systems | Jun 1, 2023 |
| August | Industrialising Drug Delivery | Jul 6, 2023 |
| September | Wearable Injectors | Aug 3, 2023 |
| October | Prefilled Syringes & Injection Devices | Sept 7, 2023 |
| Oct/Nov | Drug Delivery & Environmental Sustainability | Sept 21, 2023 |
| November | Pulmonary & Nasal Drug Delivery | Oct 2, 2023 |
| December | Connecting Drug Delivery | Nov 7, 2023 |

# DEVELOPING, MANUFACTURING AND DELIVERING A FILL-FINISH PILOT LINE FOR TUB-BASED PREFILLED SYRINGES

**In this article, Jake Canner, Project Manager at 3P innovation, discusses the latest project arising out of the company's partnership with Cambridge Pharma and its sister company Oval Medical – including the challenges involved and how they were overcome.**

The task facing 3P innovation was to develop a custom automated nest-based filling line for fill-finish of a bespoke primary drug container (PDC) with a suspension formulation, for later assembly into an autoinjector. Cambridge Pharma (Cambridge, UK) needed a fully aseptic filling and proprietary closure system, aligning with developed and pre-approved clinical processes.

The device had been developed by Cambridge Pharma's sister company Oval Medical Technologies (Waterbeach, UK) and included a unique PDC design using cyclic olefin copolymer (COC). Oval's proprietary PDCs offer a wide range of benefits over traditional glass-based systems. The use of COC allows for much greater design flexibility, and the creation of more robust containers, whilst also allowing the removal of materials that could potentially interact with the drug.

3P innovation has worked with Oval Medical in the past to help with the development of automation equipment for the sterile closure process of its COC containers on a clinical scale (Figure 1). This project was a scale-up project incorporating those processes.

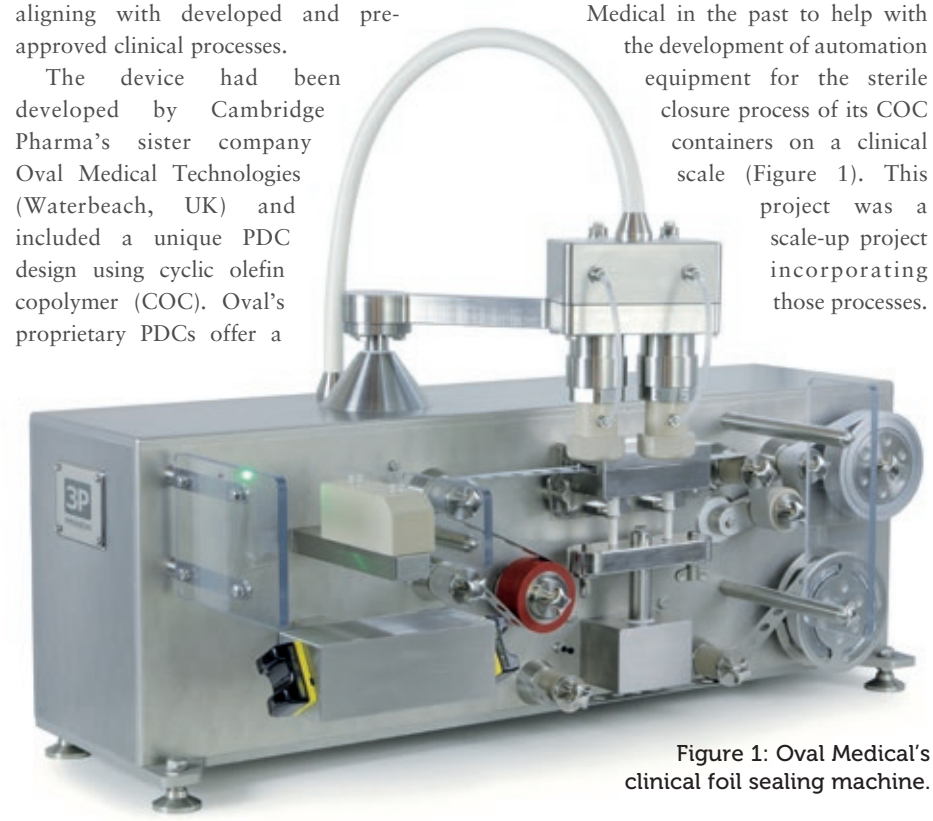

Figure 1: Oval Medical's clinical foil sealing machine.

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Figure 2: 3P innovation engineers working on the pilot line.

Cambridge Pharma specialises in small-batch sterile fill-finish operations for a range of presentations including vials, syringes and cartridges, as well as custom PDCs. The company's state-of-the-art GMP facility is equipped to work with small molecules, cytotoxic formulations and large molecules (non-active biologics), and can handle a wide range of solution viscosities, suspensions and gels.

3P innovation was commissioned to design a nest-based system, able to handle the specialist COC containers and fill them with a suspension formulation. Amongst other requirements, there was a need for 100% in-process fill weight checking, vacuum plunger insertion, the addition of a spacer component for variation of fills – and Oval Medical's proprietary container closure. One key differentiator from previous work was the requirement for processing multiple containers in parallel, in order to hit throughput requirements. Handling products "in nest" allowed for higher speed parallel processing and, more critically, a vast reduction in operator interactions with the product itself – therefore improving the sterility assurance of the process.

## PROJECT CHALLENGES

### Limited Footprint

The machine was designed to go into a bespoke cleanroom, where floor space is always at a premium. Inside the machine, products are handled, filled and closed in their nest. This potentially requires more space than processing containers individually, but there is better control compared with a system requiring more interventions, yielding a significant reduction in contamination risk.

> "The company was able to design a sterile-compatible nest-handling robot that turns a pair of axis rotations into parallel, cartesian motion of the payload."

3P innovation worked to design a novel system for handling nests so that the machine would have enough working travel to be able to process nests but be sufficiently compact so that it would not take up a lot of space. Using the principles of a five-bar linkage, the company was able to design a sterile-compatible nest-handling robot that turns a pair of axis rotations into parallel, cartesian motion of the payload.

### Avoiding Wetted Parts and Reducing Cleaning Times and Costs

Cambridge Pharma wanted to use single-use system components where possible, to speed up changeover and cleaning of the equipment. So 3P innovation incorporated peristaltic pumps in its design, which meant that only the filling lines and needles would be in contact with the liquid drug. These must be disposed of after every batch but make for a significant reduction in cleaning between batches, helping to reduce both changeover times and cleaning requirements.

### Liquid Filling of a Suspension Drug

Liquid filling of a suspension drug presented a couple of challenges – the first one being the dose size and accuracy required and the second being the nature of the formulation. Cambridge Pharma needed two different dose volumes (1 and 1.4 mL) with 1% accuracy. Each dose is check-weighed, and the dosing system operates a closed-loop trend correction algorithm to account for any variations in the formulation over the course of a batch. For more homogenous liquids, the machine can also be configured for a lower-resolution "per-nest" check, allowing for increased process speed.

### Colour Vision Sensor

The spacer components allow Cambridge Pharma to achieve variable fill volumes within the same PDC body. The spacers are a coloured device component, where the colour is specific to the spacer length and, consequently, the dose in the container. To ensure the correct match of component to dose, 3P innovation worked with the customer to incorporate a colour vision sensor to check for the presence and position of the correct spacer, based on the target fill volumes at the point of batch set-up and recipe selection. This is a cost-effective solution compared with a full vision system.

### Grade A Environment

When it came to the general handling of the open COC containers, 3P innovation had to consider the internal layout of an isolator to manage the grade A environment. The pilot line's design aims to reduce the risk of any particulates generated during processing migrating over to the open product – and the risk of the PDCs being exposed to "first-air" throughout processing (Figure 2). To this end, the closure process step – the punching of foil discs for induction sealing – was physically

Figure 3: Cambridge Pharma's fill-finish pilot line.

separated from the open product by a solid wall. In addition, the decision was taken to separate the liquid filling from the foil punch-and-seal in a wholly separate isolator chamber to ensure isolation of the highest risk step within the filling chamber.

### Validated Process

As the pilot line was required to manufacture sterile parenteral products, 3P innovation worked with Cambridge Pharma from the outset on the validation approach. Existing, validated, clinical processes were referenced and reused to de-risk the validation steps throughout the development process. This added a number of design constraints that were identified right at the start of the project and followed through the validation lifecycle.

### Reject Handling

In order to achieve required cycle times, certain machine processes included up to four containers at once. 3P innovation had to design an intelligent way of handling rejected products that minimised the impact on the containers with no flagged errors. The pilot line's reject strategy is configured such that it will always try to maximise good products (Figure 3). The system tracks rejects at a PDC level, despite generally processing at a nest level. This means that the machine is capable of selecting which process stations can be bypassed or used based on the individual PDCs presented each cycle.

"3P innovation had to design an intelligent way of handling rejected products that minimised the impact on the containers with no flagged errors."

After the process equipment was built and acceptance tested at 3P innovation's facility in Warwick, UK, it was integrated into a sterility isolator provided by Howorth Air Technology (Bolton, UK). The response from Cambridge Pharma at the end of the project was that, despite the rigorous nature of the sterile process requirements and tight timescales, 3P innovation rose to the challenge of developing, manufacturing and delivering the line to meet its needs.

## ABOUT THE COMPANY

3P innovation is a life sciences engineering and custom automation company. It works collaboratively with pharmaceutical and medical device customers to develop and industrialise new products through the design, manufacture and support of production equipment. Based in a purpose-built facility in Warwick, UK, this award-winning business employs 100 people and services a multinational customer base, with machines installed worldwide. Its specialisms include aseptic processing machines, powder and liquid filling technologies, custom device manufacture, assembly and test.

## ABOUT THE AUTHOR

**Jake Canner** is a Project Manager at 3P innovation, responsible for leading a team of engineers focused on custom automation for novel processes in the medical, pharmaceutical, food and fast-moving consumer goods sectors. Mr Canner has led a large number of process automation projects with a range of multinational clients, from concept ideation through to commercialisation – more recently, leading core design work on aseptic manufacturing systems and process development. He has extensive experience in the conception, design and development of special purpose machinery, and has recently been involved in a multi-company special interest group assessing the positive impact automation could have on the manufacture and release of advanced therapy medicinal products.

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team technik
PRODUCTION TECHNOLOGY

# INDUSTRIALISATION OF CUSTOMISABLE PRODUCT PLATFORMS IN LIFE SCIENCES

In this article, Umit Ismail Tsavous, Senior Control Engineer, Carsten Köhler, Vice-President Sales & Project Management, and Tom Nägele, Applications Engineer Team, all of the Medtech Division at teamtechnik, discuss customisation of product platforms in the life sciences field.

The desire to stand out from the crowd is not limited to the consumer market; in the life science industry, there is a strong need for individualised solutions. The drivers for this need are diverse, ranging from branding purposes to functional adaptation.

"The challenge for the machine builder is the flexibility to assemble and test all variants within the product platform."

This desire for individualisation is in marked contrast to the needs of production facilities, both in terms of the level of investment required for production equipment and the organisation of production. To limit the impact of customisation on production, product developers create product platforms. In this concept, the function stays the same but the external appearance and size can change. The challenge for the machine builder is the flexibility to assemble and test all variants within the product platform.

In the past, production lines were adapted by means of shelves full of interchangeable parts. This resulted in loss of production time and the risk of machine failure during the changeover. To limit these effects, teamtechnik offers its customers a solution with automatic adaptation for different variants. This article outlines the concepts involved in the implementation of a flexible yet stable assembly system.

"Sustainable energy consumption and efficient resource usage are more important than ever in today's world."

## CUSTOMISABLE PRODUCT PLATFORMS

Sustainable energy consumption and efficient resource usage are more important than ever in today's world. This is one of the reasons why product developers use customisable product platforms – to allow individualisation by focusing on the effective use of resources. Product platforms use as many common components as possible to design different product variants, which are then produced on the same assembly lines. In theory, there should be no limit to the number of possible variants of the product platforms that can be produced on a single assembly machine.

Systems from teamtechnik can be used to produce products based on platform design, such as autoinjectors, prefilled syringes (PFSs) and stopcocks. An autoinjector product platform, for example, supports several product variants, with each

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autoinjector consisting of ten or more components. The core function does not change between variants; only the external appearance and size are customised. The varying components are uniformly standardised in their basic concept and mainly differ in their colour and functional position. To generate product variants, the dimensions of the component variants are configured in relation to the individual PFS capacities. The PFS product range includes three basic diameters and several length variants, each consisting of a glass barrel and a needle. The glass barrel, needle diameter, needle tip and needle wall thickness form different variants of the PFS product platform.

Similarly to a PFS, the basic structure of a stopcock product platform consists of two basic components: body and handle. In total, more than 300 product variants can be implemented within one stopcock product platform. Each variant of the stopcock is based on a geometrically modified body. The connection points are almost identically designed for flexible handling in the assembly system. The body variants are essentially differentiated by their different connection ports. The bodies are equipped with an individual combination of connections, screw caps and O-rings, depending on the variant.

"Developing a machine concept for customisable product platforms starts with an understanding of the assembly steps of the product."


Figure 2: TEAMED RTS.

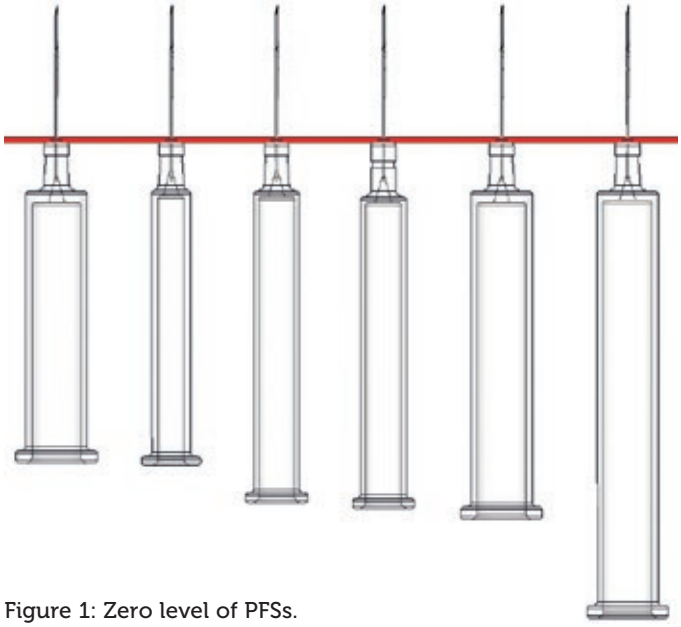

Figure 1: Zero level of PFSs.

On teamtechnik machines, the production of product platforms is now a standard feature, with the required flexibility for today's product variants as an integral part of these machine concepts.

## MACHINE CONCEPTS

Developing a machine concept for customisable product platforms starts with an understanding of the assembly steps of the product. An essential aspect of this phase of concept development is the identification of the zero level. A machine type can be selected according to whether the product platform provides such a zero level (Figure 1). If a zero level exists, mechanically controlled machines can adapt easily to different product variants, however, without a zero level, the choice is limited to servo-driven stations, as too many positions are required.

For example, with teamtechnik's platform TEAMED RTS (rotary transfer system) cam technology, a stopcock product platform is produced with over 300 variants (Figure 2). The synchronously controlled cams of the RTS are mounted on main shafts and driven by a single common servo motor. This synchronicity also contributes to low energy consumption during production. If further processes for the assembly and testing of a product are required, teamtechnik can use the TEAMED LTS (linear transfer systems) machine platform (Figure 3).

Depending on a customer's requirements, the drive can be built with mechanical cams or servo electric motion. Cam-controlled processes can achieve maximum cycle rates, whereas electric drives offer greater process flexibility. If individual flexibility for the component is required, this will lead to an asynchronously controlled LTS, with complete process versatility based on servo motion or robotic stations.

However, the variants of a product platform that can be produced on a teamtechnik machine platform are not dependent on the drive system employed. For example, an autoinjector product platform could be produced on a cam-driven RTS while an infusion set product platform would be produced on an asynchronously controlled LTS. Both machine concepts can produce a multitude of product variants without interchangeable parts (Figure 4).

To be able to react to product variants with cam-controlled systems, adjustment units are integrated into the drive of the process stations, which require flexible parameter configuration.


Figure 3: TEAMED LTS.

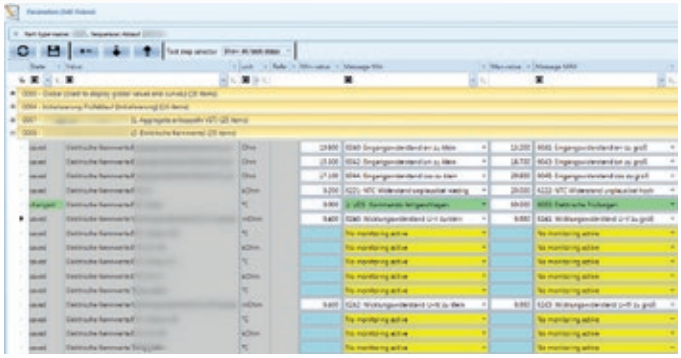

Figure 4: Variant parameters.

An adjustment unit consists of a servo axis for length adjustment, which is controlled by recipe through the human-machine interface (HMI). Consequently, the servo motor can be used to set individual product parameters for each variant. Another benefit of this approach is the limitation of asynchronous motion, as the motion profile is still driven by mechanical cams.

In an LTS for PFSs, a product-specific cam-controlled stroke can be configured according to the product recipe. In the event of a format change, the parameters of the servo motor are automatically adjusted. This product-based parameter adjustment eliminates time-consuming production stops during a changeover.

## PARAMETERS

teamtechnik systems can be easily adapted to new product variants and enable the continuous observation of settings between all components without the time-consuming adaptation of the mechanical parts or software. Flexible processes are used that can automatically decide which parameter sets certain products are manufactured and tested with. By deploying technology-driven and digitally integrated innovation strategies, the entire production line can be controlled and observed via the industrial computer HMI. The combination of assembly and testing tasks in the medical-technical field, as well as complex and precise process technologies such as micro dosing, force-displacement and torque testing, are among teamtechnik's core competencies.

The system software architecture is structured, including flexible and adaptive interfaces, and independent of the mechanical principles applied. This is the basic prerequisite for efficient production and testing of the different product variants on a single production line. The monitoring and diagnostic systems used can detect critical process states of the assembly system and other connected sub-systems in real-time and automatically trigger optimisation routines.

The standardised control, production control and testing software from teamtechnik supports secure process sequences and secure data access to ensure the complete traceability of production data. The test software collects the test data and reliably derives quality evaluations from it (Figure 5). The collected data can also be adapted to customer needs to ensure data processing and archiving on the equipment. The user interfaces are operator-friendly, ergonomically designed and oriented to the basic thought patterns of humans. The concept prevents errors and guides the production operator through all processes, even if the operator is not yet experienced in handling the system.

With virtual commissioning, the control software of the real assembly system is connected to a simulation model via appropriate interfaces for testing. This allows many parameters and device interfaces to be tested and optimised prior to system commissioning. The simulation model makes it possible to vastly reduce commissioning times and error planning, as well as the associated implementation-finding. The use of virtual commissioning allows demanding assembly and testing tasks to be completed reliably in a short time. These software solutions, especially for the automation of assembly and testing requirements, are already implemented in teamtechnik systems.

Choosing the right concept is crucial for the desired results to be achieved effectively. Having access to a complete, configurable and user-friendly package, with implemented interfaces, development, assembly, measurement technology, testing technology, feeding technology and qualification according to GMP specifications, is a great advantage for teamtechnik's customers. With the implementation of regular audits, its customers can ensure more transparency while maintaining the required quality standards.

Figure 5: Test parameter collection.

"For the production of customisable product platforms, the qualification strategy is an integral part of the concept design."

## QUALIFICATION

In the production of medtech products, large quantities of consumable products are continuously manufactured and tested. During production, compliance with quality requirements is extremely important. For the medical industry, these requirements and tech accompanying qualification processes are elementary components of the quality management system. Standardised GMP assembly platforms are only released for production if an error-free qualification process has been carried out by experienced qualification engineers. The aim is to meet the necessary quality and legal requirements and to verify that the system functions as specified prior to the design and build of the system. Especially for custom-build equipment, the engineering team needs to respond individually and carefully to customer requirements for each project.

For the production of customisable product platforms, the qualification strategy is an integral part of the concept design. To reduce the number of qualification tests at the end of the build phase, the impact of each of the different possibilities must be considered. In the case of fully flexible station concepts, the required test routines can be much more demanding than with mechanically driven systems. This is a strong incentive to choose a mechanically controlled machine platform. As described earlier, in many cases, the degree of flexibility mechanically driven systems offer is more than sufficient and only dependent on the correct analysis of the product. Finally, it is important to select the right approach at the beginning with the resulting quality routines in mind.

The qualification process should begin in the concept phase of the project and then accompanies the design throughout each phase of development, such that the assembly system is released into production in a qualified condition with the confirmed quality and process reliability. In the design phase, the product properties are analysed and, based on this, the assembly and testing processes are then developed. Because each product has individual physical, technological and chemical properties, it is a basic requirement for teamtechnik to understand the product properties in detail (Figure 6).

teamtechnik's assembly system platforms can have a modular structure and can be qualified as individual modules. If these processes are combined into one system, only the overall line functionality is qualified. After completion of the initial qualification, future changes may only be made using change control. This ensures that all changes are carried out in a co-ordinated manner and clearly documented. The quality-relevant test stations of the assembly system are regularly checked, in what are often referred to as daily checks. The actual values are compared with the target values several times using a functional sequence with external test standards to verify that the quality requirements continue to be met. The system includes a specific production mode to allow these daily checks to be performed easily. The external test standards required for verification must be calibrated in defined cycles. This is necessary because even the smallest measurement error can have a drastic impact on product quality, and thus on patient safety. Calibrating test standards provides further assurance of quality.

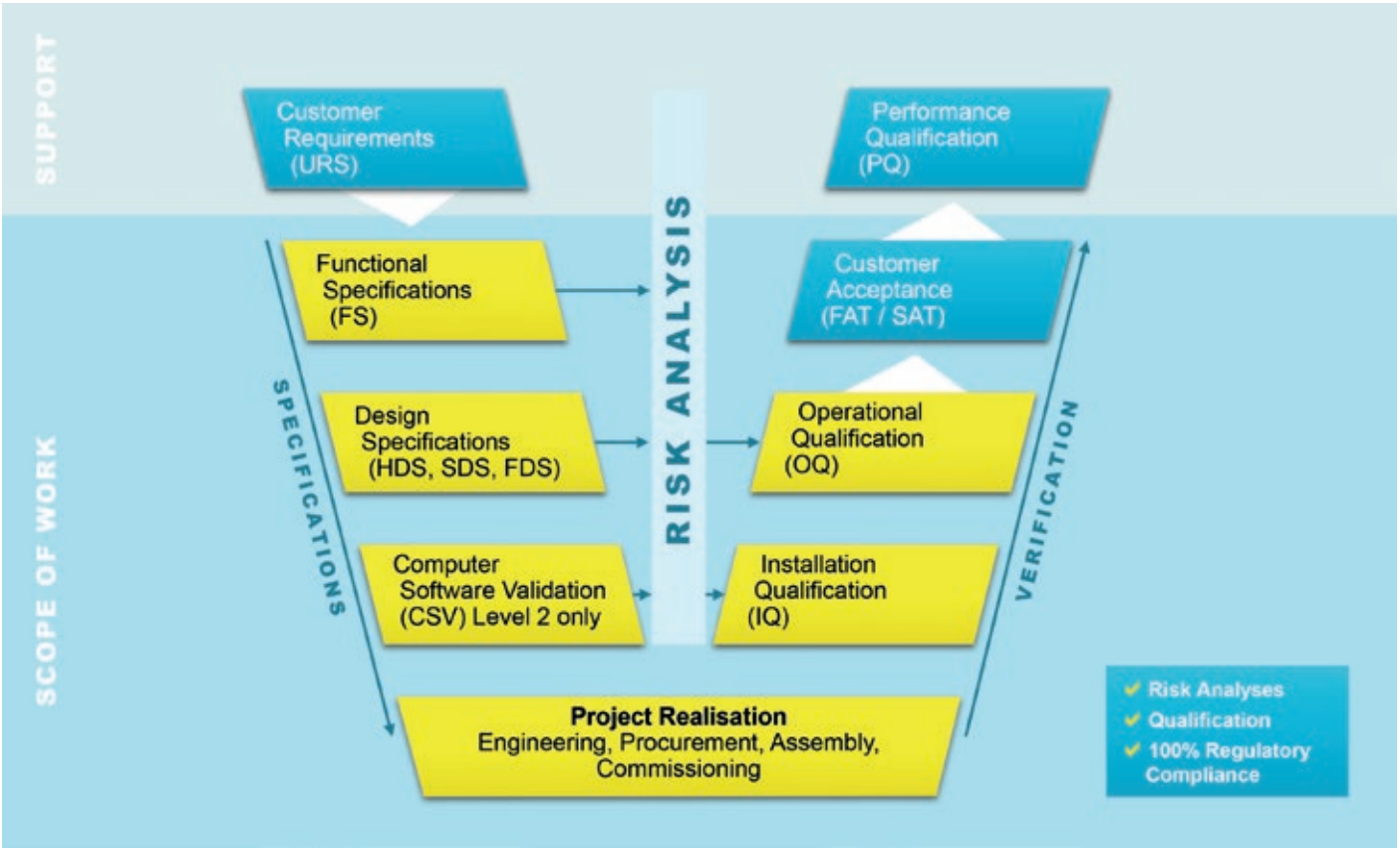


Figure 6: V-model based on GAMP 5.

## SUMMARY

The concept of customisable product platforms is driving the development of specific assembly systems. The flexibility required to produce the different product variants needs to be assessed and addressed individually. This ranges from simple solutions on flexible workpiece holders up to robotic cells. In this assessment, the call for fully flexible processes is often voiced. However, for reliability and efficiency of production, a more individual solution may prove to be the best option.

Even a rigid machine concept, such as a cam-driven machine platform, can be equipped with the flexibility to handle a large variety of products from the same platform. This combines the benefits of flexible product adjustment with the robustness and efficiency of the cam drive. The promotion of fully flexible systems is often driven by uncertainty about what products may be introduced at a later stage. In cases like these, a detailed discussion between the machine builder and the product developer is essential to find the right balance between flexibility and production requirements.

However, the mechanical concept is only part of the production system for customisable product platforms. The concept and configuration of the HMI supports the user, enabling them to control and adjust the production system for the different product variants. Intuitive management and storage of the product variant settings enables production personnel to manage the changeover between variants efficiently. The final piece of the system is the qualification and confirmation of the data integrity. Only with stable interfaces and data storage capability can medical products be reliably manufactured to the highest standards of quality.


## ABOUT THE COMPANY

teamtechnik has been involved with automation since 1976. Today, the company is part of the Dürr Group (Bietigheim-Bissingen, Germany) and one of the largest assembly and functional test system specialists in Europe. teamtechnik focuses on high-volume assembly and test solutions for injection systems, diagnostics, inhalers, medical disposables, dialysis filters and eye-care products.

## ABOUT THE AUTHORS


**Umit Ismail Tsavous** is Senior Control Engineer in the Medtech division of teamtechnik. For more than eight years, he has specialised in automation solutions for medtech devices, focusing on measurement programs for pen injectors and autoinjectors. Mr Tsavous is also studying computer science with a focus on artificial intelligence.

**Carsten Köhler** is Vice-President Sales and Project Management in the Medtech division of teamtechnik. For more than 15 years, he has specialised in automation solutions for medtech devices. Before joining teamtechnik, Mr Köhler led teams for medtech automation as a Director of Engineering. His overall competence is comprehensive, including project planning, mechanical/electrical design, software, qualification and documentation.

**Tom Nägele** is an Applications Engineer in the Medtech division at teamtechnik. For 10 years, his focus has been on the assembly, commissioning, construction and concept development of assembly systems. His specialisation results from his practical experience as a mechatronics engineer focusing on mechatronics and robotics.

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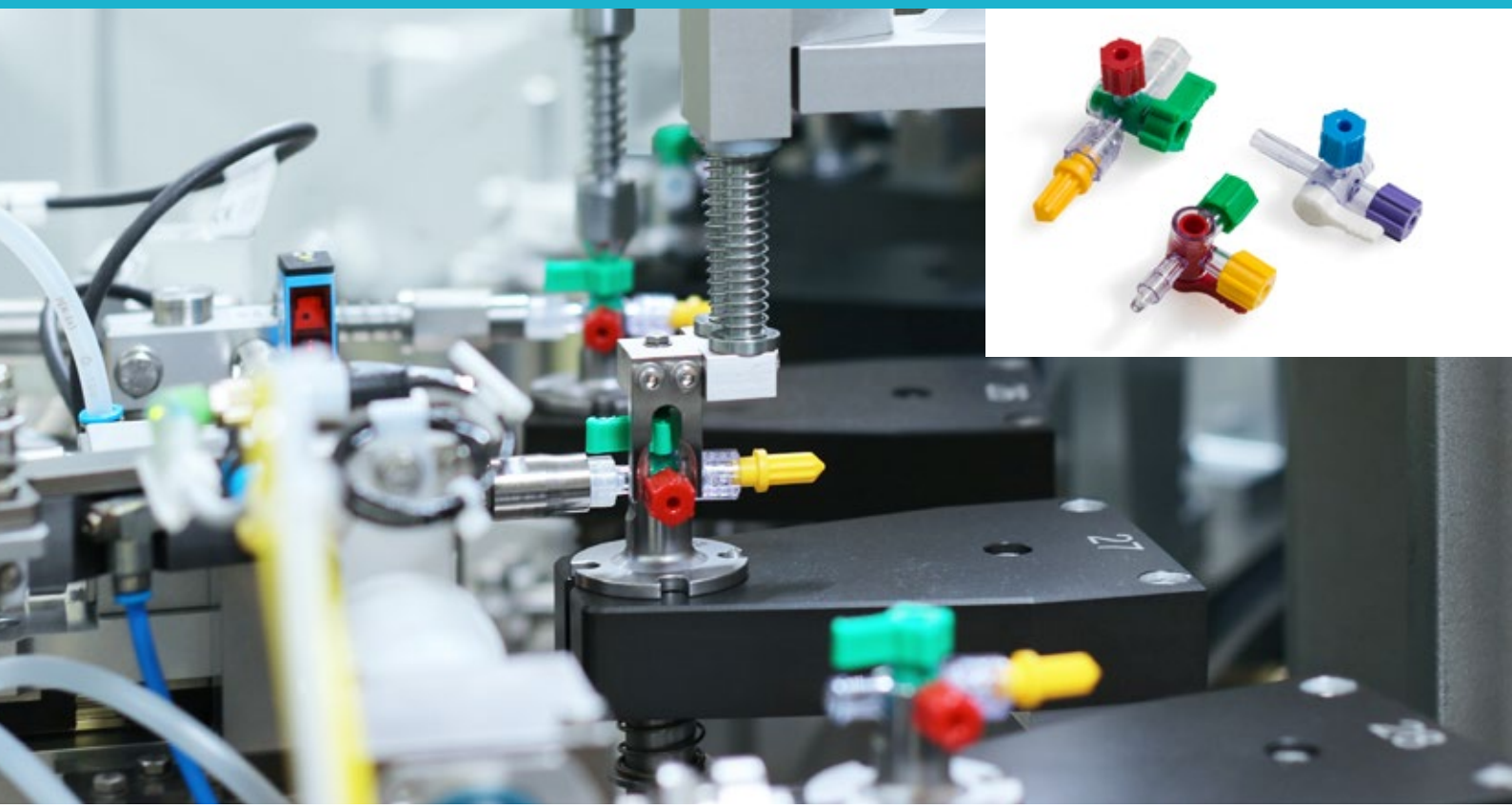

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# Technology Showcase: CCBio's I-Platform – How to Upgrade a Device in One Platform

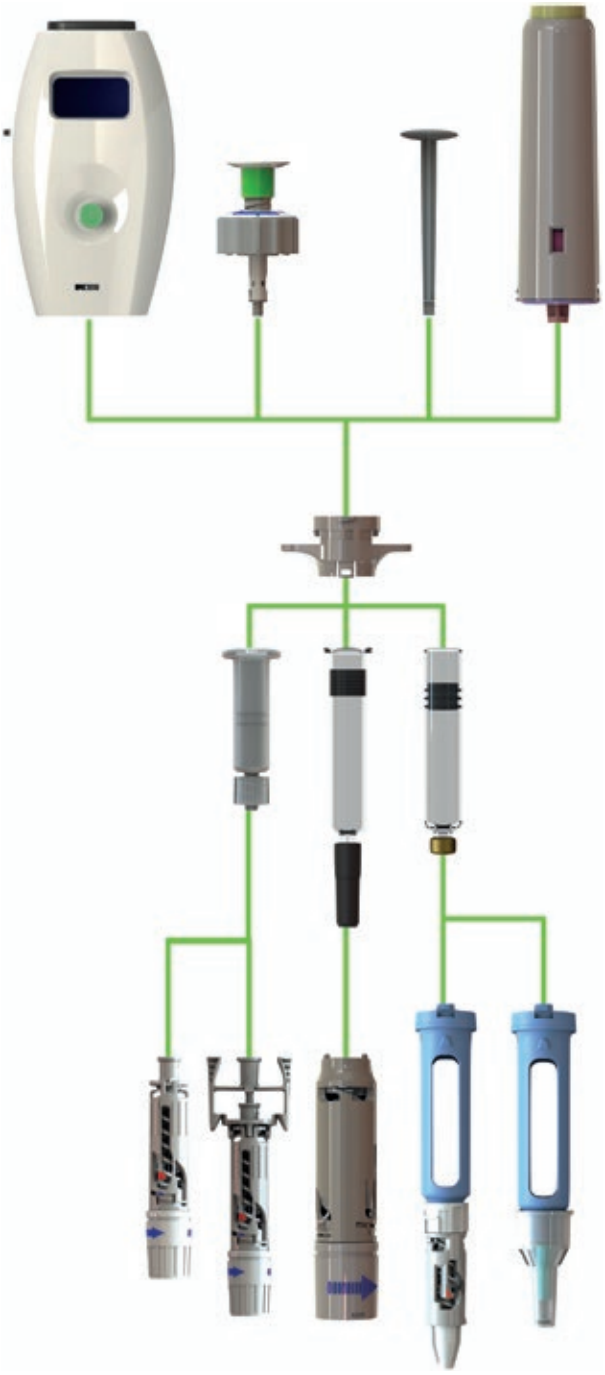

Figure 1: The I-Platform drug delivery device – showing the delivery units on the top, the containers and their adapters in the middle and the safety needles on the bottom.

In 2020 and 2021, the covid-19 pandemic had a dramatic impact on global healthcare systems. Lockdowns, limitations on mobility and concern about cross-contamination resulted in many patients with chronic diseases being unable to travel to hospitals and clinics to have their necessary medications administered. The pandemic also massively increased the workload for healthcare organisations and their staff, meaning they were often overwhelmed to the point that they struggled to serve their communities except for providing care to those in critical and urgent conditions.

This poses the question – is it possible for more patients to administer their medication at home? Historically, the injection process has involved withdrawing the drug from a vial into a syringe and then injecting into the human body. This is already a non-trivial process for a trained health provider to handle precisely and accurately, so expecting untrained users to perform their drug injections this way at home would introduce an unacceptable level of risk and danger.

Originally, pen injectors and autoinjectors were considered the solution for enabling at-home self-administration. However, even a simple fixed-dose pen injector may take years and significant investment to develop. Additionally, as became starkly clear during covid-19, limitations on business travel and increasing transportation costs can noticeably hinder the development for a new device. As such, there is pressure on healthcare systems, pharma companies and device manufacturers to come up with a better, faster and more flexible development method so that patients and users can receive more injectable drugs at home. An additional consideration for pharma companies is the need to think about what kind of device is most suitable commercially; sometimes, the marketing evaluation will require additional time to find an alternative device to the initial choice.

CCBio designed the I-Platform to solve this issue (Figure 1). The I-Platform is designed so that, at the start of development, the pharma or biotech company chooses a prefilled syringe (PFS) with holder for the initial stages, allowing them to save costs and time. During the early stage of Phase II studies, pharma can use the PFS, which enables users to perform injections easily, as the holder provides larger finger contact and a holding flange (Figure 2). CCBio designs different holders for major containers and can also fit safety devices for preventing needlestick injuries (Figure 3).

The delivery unit is the core technology of the I-Platform, which allows pharma companies to update the driver, such as a spring rod or an electric rod, during development (Figures 4 & 5), which is more convenient for assembling the PFS with the end device. Additionally, using a commercial device at this stage saves

Figure 2: The basic I-Platform PFS with holder.

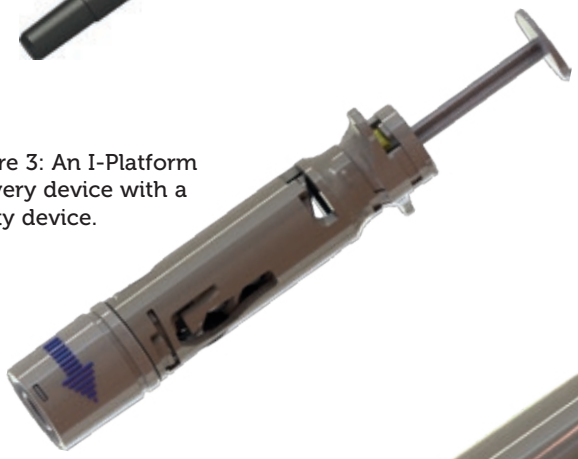

Figure 3: An I-Platform delivery device with a safety device.

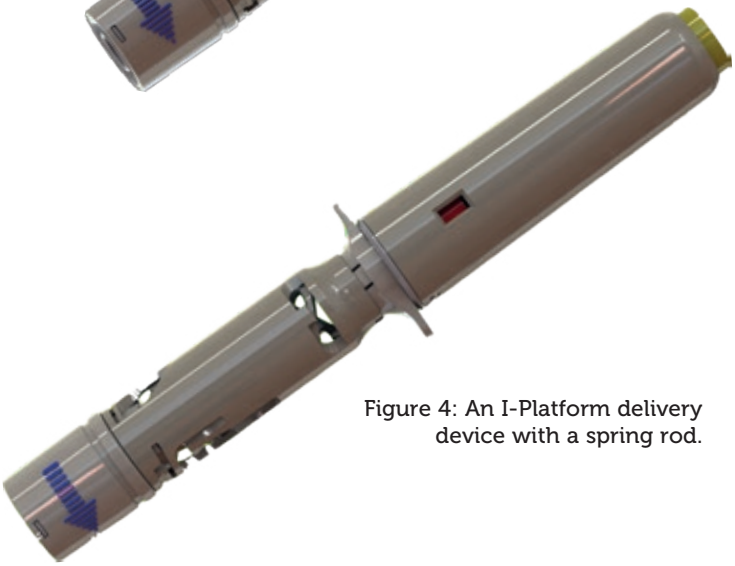

Figure 4: An I-Platform delivery device with a spring rod.

Figure 5: The I-Platform Tesla.

costs in the long run because, during Phase II and III, it enables the pharma company to upgrade the device from a simple, conventional delivery unit to a complex one quickly and easily.

The I-Platform enables pharma companies to launch their drug initially with a simple, easy-to-use device configuration that will reduce the burden on hospitals and healthcare facilities by enabling increased adoption of at-home drug administration. Then, later on in the product lifecycle, the device configuration can be further upgraded to an advanced model with much better functionality and performance.

However, the intended use of the I-Platform is not exclusively for home use. Tesla is the crown jewel of the I-Platform, with advanced and innovative features, including:

- WiFi connectivity
- Near-field communication connectivity
- LED display
- Bluetooth connectivity
- Fully customisable programming
- Powerful server motor
- Li-ion battery.

Tesla, with the I-Platform's most advanced delivery unit, is capable of handling various drug viscosities, as well as injection speeds and durations. The smart program can help patients easily control their treatment, making their daily life easier, more comfortable and less dependent on visiting hospitals and healthcare providers, in addition to reducing the overall cost of their therapy.

The I-platform Tesla also has many new functions to distinguish new biologic or biosimilar drugs on the market. CCBio can design a unique and special holder construction to distinguish specific drugs, which will significantly contribute to preventing healthcare providers from delivering the wrong medication.

The I-Platform can not only be upgraded quickly, but also it follows environmental, social and governance principles. The I-Platform Tesla can be made with a reusable part so that the pharma company will only need to provide the drug without the plunger rod for repeat uses. This reduces the required logistics space, packaging costs and shipping costs. CCBio knows that product space efficiency is key, especially in a pandemic.

In recent years, there have been more and more viruses infecting humans. The covid-19 pandemic exposed the serious truth that we are unprepared and vulnerable before nature. As such, it is imperative that the pharmaceutical industry learns the lessons of the past few years and prepares for the future. It will be key to transition more drug delivery to the home as part of these preparations. Through a joint effort between pharma companies and medical device developers, CCBio believes that it is possible to overcome the pandemic and return to normal life again.

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COMPANY SHOWCASE: Owen Mumford Pharmaceutical Services

# Owen Mumford
## Pharmaceutical Services

With more than 70 years' experience in medical devices, Owen Mumford Pharmaceutical Services is a division of Owen Mumford. Its global presence extends from its UK head office and manufacturing facilities in the UK and Malaysia to subsidiaries in the US, Germany and France.

Owen Mumford Pharmaceutical Services specialises in the design, development and manufacture of injectable drug delivery systems for the pharma, biotech and generics industries. Its trusted devices are used daily in the delivery of various medications for a multitude of conditions across the globe.

Its product portfolio includes single- and multi-dose reusable and disposable autoinjectors, pens and syringes for subcutaneous and intramuscular administration. Its flagship products include the UniSafe® platform (Figure 1), a spring-free, passive safety device for 1 mL and 2.25 mL prefilled syringes. UniSafe 1 mL has regulatory approval as a combination product in Asia and Europe, where it is also in patient use.

**Figure 1:** The UniSafe® platform is a spring-free, passive safety device for 1 mL and 2.25 mL prefilled syringes.

> "Aidaptus® can readily adapt to different fill volumes using auto-adjust plunger technology, providing a solution for formulation changes during development and lifecycle management."

The company's most recent innovation is the two-step disposable autoinjector, Aidaptus® (Figure 2), which can be used for both 1 mL and 2.25 mL syringes in the same base device.

Aidaptus can readily adapt to different fill volumes using auto-adjust plunger technology, providing a solution for formulation changes during development and lifecycle management.

Aidaptus has an innovative, patient-centric design with automatic needle insertion that provides a simple and consistent user experience. The stopper sensing technology, coupled with the independent, two-phase needle insertion and drug delivery, significantly reduces any impact forces on the syringe, mitigating the risk of syringe breakages during use.

With a needle that is shielded before, during and after use, Aidaptus provides reassurance to users who are new to autoinjectors, as well as those who experience needle phobia. It can also give users confidence that the injection has been successfully completed with an audible notification at the start and end of the procedure.

Owen Mumford Pharmaceutical Services has an exclusive agreement with Stevanato Group, a global provider of drug containment, drug delivery and diagnostic solutions.


**Figure 2:** Aidaptus® is a two-step disposable autoinjector that can be used for both 1 mL and 2.25 mL syringes in the same base device.

Stevanato is its manufacturing partner for the Aidaptus autoinjector, moulding the components, and providing final and subassembly equipment. The collaboration aims to reduce supply chain complexity and reduce risk in combination product development for pharmaceutical partners.

Owen Mumford Pharmaceutical Services also has an alliance with Noble, providing patient-focused training devices for both UniSafe and Aidaptus.

Owen Mumford Pharmaceutical Services' products are supported by its services, and the company works with its pharmaceutical partners every step of the way, assisting them throughout their combination product development.

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## intuitive delivery

Your fill volume may change, with Aidaptus® **auto-adjust plunger technology** your auto-injector doesn't need to


Accommodates both 1mL and 2.25mL glass syringes in the same device

## Want to know more?

Find out more about our new innovative Aidaptus® auto-injector by scanning the QR code or visiting **ompharmaservices.com/odd-sept2022**

Now in collaboration with Stevanato Group

*1mL version without syringe



OMPS/odd/ad/ob/1022

Owen Mumford Pharmaceutical Services

INTO THE FUTURE... WITH CONFIDENCE AND CONSCIENCE

Delivery systems

# Driving outcomes with next generation self-injection solutions.

## Industry-leading connected devices integrated with innovative digital therapy management solutions.


Proudly partnering with sidekick

Find out more at www.ypsomed.com/therapymanagement

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