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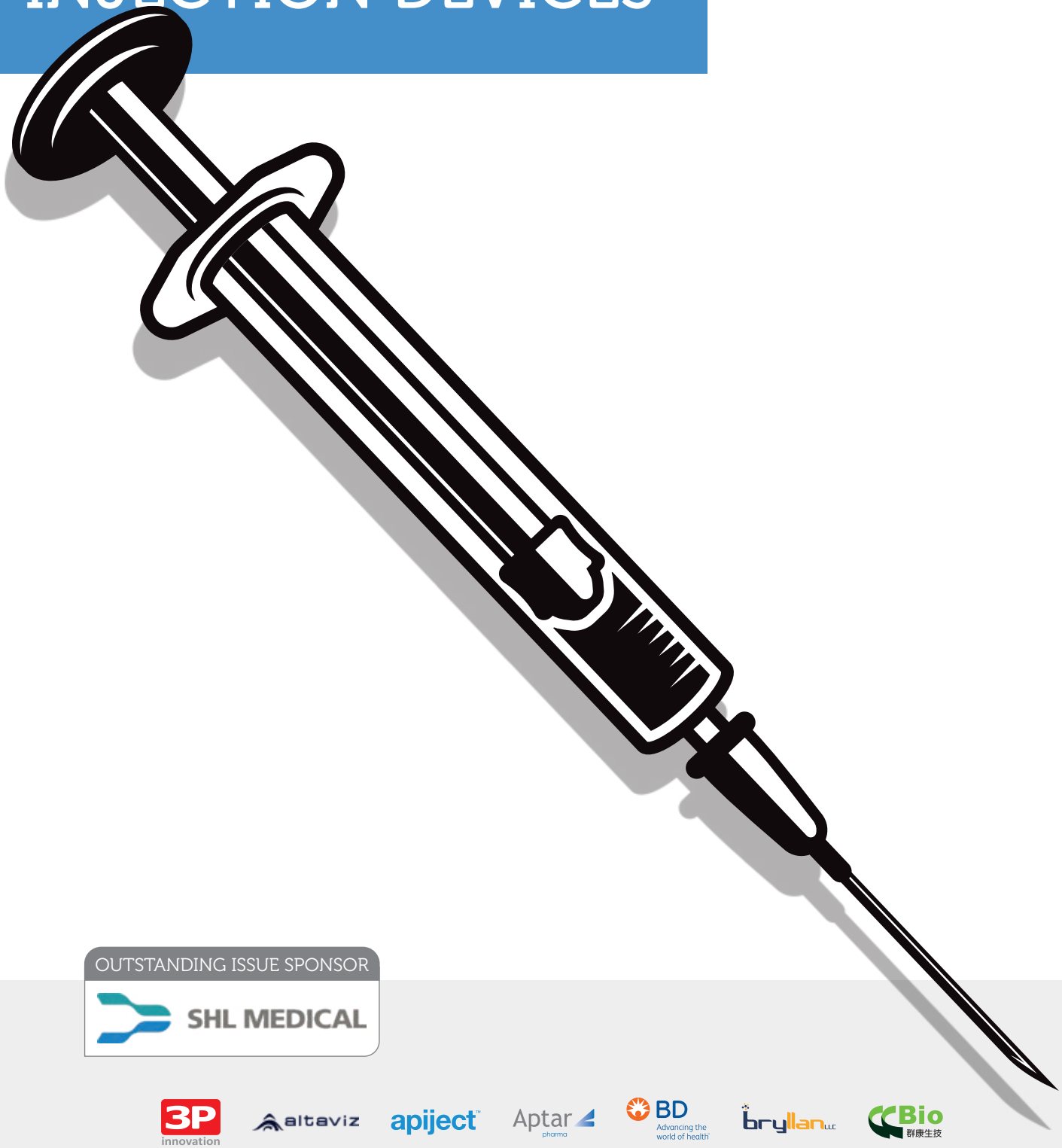



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ONdrugDelivery Issue N° 152, October 16th, 2023

## 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.

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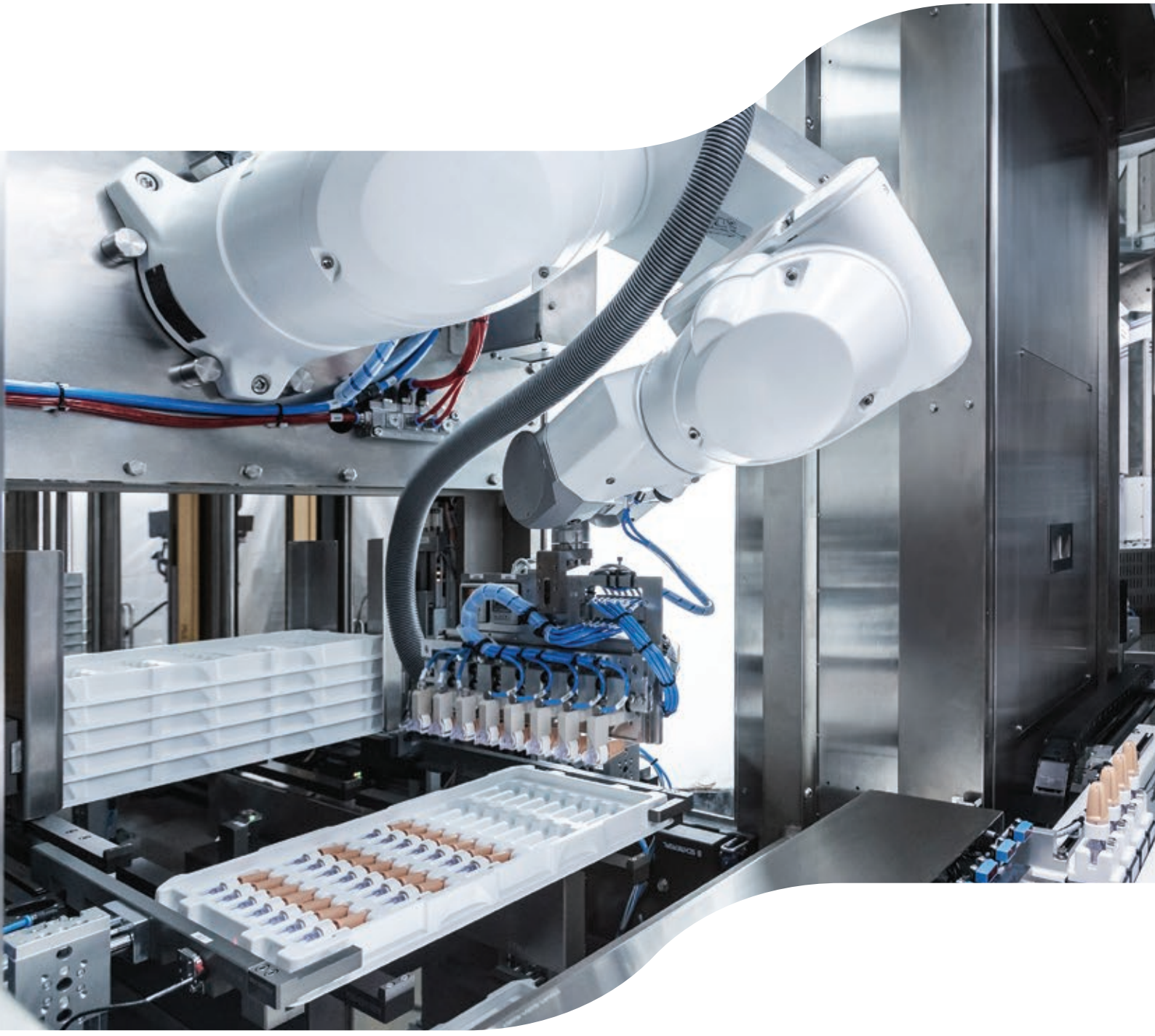
SHL MEDICAL

# Streamlined processes

## Optimizing autoinjector manufacturing with integrated capabilities





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# AN AUTOINJECTOR REVOLUTION: ENHANCED GLOBAL MANUFACTURING NETWORKS THROUGH ADVANCED SIMULATION TECHNOLOGIES

Here, Edwin Hendrawan, MBA, Process Engineer; Yi-Chi Lu, MSc, Senior Process Engineer; and Christian Walter, PhD, Global Head of Operations Engineering, all of SHL Medical, set out how SHL is building simulation capabilities, and describe how simulation will propel the business forward on every level, from individual shop floors to overall global expansion planning, in order to be able to meet the growing and increasingly complex demands from both pharma customers and patients.

We are witnessing a new global revolution across industries – a universal pursuit of bigger machines, faster production processes and smarter, more connected systems – with the objective of unleashing added value for today's manufacturing infrastructures. This stride into Industry 4.0 is a pivotal undertaking, significantly transforming the medtech industry landscape.[1]

## A BRIEF LOOK INTO THE RECENT PAST

It should be noted that, prior to Industry 4.0, in medtech, particularly in the field of autoinjectors, a few important landmarks in its relatively short history have given rise to this newfound era.

Autoinjectors commercialised in the late 1990s to early 2000s were characterised by an increasing heterogeneity in their design, development and production requirements. This bespoke approach required varying assets for each project in question.

Moving away from this resource-intensive bespoke model, explorations into the practice of platform design and manufacturing allowed device manufacturers to utilise shared production assets for different device constituents. SHL's DAI® autoinjector, which features a recognisable industrial design commercialised for various user-group scenarios, is one of the industry's first such devices.

The platform philosophy in autoinjectors then rose to the next level with the application of modularisation.[2] The modularity of platform-based manufacturing can be described by the arrangement of its discrete, standardised modules, enabling companies to benefit from enhanced scalability of production setups.

To this day, the manufacturing infrastructure behind SHL's Molly® autoinjector remains one of the most successful modular platforms within the industry. The Molly autoinjector has now been commercialised in 17 distinct combination product projects covering a wide range of disease areas.[3]

> "From platform-based manufacturing to modularisation, SHL has already left an indelible mark on the past and is poised to shape the future of autoinjectors."

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## MEETING PHARMA'S NEEDS WITH INDUSTRY 4.0

It could be argued that many of the hallmarks of industrialisation in the autoinjector space have been shaped by the efforts of SHL. From platform-based manufacturing to modularisation, SHL has already left an indelible mark on the past and is poised to shape the future of autoinjectors.

The healthcare industry's advance into Industry 4.0 translates into evolving demands at various points in the value chain. As novel drugs and several biosimilars enter the market in broadening disease areas, pharmaceutical companies seek medical device partners to address growing market demand. This growth – which can be seen on both global and local scales – is characterised by differing healthcare providers, payers, policymakers, and patients.

The portmanteau "*glocal*" (an adjective combining global and local)[4] describes the pressing challenge for pharma to bring combination products closer to local healthcare systems, a challenge in autoinjector combination product development that SHL takes very seriously.

With *glocal* challenges in pharma requiring *glocal* solutions, device companies like SHL are investigating strategies to expand manufacturing operations globally by leveraging the power of Industry 4.0 technologies. SHL has proven itself in this regard over the decades, implementing digitalisation of end-to-end processes, in-house automation, machine learning-based attention mechanisms in the assembly validation process, deep learning in the robotic systems of testing machines and extensive data analytics for scalable production – the examples are manifold.

In championing its global expansion through Industry 4.0, the next natural step for SHL is to create virtual models of its processes, production lines, machines and supply chains by applying advanced simulation methods and tools.

## THE DAWN OF SIMULATION AT SHL

Simulation is a powerful technology that is transforming the manufacturing industry by allowing for the reliable assessment and optimisation of complicated processes. While it might be the case that people are more familiar with the term "digital twins", both digital twins and simulation utilise virtual representations to reflect objects of varying degrees of complexity. Digital twins arise from libraries of simulated entities. Simulation is advantageous for the examination of one particular process, as well as the dynamic interdependencies between different processes. The capacity to carry out multiple simulation events to study varied conditions – all within a virtual environment – makes simulation a powerful technique to facilitate informed decisions on manufacturing operations and expansion plans.

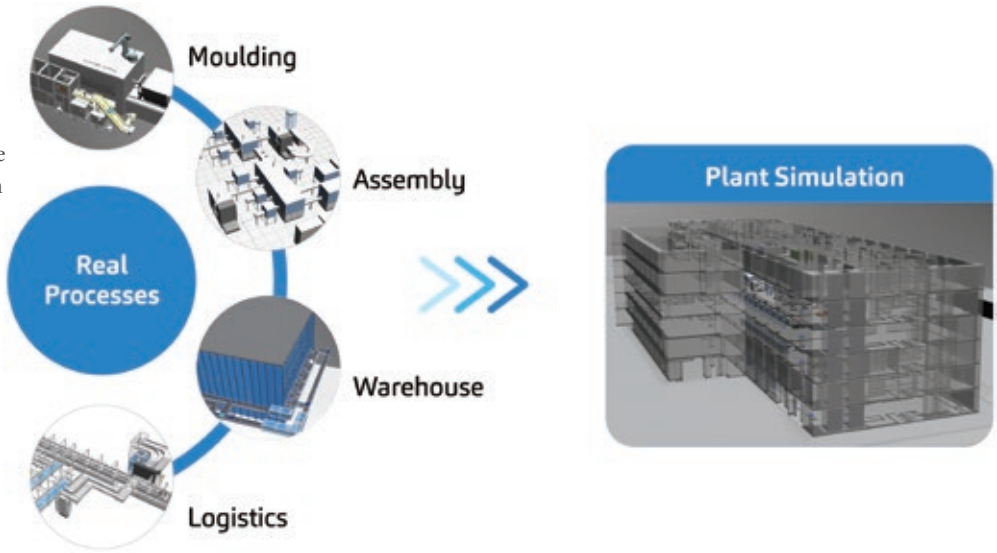


Figure 1: SHL has set up a dedicated plant simulation team to simulate complex processes during autoinjector development, using advanced simulation modelling techniques tailored to SHL's operations.

As part of SHL's end-to-end digitalisation and global expansion strategies, a dedicated team of plant simulation engineers uses advanced modelling techniques to simulate the processes that go into autoinjector development (Figure 1).

Simulation technologies perfectly fit the situational needs of the business of autoinjectors, which entails complex processes, physically large objects, well-defined supply chains and numerous related system constraints, to name but a few. Likewise, the ability to build simulation expertise in-house sets mature device companies apart from other industry players who wish to expand manufacturing operations across continents.

When seeking to harness the potential of simulation technologies, quite a few essential tools enable adequate computing power in simulation. For instance, SHL uses a combination of simple static models and dynamic simulation modelling – adopting their usage according to the contextual needs of operations and the problem statement's complexity.

"The ability to build simulation expertise in-house sets mature device companies apart from other industry players who wish to expand manufacturing operations across continents."

Simple spreadsheet-based models and static modelling are powerful tools to organise data and apply basic formulas to assess and understand specific events. Static modelling is an efficient technique to establish multiple scenarios and produce feasible results for approximation at a high level.

Consequently, the method can eliminate infeasible solutions for a problem being explored. For instance, static calculation allows us to assess production quantities easily, as well as throughputs and space constraints in individual production areas. With the correct input variables, model requirements and conditional formulas, a plant simulation engineer can quickly establish several production settings, define average and worst-case scenarios, and facilitate informed decisions on key parameters of the model setup.

On the other hand, simulation modelling using discrete event simulations (e.g. via Siemens Tecnomatix®) is a highly visual and advanced technique that allows us to build animated representations of highly complex systems and study dynamic

"Plant simulation allows the modelling of discrete and continuous manufacturing processes that constitute SHL's global facilities, specific production processes, material flows and automated machinery."

interactions of multiple processes and subsystems. Simulation modelling – or plant simulation for the purpose of this article – enables the systematic creation of well-structured and modularised 3D models of SHL's entire manufacturing infrastructure. More specifically, plant simulation allows the modelling of discrete and continuous manufacturing processes that constitute SHL's global facilities, specific production processes, material flows and automated machinery.

Managing production capacities across multiple autoinjector platforms is a highly demand-driven process. Plant simulation supports the optimisation of material flow, resource utilisation and various other dimensions of the production operation.

## VIRTUAL PLANT SIMULATION IN REAL ACTION

In what ways can one concretely demonstrate the utility of plant simulations? It should be remembered that autoinjector manufacturing entails an architectural hierarchy with dynamic and branching processes. For example, a Molly or DAI autoinjector project for a pharma customer inherits the same pathway from design to production. However, they differ in their specific steps for the same process. Additionally, these projects will also require differing amounts of time to complete the same steps.

For pharma, time-to-market is a crucial requirement in combination product development, which calls for a device partner that offers shorter lead times. For new and existing projects, SHL's pharma customers benefit from a plant simulation team that dynamically analyses real-time process improvement and optimisation opportunities.

Through an internal request management system, any function can document and investigate optimisation proposals for specific production processes or operational flows. With various production floors utilising SHL's Fully Automated Assembly Machinery (FAAM), it becomes beneficial to analyse the interactions between the people, the machines and the production layout with an eye to maximising operational efficiency.

Figure 2 demonstrates how plant simulation opens pathways for throughput modelling and optimisation. The model shown visualises one of many possible scenarios where initial production components are stacked near the material distribution station, brought to the buffer area, and then sent to the FAAM for the assembly process. In detail, it demonstrates the trade-off between low and high workforce to replenish the materials for the assembly machine. While less workforce assigned to a shopfloor can be viewed as an economic positive, it may also impact the overall equipment efficiency for the process in specific scenarios. There is an acceptable balance between these two, and simulation allows SHL to assess this at a granular level.

Thus, plant simulation allows SHL to gain comprehensive insights into the flow of materials and the use of resources, personnel and space. In the grander scheme of things, the modularity and heritability of simulation outputs allow future device projects to leverage these newfound learnings. Likewise, these attributes show how simulation can be a powerful tool for planning and expanding global manufacturing operations.

## THE ROLE OF SIMULATION IN GLOBAL EXPANSION

On the polar opposite end of granularity lies the opportunity for simulation to impact on a macroscopic scale. With a growing patient population relying on autoinjector products to administer their treatments, SHL is committed to a global expansion journey (Figure 3).

This expansion now includes manufacturing sites in development in the US and Switzerland. This ushers SHL's production lines into continents where many of the world's leading pharma and biotech companies reside, and epitomises the true essence of 24/7 operations that transcend time zones. As SHL attempts to make supply chains more efficient by

"This ushers SHL's production lines into continents where many of the world's leading pharma and biotech companies reside, and epitomises the true essence of 24/7 operations that transcend time zones."

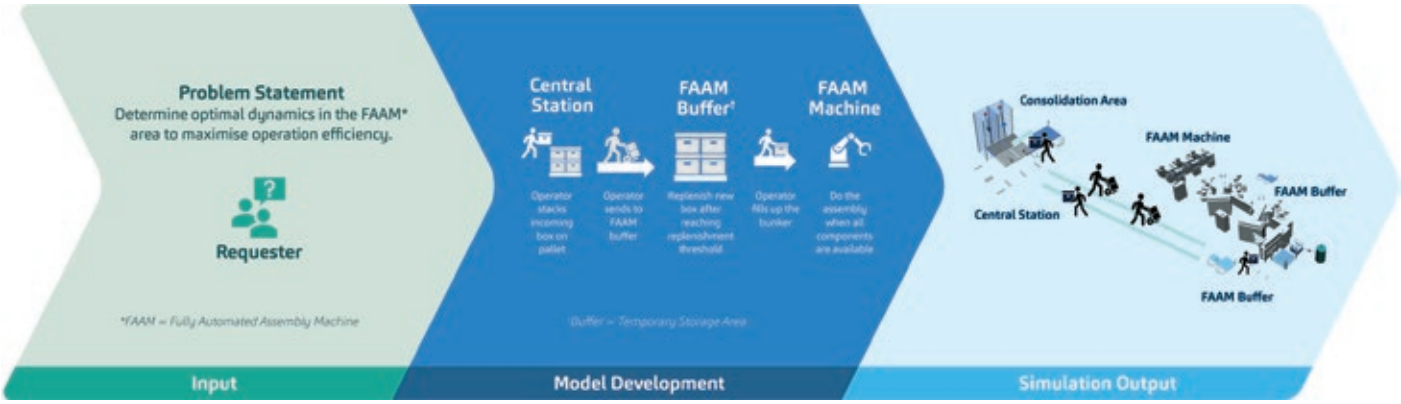


Figure 2: A scenario that mirrors actual situations encountered in SHL's production lines and how simulation can advance the solution-finding process.

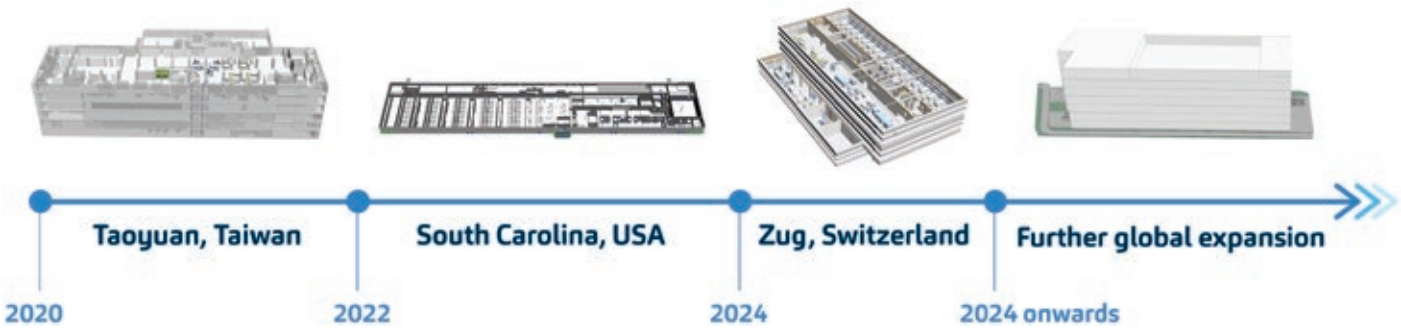


Figure 3: Expert simulations facilitate progressive global expansion plans. SHL's simulation team has created a model of each factory site that encapsulates the entire operations, including the process flow, material handling, and machine operations.

being closer to its pharma partners and their patients, the company is staying true to its promise of using digitalisation to embody operational excellence. The use of simulation technologies is a testament to this pursuit.[5]

It has been said that the future of autoinjectors is mass customisation. To this end, the flexibility and scalability of the entire manufacturing infrastructure are vital for meeting the needs of pharma and the patients. By leveraging the computing power of simulation, SHL is on course to build a sustainable process that achieves flexible, smarter factories that yield products more efficiently than ever across the entire value chain.

## ABOUT THE COMPANY

SHL Medical is a solutions provider in the design, development and manufacturing 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 Medical 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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**Christian Walter**, PhD, is the Global Head of Operations Engineering at SHL Medical. In his nearly ten years of professional service to SHL, he has held roles of increasing responsibility in engineering, project management and operations. Currently, he leads an international team of engineering professionals and is in charge of improving and optimising processes that are highly important to SHL's manufacturing operations. As the global head of operations engineering, his role is pivotal to the success of SHL's expansion plans in Taiwan, the USA, Switzerland and other countries. Dr Walter received his PhD in Production Engineering from the ETH Zurich (Switzerland).

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# IDENTIFYING AND OVERCOMING THE CHALLENGES OF INJECTABLE COMBINATION PRODUCT EVOLUTION

In this article, David DeSalvo, Vice-President of Combination Product Development at Kindeva Drug Delivery, considers some potential challenges that the rapid evolution of autoinjectors (and combination product injectables in general) raises, along with how the industry can successfully address this cycle of reinvention.

Since the creation of the rescue autoinjector in 1959, these drug-device combination products have evolved significantly in functionality, capabilities and popularity. The transition of autoinjectors from emergency-use military devices to becoming an at-home therapeutic delivery method has made them a part of many people's daily lives, and the sustained preference for these devices is based primarily on their ease of at-home use and the reduced burden they offer for all stakeholders. This popularity has helped propel innovation for both the devices and the drugs they contain, which means rapid adjustment continues to be necessary on the part of patients, sponsors, contract development and manufacturing organisations (CDMOs) and everyone using or creating these products.

A critical benefit offered by autoinjectors and related devices is their at-home use, which provides all-around savings in time and costs. For patients who need, for example, weekly injections, this means that there is no need to routinely schedule appointments, travel to the doctor's office, wait to be seen, get the injection and go home. Having a device that the patient can safely and effectively operate delivered directly to them means that they can avoid the potential disruption to their day, lost family or work time and wasted time on the road and in the office, while simultaneously saving money on transportation costs (and, in doing so, cutting emissions). In addition, physicians and other qualified practitioners can focus on providing treatment options for more patients, possibly reaping financial benefits as a result. These factors are all key to the continuing push towards new patient solutions that still offer similar benefits.

## THE PROMISE AND THE PITFALLS

As with any technology, the ongoing evolution of these devices brings plenty of potential challenges with it (Figure 1). While many of these nascent innovations are still finding their footing, furthering their development while keeping a critical eye open for identifiable trouble spots can help counter those difficulties head-on, saving headaches down the road.

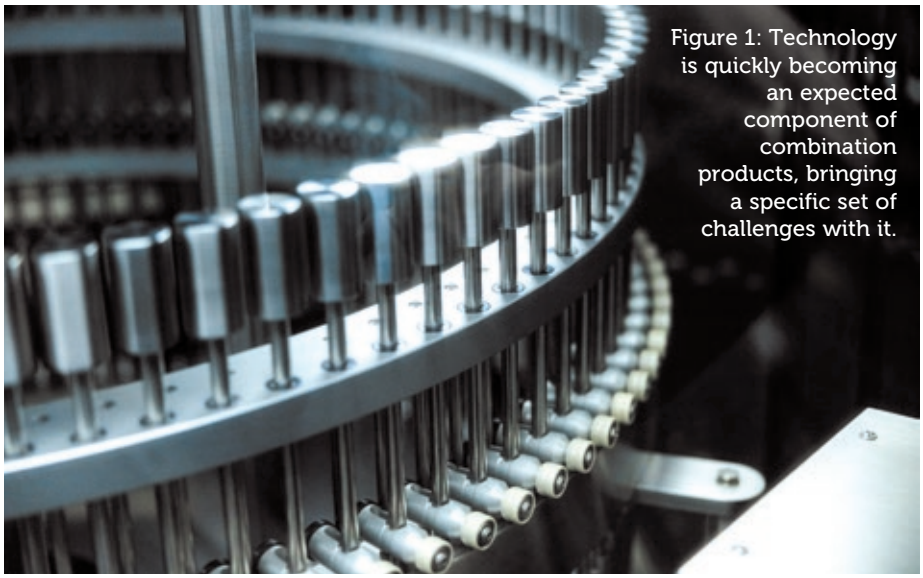

Figure 1: Technology is quickly becoming an expected component of combination products, bringing a specific set of challenges with it.

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## Long-Acting Injectables

For decades, long-acting injectables (LAIs) were associated primarily with antipsychotics to aid patients with schizophrenia who struggled with adherence to oral formulations, but the same principles are now being applied more regularly to other therapeutic areas.[1] These drugs are formulated for controlled release over an extended period, promising increased adherence and additional opportunities for time savings for patients and healthcare providers, such as those previously discussed, even in clinical settings.[2] The move of LAIs to at-home delivery could increase those benefits on all sides, but that potential comes with its own set of risks.

The ongoing desire to extend the timeline from one injection a week to one every two weeks, or even one a month or more, may begin to impact the ability of the patient to use their device correctly. The lower the frequency of injection, the more deterioration in training is likely to occur. With that comes a greater potential for injection and other user errors that could impact the efficacy of the therapy, particularly when the next dose may not be administered for weeks. The possibility of training degradation must be considered when evaluating and planning the ease of administration and the availability of instruction to ensure that the LAI achieves its goal.

Given the increased payload required for these formulations to release over extended periods, the need for greater volumes may necessitate delivery in the form of wearables in place of hand-held autoinjectors. While these devices can help correct some training issues in terms of delivery, their complexity raises a different array of related problems. Patients who may have difficulty retaining their training with autoinjectors are no more likely to recall the right steps for more complicated devices that integrate injectables with electronics. In addition, wearables raise specific challenges due to the duration of use, including becoming dislodged or negatively impacting user compliance due to discomfort, among other issues. As with autoinjectors, ease of use and instructions are vital to ensuring that these devices work as planned for the patient.

> "Weekly injections enable high-production volumes, which, in turn, bring down the per-unit cost for the pharmaceutical company."

Figure 2: When creating a technologically advanced injectable product, it is important to ask whether there is adequate benefit to the patient to offset the potential problems associated with the upgrades.

On a more practical note, the savings patients achieve from at-home administration could easily be offset by the cost of LAIs. Weekly injections enable high-production volumes, which, in turn, bring down the per-unit cost for the pharmaceutical company. Once the rate of injection slows to once a month or once a quarter, production volume drops and the cost per unit soars. Furthermore, devices that deliver large volumes of medicine over longer periods tend to be significantly more complex and disproportionately more expensive to produce. To determine the effect on the patient, the price for a monthly LAI should be compared with the cost for a month's worth of its weekly counterpart. With the change in production costs, the potential for them to be equitable needs to be considered. Given that device quality should remain uncompromised, the financial burden for the payers and patients must be considered when extending the time between doses.

## Technical Advances

Information technology is quickly becoming an expected component of combination products, which, as discussed, brings with it a specific set of challenges. These devices can, however, also offer several benefits, including tracking of dose adherence and therapeutic response through connected devices. Some wearable smart injectables can even ensure that the device is being used properly.

While the complexity of these products and the associated potential for higher pricing are both possible issues for patients, privacy and payer problems are also concerns. Built-in security for these systems may be high (and highly regulated), but no technology is impenetrable, which is a risk when dealing with protected health information. On the payer side of the equation, there is the risk of denial if there is an electronically tracked adherence issue or the benefit is not deemed significant or fast enough to warrant the price tag.

When creating a technologically advanced injectable product, it is important to ask whether there is adequate benefit to the patient to offset the possible problems associated with the upgrades. If the downsides outweigh the upsides, it is necessary to consider whether the technology is necessary or simply nice to have (Figure 2).

## Increased Expectations

While the initial consideration of a 1 mL maximum dosage for subcutaneous injection held for years, the boundaries have been shifting in a manner that resembles one-upmanship. The theory had long been that larger doses would be delivered by wearables or other devices, but the initial push in autoinjectors to 1.2 and 1.5 mL was

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well tolerated, which led to a push to 2 mL, then 3 mL, and now we have seen launches of 5 mL devices for subcutaneous delivery.

The original limitations of hand-held autoinjectors have been disproven, but caution should still be exercised when pushing their limits. As discussed in a previous article, among the issues to consider when creating a large-dose autoinjector are tolerability (including an increase in pain, adverse events, injection-site reactions and leakage), the suitability of the device for self-administration and pharmacokinetic equivalence with other options.[3] If there are increased risks for the patient or better options already available, the reward for increasing the dosage is potentially outweighed by the consequences.

> "The original limitations of hand-held autoinjectors have been disproven, but caution should still be exercised when pushing their limits."

One alternative to these increased volumes is packing more of the API into a smaller dosage, which will often increase the viscosity. Along with some of the same issues already discussed, this switch often requires a significant reconfiguration of the device itself. A spring-driven device, for example, is limited by the amount of liquid that it can push through a very small needle, and when the drug being administered is thickened, there is a commensurate need for more power from the autoinjector. The easiest solution in this case is increasing the size of the needle, but this requires a determination of whether patient comfort or flow characteristic is the more important element. This, in turn, leads to the debate over whether you should adjust the formulation development, the device development or both – a decision made more complex by the fact that they are often handled by separate, unaffiliated organisations and separated by months, or even years, within an overall drug development programme. There is no easy answer in this instance, but consideration of both basic device effectiveness and the ability of patients to operate it and adhere to their dosing regimen must be made.

## TRANSFORMING TOMORROW

Knowing where the challenges are in the ongoing evolution of autoinjectors and other injectable combination products makes it possible prepare in advance for what is to come. While there is no way to future-proof against the forming tides of tomorrow, there is an opportunity to avoid being swept away by them. One place to start is with early and close collaboration with partners; forging solid relationships between sponsors, CDMOs and other stakeholders is key to creating a comfortable working relationship and ensuring that all parties are involved in projects from as early in the project as possible. This can help to identify the potential issues so that they can be addressed immediately, saving time and money while ensuring the best chance of creating an optimal product.

While it may seem premature to engage a device partner during formulation, these devices are called "combination

products" for a reason. There is wisdom to be gleaned from all sides in terms of how to develop the right product for the intended use. Along with determining that the formulation that fits the device, early and consistent collaboration allows for the syncing of reliability and durability expectations, as well as acceptable cost per dose or device. By bringing the two halves together from the beginning, it is possible to ensure that a truly cohesive product is created based on the respective expertise on each side of the equation.

What the future holds for autoinjectors and other at-home injectables is an open question. Should there eventually be a move from a weekly dose to an annual dose, does it simply make more sense to return to the doctor's office instead of asking the patient to recall proper administration from a year ago? Do devices become so complex that each patient needs a dedicated technical support person working alongside their physician (Figure 3)? If viscosity continues increasing, how large a needle will patients agree to endure? The key to ensuring that these questions are answered before they become reality is communication. Injectable combination products are already complex, and if that complexity continues to increase, true co-operation and discussion among the experts developing them is the only way to ensure that the products delivered to patients live up to their promise.

## ABOUT THE COMPANY

Kindeva is a global CDMO focused on drug-device combination products. It develops and manufactures products across a broad range of drug delivery formats, including pulmonary and nasal, injectable and transdermal. Kindeva's service offerings span early-stage feasibility through commercial scale drug product fill-finish, container closure system manufacturing and drug-device product assembly. Kindeva serves a global client base from its nine manufacturing, research and development facilities located in the US and UK.

Figure 3: Injectable combination products are already complex, and that complexity continues to increase.

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## ABOUT THE AUTHOR


**David DeSalvo** is the Vice-President of Combination Product Development at Kindeva Drug Delivery. He is an expert in drug delivery devices (combination products) and has invented, designed, developed and launched multiple devices. His work has resulted in dozens of highly successful unique drug-device combination products, including many industry-first innovations. Mr DeSalvo's previous roles include Senior Director of Device Development at Emergent BioSolutions, Chief Executive Officer at Nuance Designs, Senior Director at Scandinavian Health Limited and New Product Development Lead at Becton Dickinson. Mr DeSalvo holds a Bachelor's and Master's degree in Mechanical Engineering from Rensselaer Polytechnic Institute (NY, US) and an MBA from Marist College (NY, US).

# ACCELERATING ACCESS: THE FUTURE OF INJECTABLES IS PREFILLED AND PLASTIC – *AN INTERVIEW WITH BO KOWALCZYK & JON ELLENTHAL OF APIJECT SYSTEMS*

Bo Kowalczyk, Chief Commercial Officer, and Jon Ellenthal, President, both at ApiJect Systems, discuss the need for greater fill-finish capacity in the pharmaceutical industry highlighted by the covid-19 pandemic, and how ApiJect's Blow-Fill-Seal prefilled injector platform aims to meet this need.

## BO KOWALCZYK, CHIEF COMMERCIAL OFFICER

Bo Kowalczyk, Chief Commercial Officer at ApiJect, has nearly three decades of experience in the pharmaceutical and medical device industries. Prior to his current role, he served as Vice-President of Sales, North America, at Syngene International, aligning operational expertise with prospecting efforts to optimise client satisfaction. As President at Eurofins Bioanalytical Services, Mr Kowalczyk oversaw division strategy, profit and loss, mergers and acquisitions support, corporate partnerships, and daily operations for large molecule bioanalysis. As Global Vice-President at Eurofins Bioanalytical Services, he integrated services and supported global business development in biopharma services. He also held the position of Vice-President, Business Development and Marketing at AIT Bioscience, achieving sales and profitability growth by establishing a network of preclinical toxicology service providers. His professional journey and extensive industry knowledge demonstrates his dedication to providing safe and effective medicines to patients in all markets.

## JON ELLENTHAL, PRESIDENT

Jon Ellenthal has spent the last 35 years starting, building and leading early-stage companies that seek to change how an established industry does business. He is currently the President of ApiJect Systems, setting company goals, allocating resources and fostering a community-centric work environment. Previously, Mr Ellenthal co-founded The Upside Travel Company; served as Chief Executive Officer of Walker Digital, a private R&D lab for designing new commercial models; and was Chief Executive Officer of Synapse Group, which grew from an idea to an exit valuation approaching US$1 billion. Mr Ellenthal is also a Founding Patron and former President of TEDMED, the health and medical edition of TED. His career reflects a commitment to innovation and transformative leadership.

**Q What are the supply chain issues impacting glass based sterile fill-finish services during and after covid-19?**

JE Supply chain constraints and failures were so widespread during the covid-19 pandemic that the Merriam-Webster dictionary added the term to its dictionary in 2022. And it's no wonder. The pain was universal across industries, and sterile fill-finish processes for glass vials were severely impacted. We frequently hear stories of wait times of 12–18 months to get on filling lines.

The larger CDMOs have access to the necessary raw materials for sterile fill-finish, but increased demand has consumed their capacity for about the next 12 months. On the other hand, the smaller sterile fill-finish CDMOs have capacity, but are finding it challenging to procure the required raw

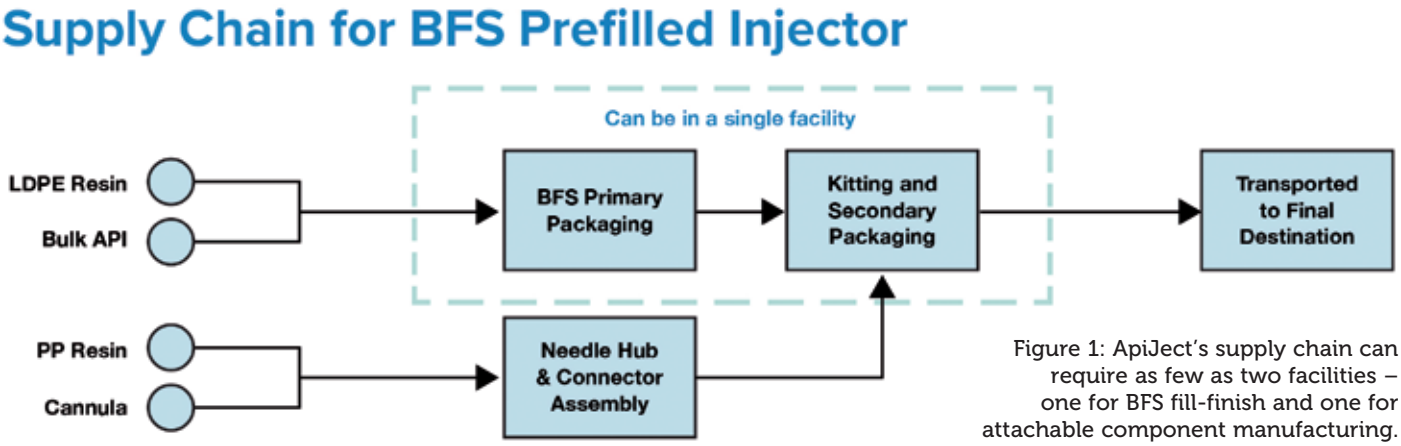


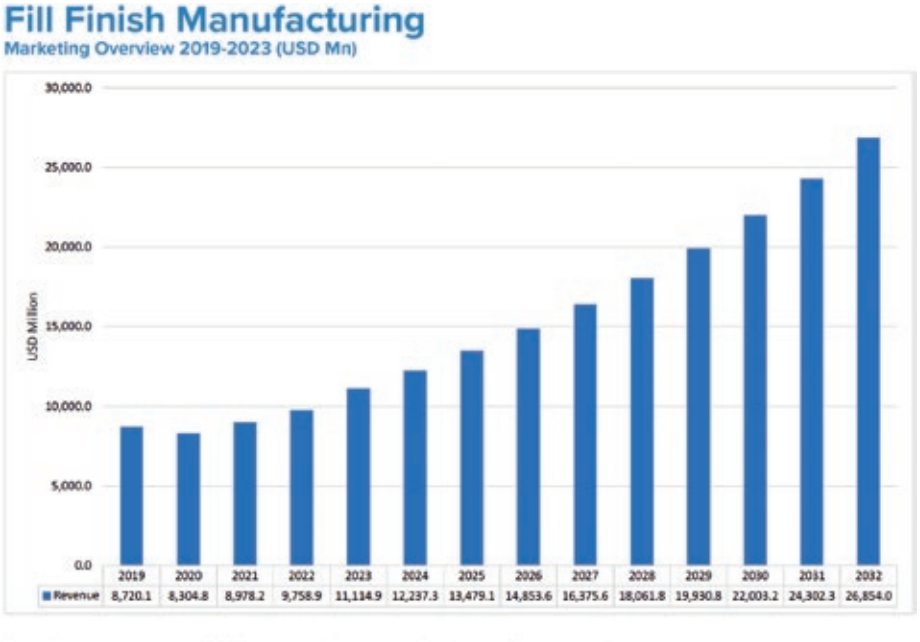

Figure 1: ApiJect's supply chain can require as few as two facilities – one for BFS fill-finish and one for attachable component manufacturing.

materials in a timely manner. In either case, pharma and biotech companies that don't already have contracts in place face long lead times, impacting product launch, limiting response to increased patient demand, or creating delays in clinical trials.

The problem is made worse by the limited surge capacity in the system for manufacturing and fill-finish of glass vials. There simply isn't enough unused capacity at any moment to respond to completely unexpected spikes in demand, such as happened during the pandemic. The reality is that building new capacity is both costly and time-intensive, and few companies are prepared to expand capacity until there is proven, tangible long-term demand.

However, limited surge capacity is only part of the dynamic that limits resilience in sterile fill-finish services. The current process for making and filling glass vials is a complex, multi-dozen step process, using up to seven locations and depending on more than a dozen raw materials. Borosilicate glass, rubber stoppers, aluminium crimps, silicon and other materials need to be sourced from vendors across the globe with each component being critical to complete the process. And, as we saw during the pandemic, international agreements were sometimes overridden in the interests of vaccine nationalism.

Contrast this with ApiJect's compact supply chain (Figure 1), which consists of the three raw materials, all locally sourced and stockpiled, used to make ApiJect's device in a single facility using a highly automated, advanced aseptic Blow-Fill-Seal (BFS) manufacturing process. Glass vial and prefilled syringe sterile filling is a complex process with demanding logistics that are challenging under normal commercial conditions, let alone during global emergencies.




*Source: Company annual reports, SEC filings, Association publications, Polaris Market Research analysis*

Figure 2: Rising demand for affordable drugs and prefilled syringes is driving fill-finish manufacturing growth.

> "Absorbing a giant unexpected spike in demand created dangerous shortfalls in parts of the injectable medicines industry."

**Q What is the outlook for the injectable medicines and vaccines market until 2030, and to what extent has the covid-19 pandemic influenced this market?**

BK The market for medical injections continues to grow at a healthy pace. Experts estimate current global demand to be near 50 billion injections annually, which is expected to grow to 70 billion over the next five years. This translates to a global injectable drug delivery market size that was valued at US$434 billion (£351 billion) in 2022 and is expected to reach $1,040 billion (£841 billion) in 2032 at a CAGR of 10.2% during the forecast period (Figure 2).[1] Prefilled formats are the fastest growing segment (Figure 3). The increasing use of biologics, which are primarily administered through injection; the rising incidence of chronic disease; an ageing population; and the rising urbanisation and medical infrastructure all indicate the market for injectable medicines will continue to expand.

Keeping up with growth can be challenging under the best of conditions, but the covid-19 pandemic created an environment that is far from ideal. Absorbing a giant unexpected spike in demand created dangerous shortfalls in parts of the injectable medicines industry.

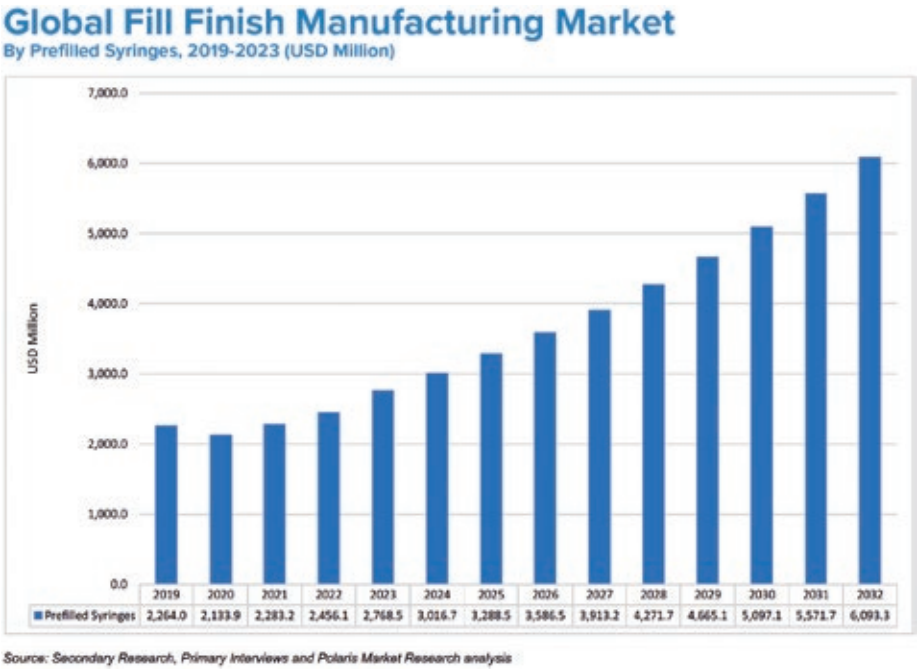



Figure 3: Growth in fill-finish manufacturing is being driven by affordable drug demand and increasing adoption of prefilled syringes.

That means the industry must prepare for organic growth and play catch-up at the same time. Clinical trial enrolment declined by up to 70% between 2020 and 2022 due to covid-19 quarantine protocols and diversion of resources to covid-19 related therapies and vaccines.[2] Since the pandemic ended, clinical trial enrolment has reached pre-pandemic levels, further increasing the demand for sterile injectable fill-finish services.

Looking at the impact of covid-19 on childhood immunisation rates, capacity and materials that would have otherwise gone to childhood vaccination programmes were redirected to meet the demand for covid-19 vaccinations, mostly for adults.[3] This has created a crisis in which an estimated 50 million "zero-dose" children have received no standard vaccinations whatsoever, while another 20 million have received some, but not all, of their needed vaccinations.

**Q What are the market trends, both in terms of technology and patient needs?**

BK Changes in technology and patient needs are creating exciting new opportunities for innovation in drug packaging and delivery. The industry is seeing new primary containment materials that reduce the industry's reliance on complex and energy-intensive glass manufacturing; injection formats that lend themselves to easier self-administration for at-home use; and simplified manufacturing processes using compact supply chains that improve reliability and resilience.

The use of biologics continues to grow, most of which are administered by injection. In fact, 55% of all new drug candidates in the global R&D portfolio are injectables. There are more than 5,000 biopharmaceuticals in the development pipeline alone.[4]

Work is also being done in the area of emergency response to better prepare us for the risks of modern life. The pandemic exposed the need for rapid manufacturing scale-up for vaccine fill-finish. In a world where a pandemic is no longer an abstract idea and advances in synthetic biology increase the risk of a man-made pathogen being released, some in the industry are working on building much more robust emergency capabilities for the next time.

**Q What is ApiJect, what was the impetus to start the company and what are the key problems and challenges you're trying to solve?**

JE ApiJect is a medical technology company with a mission of making injections safe and accessible for everyone worldwide. Our founder is Marc Koska, the inventor of the K1 auto-disable syringe (Star Syringe, London, UK), for which he was awarded an OBE. Approximately 20% of all syringes used during covid-19 were the K1. Originally, Mr Koska was focused on eradicating the scourge of unnecessary death from unsafe injections in medical settings in the developing world, largely from the reuse of syringes. Believe it or not, globally, more people die from syringe reuse and unsafe injection practices each year than from car accidents. That's more than one million people every year.

> "No-one had ever figured out how to attach a needle to a BFS container and turn it into a prefilled injection device."

Mr Koska realised that his auto-disable syringe helped, but he needed something more to eliminate the problem. His search for a single use, prefilled device at an affordable cost for low- and middle-income countries led him to the extraordinary scale and efficiency of BFS manufacturing. BFS uses medical-grade plastic resin instead of glass. Today, more than 50 billion sterile liquid doses every year are packaged in BFS containers. However, no-one had ever figured out how to attach a needle to a BFS container and turn it into a prefilled injection device.

That was the problem that Mr Koska aimed to solve, and his invention is the basis for an entire medical technology platform that can be used to create a range of BFS-based injection devices. Plastic is incredibly flexible, lightweight, durable and has a lower carbon footprint than glass. That is why, back in the early 1970s, glass bottles for intravenous infusion were replaced by plastic. And we have seen the same story across many industries.

While initially developed with global health markets in mind, the underlying technology has a broad range of applications across the industry. Today, ApiJect is focused on commercial pharma, global health and bio-emergency response. In 2019, when the US government signed an agreement with the company to begin development of emergency response capacity, it was before the emergence of covid-19. Months later, when covid-19 emerged, ApiJect intensified its focus with additional support from the US government on creating a device and sterile fill-finish process that could be manufactured at population scale.

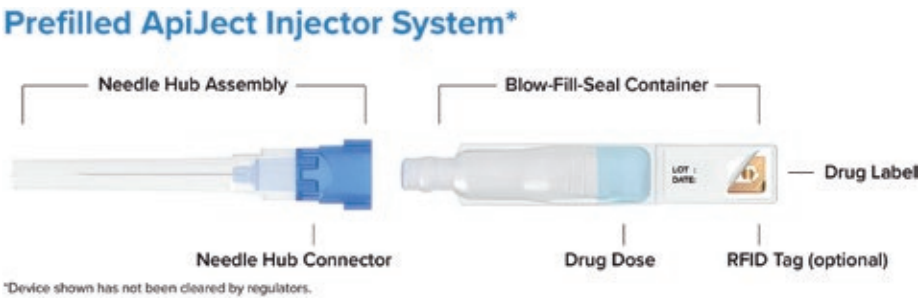



Figure 4: The ApiJect single-dose prefilled injector.

**Q What distinct advantages does the ApiJect platform offer compared with injectable platforms reliant on glass, and how will both sponsor and patients benefit?**

JE The ApiJect platform enables an entirely new category of prefilled injection devices (Figure 4) that can be produced at a cost that makes prefilled devices available to many more injection types and environments. It provides the safety, quality and convenience of a prefilled format at the same or comparable cost per dose to that of a multi-dose vial and disposable, manually-filled syringe – which was previously the market's low-cost leader. The entire process is supported by a simple supply chain that relies on three readily available and widely used raw materials – LDPE plastic and polypropylene resin and cannula – all of which can be stockpiled.

> "The entire process is supported by a simple supply chain that relies on three readily available and widely used raw materials – LDPE plastic and polypropylene resin and cannula – all of which can be stockpiled."

The BFS manufacturing process creates, fills and seals the drug container in one continuous aseptic process that takes seconds and can create as many as 25 containers at a time (Figure 5). A single BFS production line can manufacture up to 15 million prefilled units per month. ApiJect combines the finished container with a proprietary, insulin-style needle hub to create a high-quality, ready-to-use injection device.

The key advantages are a flexible, rapid device design process that can meet many pharmaceutical products' needs; an affordable prefilled format; a simple supply chain; a giant production scale; short lead times; a simple, easy to use design that opens the door to self-administration or use by community health workers in low and middle-income countries; and a lower carbon footprint by avoiding glass and using less plastic than a traditional syringe.

**Q What is ApiJect's strategy to bring forth this new technology platform and what measures are in place to mitigate risk for sponsors in an industry filled with fast followers?**

BK The company is close to filing for regulatory clearance for our first prefilled BFS injection device, which is suitable for sterile liquid doses of 1.0 mL or less and intramuscular administration. Additionally, we have a deep product development pipeline. We aren't aware of another company making the type of investment we are in developing affordable, BFS-based injection devices.

ApiJect operates a concept design studio in London (UK) led by Mr Koska. The studio does a great job of showing the potential for all kinds of problem-solving devices. We also have a technology development centre in Orlando (FL, US) to accelerate R&D in both process and format. We employ a full in-house product development team that takes prototypes through all the design and development steps needed to manufacture at scale. Additionally, Tae-Chang Industrial (Gongju-si, South Korea) is our exclusive partner for needle hub development, and we greatly benefit from its engineering expertise.

Our job is to make to make injectable medicines and vaccines safe and accessible to everyone and, as long as we stay dedicated to this mission, we will deliver

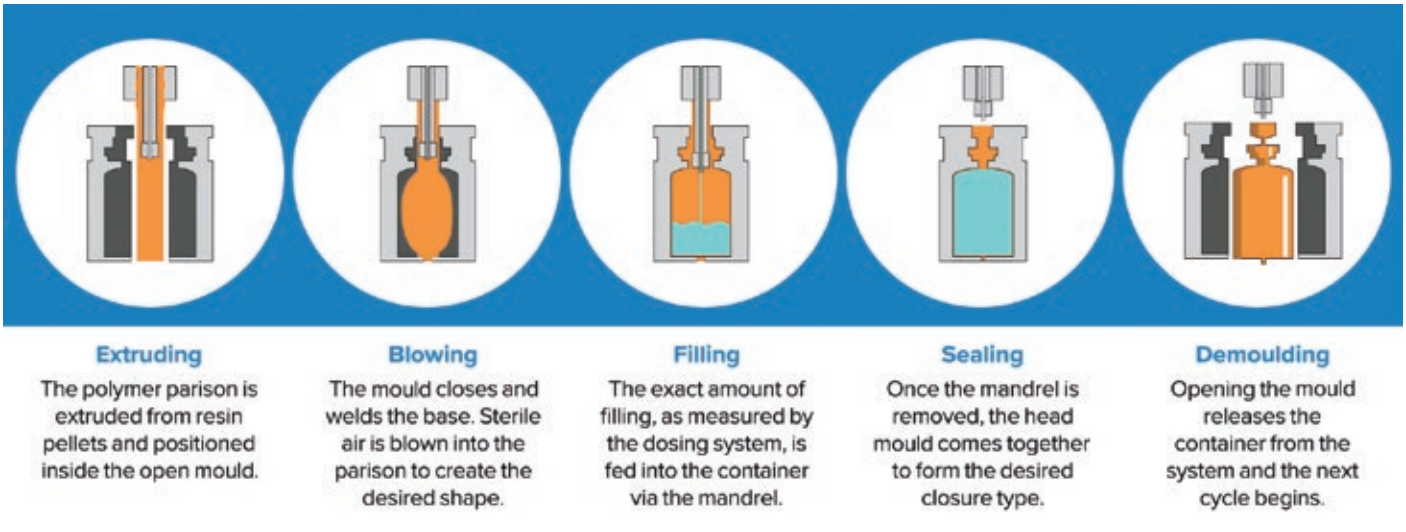



Figure 5: BFS technology creates, fills, seals, inspects and labels a container in a single integrated process that takes 3–7 seconds.

significant value to our sponsors for the long-term. We're looking for sponsors to co-develop a combination product of their vaccine or therapeutic drug using the ApiJect device. There are well-established development and regulatory paths to reach regulatory authority submission within 18 months of starting a programme. We have a low-risk, low-cost plan to make it happen.

## ABOUT THE COMPANY

ApiJect is a global medical technology company that aims to create the future of pharmaceutical injections. The company's mission is to provide products with the superior convenience, quality and safety of prefilled syringes at the manufacturing scale and cost-efficiency of multi-dose formats, regardless of manufacturing volume. ApiJect's platform brings together two globally trusted manufacturing technologies – Blow-Fill-Seal aseptic filling and high-precision plastic injection moulding. The company's supply chain is simple and compact, using widely available raw materials, ensuring reliability and resilience.

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# AUTOINJECTORS FOR LARGE-VOLUME SUBCUTANEOUS DRUG DELIVERY

Here, Ian Thompson, Vice-President Account & Business Development at Ypsomed Delivery Systems, provides a summary of a recent literature review[1] on subcutaneous administration with dose volumes greater than 1.0 mL, which examines how previous studies have addressed the limitations and considerations for designing and developing large-volume autoinjectors.

## EMERGENCE OF LARGE-VOLUME INJECTIONS

Subcutaneous drug delivery has emerged as a viable, and often preferred, alternative to intravenous infusion of biologics, offering patients and healthcare providers new home-based treatment options that improve treatment adherence, reduce the cost of therapy and decrease the burden on healthcare resources. Although subcutaneous delivery options advance patient-centric care, they face numerous development challenges, ranging from pharmacokinetics and efficacy to bioavailability, viscosity, stability and designing delivery devices that are safe and effective for home use.

The availability of user-tested device platforms has broadened access to handheld autoinjectors for biologics in chronic diseases such as rheumatoid arthritis, cardiovascular diseases, obesity, asthma, migraine, psoriasis, rare diseases and immuno-oncology (Table 1). Simple two-step handheld autoinjectors (Figure 1) have become a preferred option for the safe and effective self-administration of single doses and have been widely adopted as the industry standard for subcutaneous drug delivery.

For a long time, the pharma industry has assumed the delivery of 1.0 mL in less than 10–15 seconds to be the feasible upper limit for handheld autoinjectors.

| Product | Manufacturer | Presentation |
|---|---|---|
| AJOVY (Fremanezumab) | Teva Pharma | AI, PFS |
| COSENTYX (Secukinumab) | Novartis Pharma | AI, NSD |
| DUPIXENT (Dupilumab) | Sanofi/Regeneron | AI, NSD |
| LEQVIO (Inclisiran) | Novartis Pharma | PFS |
| PRALUENT (Alirocumab) | Sanofi/Regeneron | AI |
| SILIQ (Brodalumab) | Valeant Pharmaceuticals | PFS |
| TEGSEDI (Inotersen) | Akcea/Ionis | PFS |
| TEZSPIRE (Tezepelumab) | AstraZeneca/Amgen | AI, NSD |
| TAKHZYRO (Lanadelumab) | Takeda Pharma | PFS |
| WAYLIVRA (Volanesorsen) | Akcea/Ionis | PFS |

Table 1: Approved products from the US FDA and EMA using 2.25 mL PFSs (prefilled syringes), NSDs (needle shield devices) and prefilled handheld autoinjectors (AIs).

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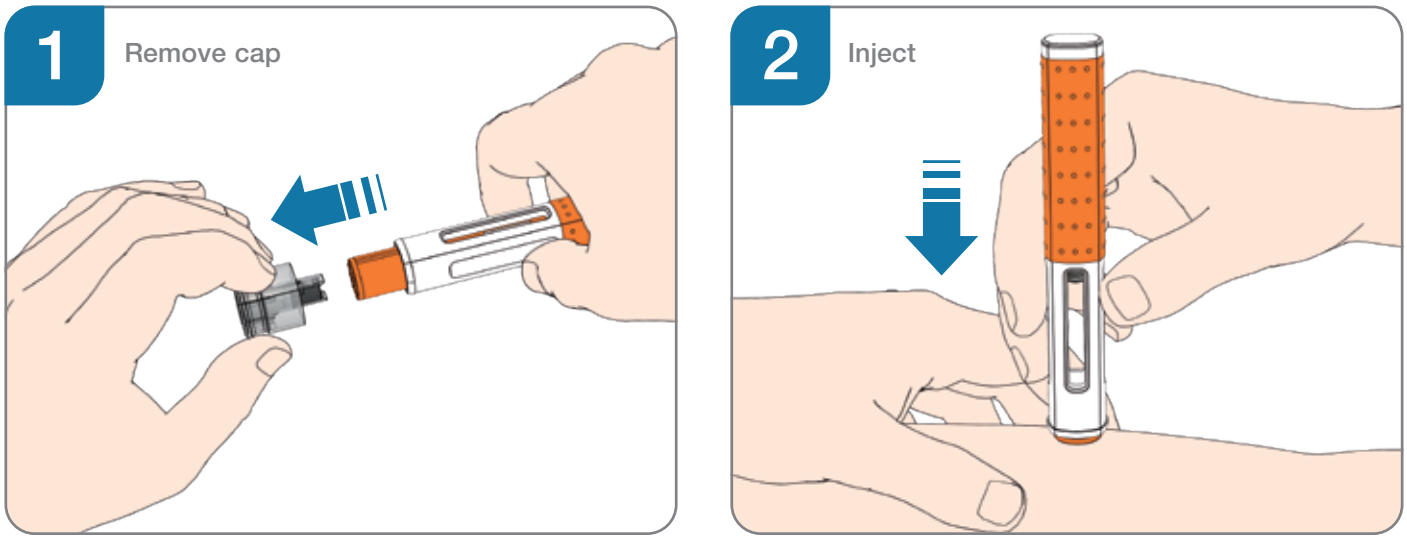


Figure 1: Two-step handling for autoinjectors.

However, since 2020, approvals of products with single-dose volumes up to 2.0 mL have demonstrated the successful delivery of larger volumes.

These recent advances have energised attempts to expand the feasible volume limit for handheld autoinjectors. Higher injection volumes not only reduce the required frequency of injections, prove preferable to patients and enhance therapy adherence, but also help establish subcutaneous dosing for new therapeutic areas and drug modalities that require larger single-dose volumes. As such, the advent of handheld autoinjectors exceeding 2.0 mL capacity has garnered significant attention.

Most recently, Ypsomed has introduced the YpsoMate 5.5 (Figure 2) autoinjector for 5.5 mL prefilled glass syringes triggered by push-on-skin activation based on a new ready-to-use 5.5 mL staked-needle prefilled syringe format. Only further clinical studies will determine what upper limits of injection volumes can be achieved practically with high-volume handheld autoinjectors.

## LITERATURE REVIEW OF LARGE-VOLUME SUBCUTANEOUS INJECTIONS

Ypsomed recently published a review evaluating the literature on subcutaneous administration with dose volumes greater than 1.0 mL.[1] The review concluded that the literature supports the feasibility of delivering single large-dose subcutaneous volumes, providing a foundation for more widespread use of large-volume autoinjectors. It covered 31 studies on large-volume subcutaneous delivery and structured


Figure 2: YpsoMate 5.5 large volume two-step autoinjector taking handheld self-injection beyond volumes of 2.0 mL.

findings based on three aspects critical to developing large-volume autoinjectors:

- **Injection tolerability**, as larger injection volumes, which may intensify injection-site reactions, change the subcutaneous depot location and increase pain
- **Suitability for self-administration**, as manufacturers must ensure safe and effective drug self-administration as autoinjectors help shift the point of care from the hospital to the home
- **Pharmacokinetic equivalence** with existing dosing options tested in multicentre pivotal studies with safety and efficacy end points in subsequent bridging studies.

The review analysed prior research on large-volume subcutaneous injections across therapeutic contexts and device categories, such as manual syringes, syringe pumps, wearable large-volume injectors and handheld autoinjectors. While these studies have advanced understanding of large-volume subcutaneous injections in general, they do not address certain issues specific to high-rate and large-volume injections with handheld devices. Therefore, this review suggests avenues for future work on large-volume autoinjectors within the three aspects previously described (Table 2).

These themes are not only helpful in organising the existing literature but also provide the basis for categorising future research. First, the results of the review call for future studies within the three themes that address questions related to high-rate injections with high-volume autoinjectors. Second, they highlight the need for integrative work that spans the three themes. Advancing topics at the intersection of these themes will promote comprehensive views of the feasibility of large-volume autoinjectors and help to address critical trade-offs in their design and development.

> "The review concluded that the literature supports the feasibility of delivering single large-dose subcutaneous volumes, providing a foundation for more widespread use of large-volume autoinjectors."

| Future Research Topic | Injection Tolerability | Suitability for Self-Administration | Pharmacokinetic Equivalence |
|---|---|---|---|
| **Injection tolerability** | • Effects of device technical attributes (e.g. needle guard geometry) on injection tolerability<br>• User-related force and its relationship with pain and injection-site leakage (e.g. force required to trigger injection)<br>• Relative importance of injection volume and rate versus other drug-specific parameters (e.g. formulation) for injection tolerance<br>• Pain related to large-volume autoinjectors versus other device categories (e.g. syringe pumps and large-volume wearable devices). | • What injection duration keeps pain low while ensuring safe and effective device use (i.e. no premature device removal due to pain). | • Injection tolerability/pain-related end points in pharmacokinetic bridging studies. |
| **Suitability for self-administration** | – | • Optimising user experience and interface for prolonged injection duration (e.g. continuous injection feedback)<br>• User preferences for different autoinjector-based dosing options (e.g. injection duration versus frequency)<br>• User preferences across large-volume device alternatives (e.g. manual syringes, handheld autoinjectors, syringe pumps, large-volume wearable devices). | • Virtual at-home clinical trials to include usability-related end points and self-assessment on patient preference. |
| **Pharmacokinetic equivalence** | – | – | • Impact of formulation advances that enable rapid injection of high-concentration biologics on pharmacokinetic profiles<br>• Validation of robustness of pharmacokinetic profile against changes in injection frequency<br>• Innovative approaches to molecule-independent pharmacokinetic bridging to simplify access to large-volume autoinjectors. |

Table 2: Proposed avenues for future work on large-volume autoinjectors covering injection tolerability, suitability for self-administration and pharmacokinetic equivalence.

### Injection Tolerability

The review advances the key insights that, although higher injection volumes and rates may increase pain, the impact was low on the pain scale and that drug formulation may mask these effects. These findings will inform future work on handheld autoinjectors for high-volume dosing. Effective subcutaneous dosing with handheld autoinjectors will likely hinge on new formulations that allow rapid absorption of highly concentrated biologics in subcutaneous tissue; for example, the co-formulation of the dispersion enhancer hyaluronidase has effectively improved subcutaneous delivery.

Still, new formulations may also affect pain perception. Pain is particularly significant in the case of large-volume autoinjectors, as users may remove the device prematurely from the injection site during prolonged injection times if it is too painful. Future work should therefore study the impact of such formulation advances on pain-related clinical outcomes.

### Suitability for Self-Administration

The review presents strong evidence of the feasibility of self-administrating single large-volume doses. Researchers have demonstrated safe and effective use for handheld autoinjectors up to 2.25 mL, wearable large-volume injectors and large-volume manual syringe and infusion pumps.

"Future work should examine how user preferences for large-volume autoinjector-based dosing options change with differences in dosing regimens."

Studies show that increasing injection volume and time was feasible for handheld autoinjectors.

However, the review shows conflicting views on user preferences for different dosing options. Therefore, future work should examine how user preferences for large-volume autoinjector-based dosing options change with differences in dosing regimens. Previous studies have shown that injection duration and frequency play a significant role in treatment choices and adherence.

The review also calls for future work on user preferences across device categories, such as manual syringes, handheld autoinjectors, wearable large-volume injectors and syringe pumps. As the variety of devices continues to increase, research must provide healthcare professionals and patients with the necessary evidence to make treatment decisions for optimal adherence and therapy outcomes.

### Pharmacokinetic Equivalence

The review found the pharmacokinetic profiles to be stable in response to changes in injection parameters. These findings are in line with the slow absorption rate of therapeutic proteins from the subcutaneous extracellular matrix. However, previous studies have focused mainly on switching from multiple small-volume injections to a single large-volume dose without adjusting the time intervals between injections. Future research should examine the effects of reducing injection frequency using large-volume autoinjectors on pharmacokinetic equivalence. Such a shift in dosing could potentially lead to improved treatment adherence and patient preference.

The review also highlights the potential for future work to evaluate novel approaches to assess the pharmacokinetic equivalence of high-volume autoinjectors compared with low-dose injections that are administered more frequently. Currently, new subcutaneous dosing options are established through dedicated drug-by-drug bridging studies. However, future work could consider molecule-independent approaches to clinical bridging studies to facilitate access to and accelerate the time-to-market of new large-volume handheld autoinjectors.

## A VIBRANT FIELD OF RESEARCH

Autoinjectors have effectively emerged as a viable option for safe and effective subcutaneous self-injection of up to 2.0 mL.

"The study of large-volume subcutaneous drug delivery has developed into a vibrant field of research, where researchers have made significant headway in exploring the upper limits of subcutaneous injection."

Handheld devices for single doses exceeding 2.0 mL would be the next step in this incremental development. Devices under development leverage the well-accepted and proven push-on-skin handling principle, which may allow more seamless healthcare provider and patient onboarding with lower training requirements.

The study of large-volume subcutaneous drug delivery has developed into a vibrant field of research, where researchers have made significant headway in exploring the upper limits of subcutaneous injection. While researchers have yet to convince the industry, healthcare providers, patients and regulatory authorities of the feasibility of large-volume handheld autoinjectors for volumes between 2.0 and 5.0 mL, or even beyond, this review provides a valuable basis for developing these new dosing options. With the increasing demand for safe and effective self-administration options, large-volume autoinjectors could soon gain a foothold in the market.

## COMPATIBILITY WITH EXISTING MANUFACTURING INFRASTRUCTURE

Novel large-volume autoinjectors may be able to leverage the potential of established technologies, manufacturing processes and regulatory pathways. These advantages could enable pharmaceutical companies to reinforce existing capabilities, mitigate risks in device development and accelerate time-to-market. For example, some large-volume autoinjector device platforms are largely compatible with existing infrastructure and manufacturing processes, such as fill-finish, final assembly and packaging.

Finally, large-volume handheld autoinjectors reduce injection duration, which has been shown to increase treatment preference and contribute to the widespread market acceptance of subcutaneous drug delivery. By allowing faster injection of large single-volume doses, large-volume autoinjectors may further boost the acceptance of subcutaneous injections.

While large-volume autoinjectors offer significant potential benefits, these devices also face barriers to adoption. Pharmaceutical manufacturers must establish new primary packaging suitable for high-volume drug delivery and address questions around high-concentration drug formulation, process development, analytical methods and drug stability. For investigational new drugs where time-to-market is critical, pharmaceutical manufacturers are more likely to adopt well-characterised syringes or cartridges for low-volume dosing systems and turn towards innovative large-volume dosing options only later in the lifecycle management process.

## CONCLUSION

Large-volume handheld autoinjectors have the potential to offer new dosing regimens for drugs already injected subcutaneously and to expand subcutaneous injections to new fields, such as oncology. Therefore, these devices may become instrumental in broadening access to innovative medicines as they help shift the point of care from the hospital to the home. In oncology, for example, efforts are underway to establish more flexible care concepts where nurses can perform at-home injections and patients self-report symptoms during therapy.

The high-rate delivery of biologics with large-volume autoinjectors may further improve patient satisfaction, reduce healthcare resource use and increase advantageous effects on the total healthcare and societal costs of subcutaneous drug administration. However, patient preferences for devices and dosing regimens are complex and subject to change. Thus, we anticipate multiple dosing and delivery options to co-exist in the future, providing more flexibility to personalise treatment decisions to patients' diverse needs. The potential benefits to patients and healthcare providers make handheld autoinjectors for the subcutaneous delivery of large-volumes a field worth exploring.

## ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms consist of autoinjectors for prefilled syringes in 1.0 and 2.25 mL formats, disposable pens for 1.0 and 3.5 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 35 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has invested strategically in the development of connected solutions and therapy-agnostic digital device management services.

Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, 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 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

**Ian Thompson** has been with Ypsomed, formerly Disetronic, since 1995 in a number of roles in key account management and business development, working with pharma companies to develop and bring innovative self-injection systems to market. He studied biochemistry and biotechnology in the UK, working initially in commercial roles in fermentation technology. He has worked in medical device companies since moving to Switzerland in 1990. Since 2003, Mr Thompson's main focus has been business development and new product innovation leading to the successful development and launch of a range of new pen injector, autoinjector and patch injector customisable platform products for Ypsomed Delivery Systems.

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# GX INBENEO® – DEVELOPING AN AUTOINJECTOR THAT RESPONDS TO THE CHALLENGES OF BIOLOGICS

Daniel Primavessy, PhD, Project Manager, and Sigrid Saaler-Reinhardt, PhD, Scientific Advisor and Consultant, both at Midas Pharma, and Katarzyna Maksymowicz, Product Manager, and Marie Stockton, Marketing Manager, both at Gerresheimer, discuss how the Gx Inbeneo® autoinjector from Gerresheimer was purpose-designed to provide an effective, easy-to-use solution for the subcutaneous self-administration of sensitive biopharmaceuticals.

Over the past few years, there has been a significant shift towards the development of biologic drugs due to their effectiveness in treating chronic conditions, such as cancer, rheumatoid arthritis and psoriasis. Since 2017, seven out of the top ten drugs on the market by sales are biopharmaceuticals.[1] However, biologic drugs present a number of challenges to effective delivery, including the potential for elevated viscosity with increased concentration, larger volumes, and the sensitive nature of the biomolecules.

In parallel, there is a growing preference for subcutaneous self-administration in an at-home setting within the sector, as it facilitates patient independence and a decrease in cost for the healthcare system. To support effective delivery of biologic drugs, a device therefore needs to overcome the challenges presented by the drug formulation and, at the same time, facilitate autonomous patient usage.

## GOING BEYOND THE AUTOINJECTOR STATUS QUO

In the past, the most common delivery method for biologic drugs has been administration in a clinical setting by a healthcare professional, either intravenously or subcutaneously via a prefilled syringe (PFS).[2] Transferring to a home-care setting has led to the development of autoinjectors that offer advantages such as easier administration and needlestick injury prevention. The standard approach to autoinjector design for biologics is to encapsulate the primary container of a staked-needle PFS within a device, adding a spring mechanism to apply force to the plunger. Such autoinjectors employ a compressed spring held in place with a locking mechanism that must be reliably released at the moment of injection. The dual role as "force barrier" and release mechanism is a challenge for many autoinjectors when the spring force is increased to deliver elevated volumes, viscosities or both. This has resulted in several incidences of misfiring over the past two decades.[3]

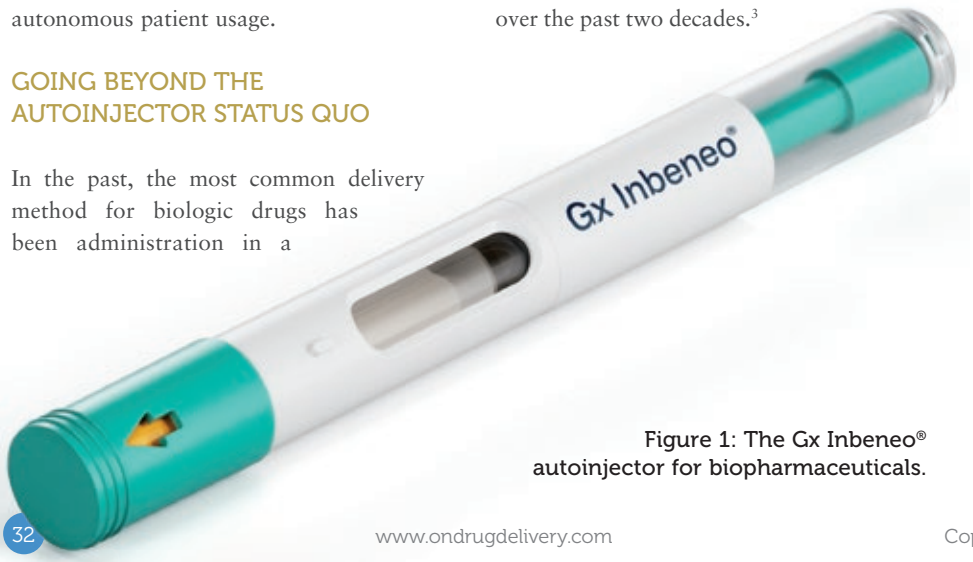


Figure 1: The Gx Inbeneo® autoinjector for biopharmaceuticals.

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To overcome this challenge, Midas Pharma and Gerresheimer chose a cartridge-based, pre-pressurised design for the Gx Inbeneo® autoinjector (Figure 1). The autoinjector is based on the NIS autoinjector prototype.[4] The unique, patented design employs a robust prefilled glass cartridge to retain the spring force, thus making the primary packaging the force barrier. No additional spring locking mechanism is required, which eliminates the associated risk of failure. This innovation enables the use of springs strong enough to inject drug products with viscosities up to 100 cP at volumes of up to 3 mL (based on calculations).

Rather than using a staked-in needle, as with a PFS, the Gx Inbeneo® design concept uses a double-ended needle that is separated from the primary container. The needle is held separately in a needle carriage protected by the device's needle safety shield (Figure 2, State 1). To begin injection, the patient presses the device against the skin, the needle safety shield moves backwards and the front of the needle pierces the skin (Figure 2, State 2). Subsequently the needle carriage moves backwards, and the other end of the needle pierces the septum of the cartridge. The fluid pathway is then established, and the drug is automatically and smoothly injected (Figure 2, State 3). The separation of the needle from the primary packaging until administration and the double-ended design additionally address other challenges of biologic drugs, as detailed in subsequent sections of this article.

## PROOF OF CONCEPT FOR THE CARTRIDGE-BASED DESIGN

The concept of using the prefilled cartridge as the force barrier was successfully validated during extensive testing by Midas Pharma and Gerresheimer. ISO-standard cartridges from Gerresheimer and two other suppliers were tested along with septa and plunger stoppers from several different manufacturers. The results demonstrated that the device's break-loose and glide forces were within acceptable ranges. At maximum pressure, the septa did not rupture when pierced, and piercing forces were also within acceptable ranges. Cartridge septa showed slight bulging for the first 14 days, after which they became stable. The Type I non-hardened pharma-grade glass of the cartridges remained stable at pressures of magnitudes above those employed in the Gx Inbeneo®.

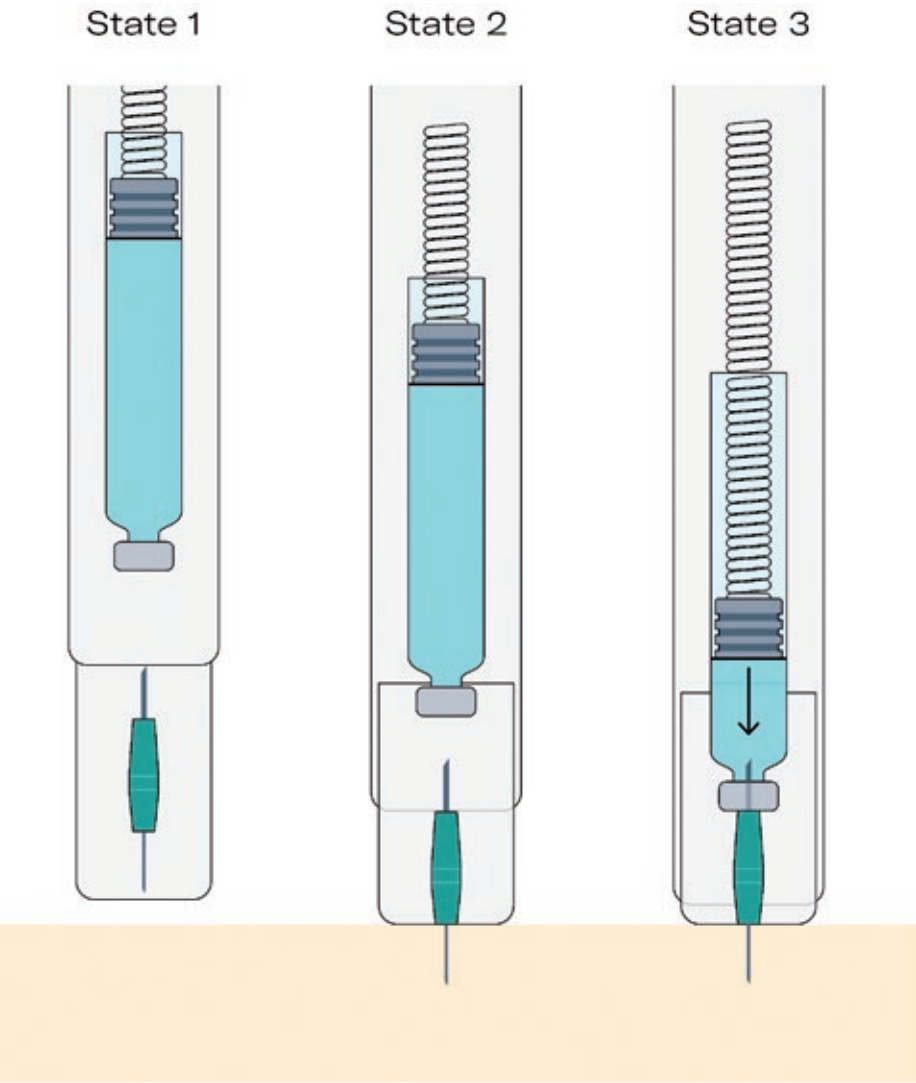


Figure 2: An overview of the injection mechanism of the Gx Inbeneo®, showing how the fluid path is established in a single user step.

In a second set of tests, cartridges were filled with a commercially available adalimumab formulation and stored under pressure for six months. The drug formulation was expelled through the fluid pathway and then subsequently tested with size exclusion chromatography and gel electrophoresis. No signs of aggregation or protein denaturation were found.

## ADDRESSING THE SENSITIVE NATURE OF BIOLOGIC DRUGS

Sensitive biotherapeutics, such as monoclonal antibodies are vulnerable to aggregation, which can result in a loss of biologic functionality. This can be caused by interaction with substances such as tungsten, glue residues, silicone oil droplets or a gas-liquid interface present as gas bubbles. Three design features of the Gx Inbeneo® autoinjector respond to the risk of aggregation – the separation of the needle from the primary container prior to activation, the use of cartridges with baked-on siliconisation and the pre-pressurised system.

> "Three design features of the Gx Inbeneo® autoinjector respond to the risk of aggregation – the separation of the needle from the primary container prior to activation, the use of cartridges with baked-on siliconisation and the pre-pressurised system."

### Separated Needle

Unlike with a staked-in needle PFS, there is no contact between the drug product and needle during storage in the Gx Inbeneo® as the needle is separated from the primary packaging. Therefore, the possibility of the drug product entering the needle and causing clogging is eliminated. Furthermore, if there were to be glue or tungsten residues, they could not negatively affect the drug product.[5–7]

### Baked-On Siliconisation

The risk of protein aggregation caused by silicone oil droplets migrating into a sensitive biologic drug is significantly reduced by using a baked-on siliconisation process.[8] This process is generally challenging with a staked-in needle PFS, due to potential impact of the required high-temperature on the staked-in needle bonding; however, it can easily be applied to cartridges, such as those used in the Gx Inbeneo®.

### Reduced Gas Bubble Presence

An inherent property of the Gx Inbeneo® technology is that any gas bubbles present in the liquid within the cartridge are reduced or dissolved due to the applied pressure, according to Henry's Law. This minimises gas-liquid interface in the primary container, which limits the potential for protein aggregation in drug products with sensitive biotherapeutics.[9]

## STERILISED AND READY-TO-USE

Considering the sensitive nature of biologics is crucial when developing a sterilisation approach for a drug delivery device. To address this topic, Gerresheimer offers two sterilisation options for the Gx Inbeneo® that are compatible with biologic drugs – terminal gas sterilisation with nitrogen dioxide ($NO_2$) and aseptic assembly. For sensitive biologics, terminal gas sterilisation with $NO_2$ is superior to the commonly used process with ethylene oxide, as $NO_2$ sterilisation can be carried out at lower temperatures and $NO_2$ ingress has been shown to be negligible.[10] An alternative strategy is aseptic assembly of the device in a cleanroom environment, which avoids the need for terminal gas sterilisation entirely. Regardless of the sterilisation method, the autoinjector is delivered blister-packed, ensuring that it maintains sterility for its entire shelf life and is ready to use as soon as it is needed.

## BALANCING INJECTION TIME AND PATIENT EXPERIENCE

Other than employing a spring with a higher force, there are two approaches for administering higher viscosities and larger volumes of a drug – increasing injection time or employing a thicker needle. Both these options come with compromises. A thicker needle is less comfortable for the patient, which negatively impacts the patient experience. Extending the injection time can make it difficult for some patients to hold the autoinjector stable for the full duration of the dose, which creates a risk that the full dose is not delivered, decreasing effectiveness of the treatment.

Rather than accept these compromises, the development team at Gerresheimer and Midas Pharma came up with a solution – a double-ended needle with different thicknesses at each end. The thicker end of the needle pierces the septum of the primary container while the end of the needle that pierces the patient's skin is thinner. This innovation mitigates the potential for discomfort caused by a thicker needle piercing the patient, while also enabling higher viscosities to be delivered in less time than with a standard needle.

## PROVEN USER BENEFITS

As well as being able to deliver biologic drug formulations reliably, the development team at Gerresheimer and Midas Pharma also ensured that the Gx Inbeneo® autoinjector is safe and simple to use, thereby supporting effective delivery of therapy.

> "For sensitive biologics, terminal gas sterilisation with $NO_2$ is superior to the commonly used process with ethylene oxide, as $NO_2$ sterilisation can be carried out at lower temperatures and $NO_2$ ingress has been shown to be negligible."

> "As well as being able to deliver biologic drug formulations reliably, the development team at Gerresheimer and Midas Pharma also ensured that the Gx Inbeneo® autoinjector is safe and simple to use, thereby supporting effective delivery of therapy."

As previously described, Gx Inbeneo® has significant advantages in terms of limiting potential discomfort and inconvenience when self-administering biologics. The design of the autoinjector also reduces the number of user steps and their complexity, which decreases the potential for use error. For example, there is no need for the patient to attach the needle themselves, as is the case with some other cartridge-based autoinjectors. Additionally, the pre-pressurised system allows for straightforward push-on-skin activation, with no need to press a button.

Further optimisations were made to the design to support the patient during drug administration. Most autoinjectors currently on the market include a viewing window, located in the middle of the device, to inspect the medicinal product and visually track injection progress. When designing the Gx Inbeneo®, it was observed that many patients need to grasp the device with their whole hand – often due to dexterity problems caused by their disease, thereby covering the central window. To overcome this issue, the Gx Inbeneo® has been equipped with a transparent top casing, through which the patient can view a coloured indicator move downwards as the drug is injected.

All of the features relevant for patient administration were tested during a formative usability study. The results of the study were highly positive – the feature to visually track the injection progress via the transparent top casing was very well received and participants were observed to position the device correctly against the body for the full injection time. As a further indication of the end of dose, Gx Inbeneo® makes an audible click at end of dose.

## READY FOR A SPECIFIC BIOLOGIC DRUG

With biopharmaceuticals becoming increasingly prevalent on the market, pharmaceutical companies need to select a device that effectively and reliably delivers their sensitive drugs. They are also looking to provide therapeutic support to patients as quickly as possible, making time-to-market another important consideration. With the Gx Inbeneo® autoinjector platform, Gerresheimer and Midas Pharma have drawn on their experience and gathered patient feedback to ensure these requirements have fully informed the device design.

The modular platform concept of the Gx Inbeneo® means that it can be quickly customised to a wide range of drug formulations. Patient needle gauges of 25G, 27G or 29G can be combined with ISO standard cartridges from Gerresheimer or other suppliers with up to a 3 mL fill volume. Spring forces can also be adjusted, allowing for an optimal balance of patient experience and injection time, even with highly viscous biologics (Figure 3). The modular design concept and manufacturing readiness reduces the timeframe for clinical trial and market launch.

What is more, Gerresheimer is a full-service provider with many years of experience in primary packaging, device development, manufacturing and regulatory submission. All of these factors enable Midas Pharma, Gerresheimer and their pharmaceutical customers to reduce time-to-market for the combination product. Thus, new drug therapies can be provided to patients as quickly as possible to help them manage their health conditions and maintain their quality of life.

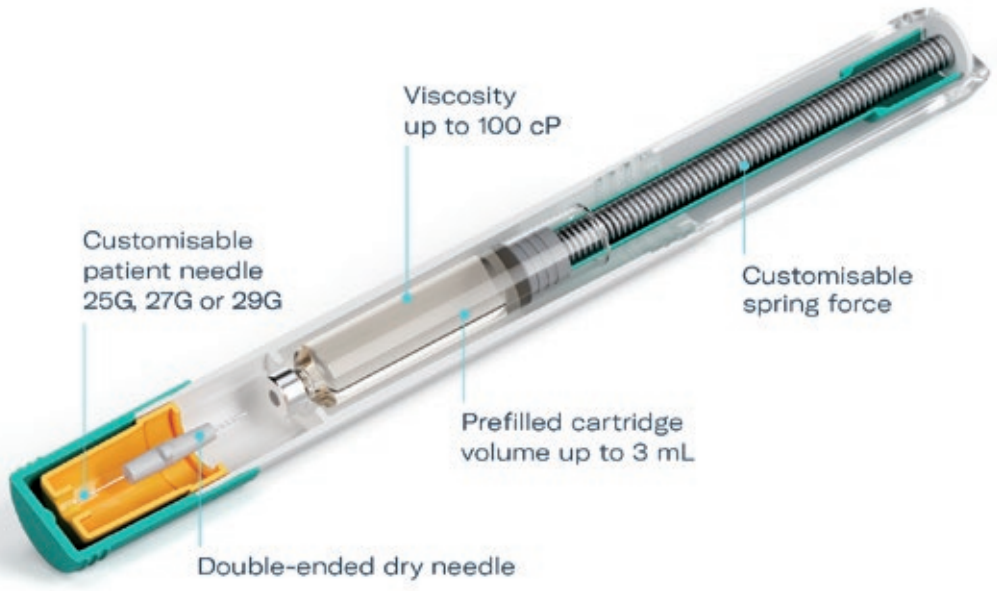


Figure 3: Gx Inbeneo® modular platform concept.

## ABOUT THE COMPANIES

**Midas Pharma** is a mid-sized pharmaceutical company that offers products, services and expertise along the entire pharmaceutical value chain, from starting materials and APIs to the development of market-ready finished products and medical devices, as well as being marketing authorisation holder for medicaments. With more than 280 employees and 10 locations across all major pharmaceutical markets worldwide, Midas Pharma has excellent local know-how, local contacts and well-established networks in different pharmaceutical sectors.

**Gerresheimer** is a global partner for pharmaceutics, biotech, healthcare and cosmetics, with a very broad product range of packaging solutions and drug delivery systems. The company is an innovative solution provider from concept to delivery of the end product. Gerresheimer achieves its ambitious goals through a high level of innovative strength, industrial competence and concentration on quality and customer focus. In developing innovative and sustainable solutions, Gerresheimer relies on a comprehensive international network, with numerous innovation and production centres in Europe, the US and Asia. Gerresheimer operates close to its customers worldwide, with around 11,000 employees, and generated annual revenues in 2022 of €1.82 billion (£1.57 billion). With its products and solutions, Gerresheimer plays an essential role in people's health and wellbeing.

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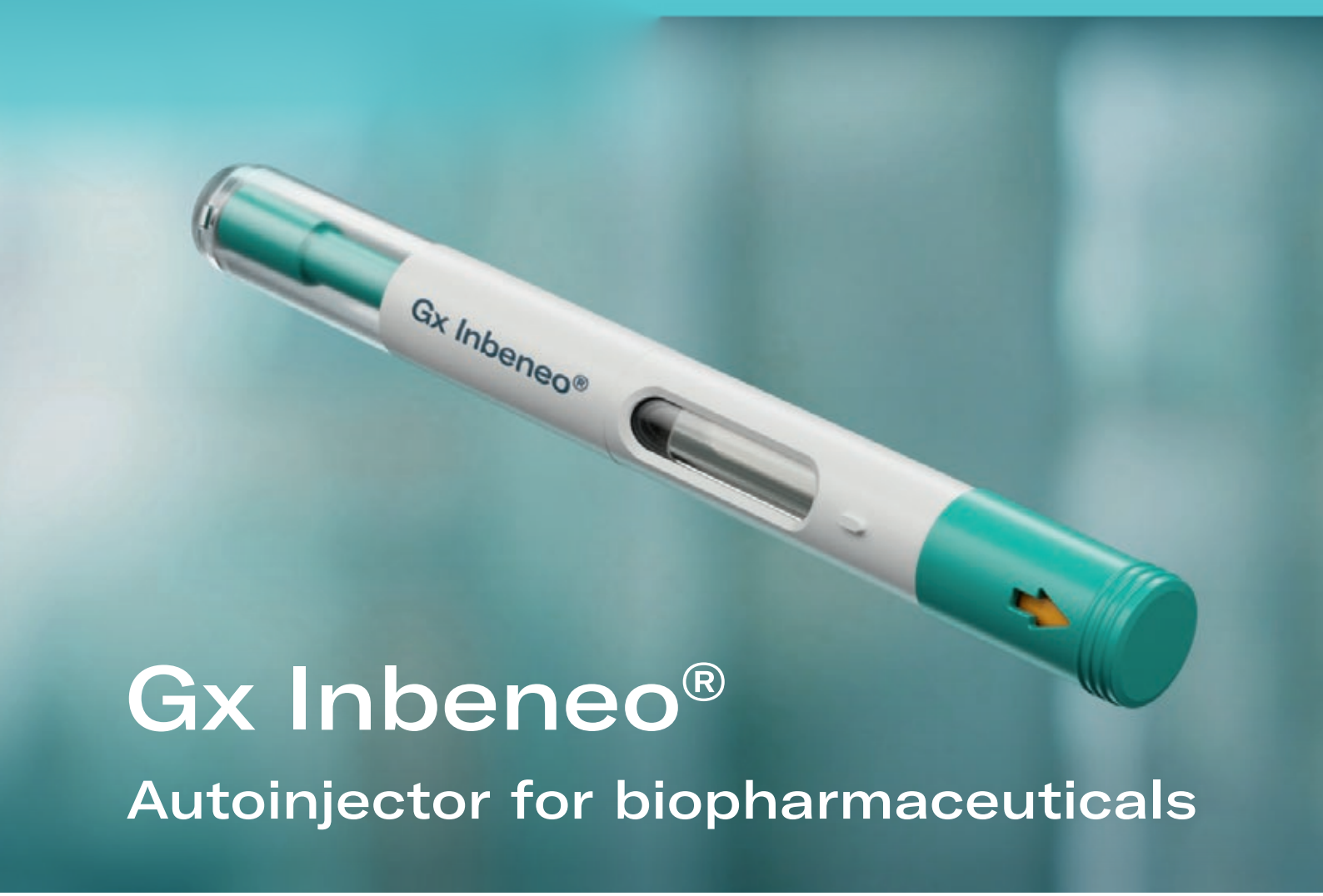
## ABOUT THE AUTHORS

**Daniel Primavessy**, PhD, studied Bioinformatics and Biotechnology at Saarland University (Germany) and completed his PhD from 2011 to 2017 at Philipps-University (Marburg, Germany) on peptide encapsulation into polymeric particulate systems. He worked for two years as a post doctoral researcher and for two years in a contract research organisation. In 2021, he joined Midas Pharma. As Project Manager and Scientist, Dr Primavessy's work focuses on the evaluation of pharmaceutical innovation projects in device and formulation technology and the development of pharmaceutical products.

**Sigrid Saaler-Reinhardt**, PhD, studied Biochemistry at the Free University of Berlin (Germany) and received her PhD in Cell Biology and Oncology and became Professor of Molecular Genetics at the Johannes Gutenberg-University of Mainz (Germany). Prof Saaler-Reinhardt has more than 30 years of experience in academic research and the pharmaceutical industry, most of it at Midas Pharma, with responsibilities for R&D and intellectual property management, and subsequently for custom synthesis, biotechnology and drug-device combination products. She is founder and consultant of her own company, EDUMO Consulting.

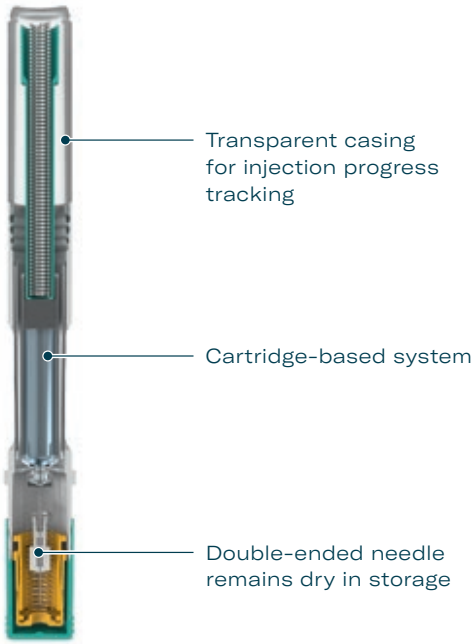
**Katarzyna Maksymowicz** is a Product Manager at Gerresheimer's Advanced Technologies division, where she drives the development of the Gx Inbeneo® autoinjector platform. As a pharmacist (MPharm), she gained invaluable insights into patient experience with drug delivery devices, which she then augmented with a Pharma MBA and product management experience. She is passionate about applying her skills and knowledge to develop innovative products that meet the needs of patients, pharma customers and healthcare systems.

**Marie Stockton** is Marketing Manager in Gerresheimer's Advanced Technologies division. With extensive experience in the medical device and scientific instrumentation fields, she leads global marketing strategy, planning and execution for the division.




# Gx Inbeneo®

## Autoinjector for biopharmaceuticals




### Patient-friendly design

- Push-on-skin activation for ease of use
- Double-ended needle shortens injection time

### Created for biologic drugs

- Dry needle prevents clogging in storage
- Accommodates cartridges with baked-on siliconization

### Quick customization

- Platform concept reduces time-to-market
- Volumes up to 3 mL and viscosity up to 100 cP

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# DEVICE INTERCHANGEABILITY STUDY OF THREE-STEP AND TWO-STEP AUTOINJECTORS

**In this article, Alex Fong, Head of Insight at Owen Mumford, discusses the results of a study assessing patients' ability to switch from a three-step autoinjector to a two-step device.**

Biological medicines are currently the largest cost in the medicines budget of the UK NHS, and the largest area of cost growth.[1] By making more biosimilar alternatives available, the service expects to save up to £300 million each year,[2] while also enabling wider patient access to life-saving and life-enhancing treatments. In the US, one study estimates savings of US$38.4 billion (£30.5 billion) from 2021 to 2025, compared with 2020, as the wider availability of biosimilar products creates a significantly more competitive market.[3]

With an increasing number of patents for biological medicines now expiring, we are closer to seeing whether these estimates are accurate. Adalimumab, initially only available under the brand name Humira® (Abbvie, US), was the world's top grossing drug prior to covid-19 vaccines.[4] Humira's patent expired in Europe in 2018. In the UK, there are now five adalimumab biosimilars available, under different brand names.[5] By enabling access to adalimumab biosimilars, the NHS saved £400 million in the three years following expiry – equivalent to almost a full year's supply of Humira.[6]

In the US, Humira lost market exclusivity more recently, in January 2023. The first biosimilar launched in the same month, and a total of eight have now been approved.[7] Only one of these, Cyltezo® (Boehringer Ingelheim, Germany), has interchangeability status, although others have applied to the US FDA for designation.[8] As more biosimilars enter an increasingly competitive market, more companies are aiming for interchangeability status to gain commercial advantage.

## PROTECTING THE PATIENT EXPERIENCE

Cost is not the only consideration when switching from biologics to biosimilars; the patient experience may also be affected by any change in drug formulation or the drug delivery device provided. As one study notes, "there is scarce information on the patient's attitude toward such switching, especially studies comparing the injection devices".[9] To safely identify the most suitable device for their biosimilar product, pharmaceutical companies should have access to data from human factors testing and other data attesting to device ease of use. This data would then also support regulatory applications for interchangeability determination.[10]

In the US, an interchangeable biosimilar drug may be substituted at the pharmacy for the reference product without the intervention of the prescriber. Not all biosimilars, however, have interchangeable status. Companies must apply to the FDA for their product to be approved as an interchangeable biosimilar, providing adequate information to support an interchangeability determination.

In contrast, biosimilar medicines approved in the EU are already deemed interchangeable with their reference medicine or with an equivalent biosimilar.[11] The EMA specifies that, "Interchangeability in this context means that the reference medicine can be replaced by a biosimilar without a patient experiencing any changes in the clinical effect".[11] Unlike in the US, "Any

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decision on switching should involve the prescriber in consultation with the patient".[12] However, individual member states manage decisions regarding "substitution" at pharmacy level, where substitution means to dispense one medicine instead of another without consulting the prescriber.[13]

When it comes to the device component, the FDA stipulates that any regulatory application should provide evidence that the impact of switching between delivery devices has been assessed, stating, "Data and information supporting the appropriate use and performance testing of the delivery device constituent part of the proposed interchangeable product should be submitted."[14] For manufacturers of biosimilar products, it is therefore important to de-couple the device element from any biosimilar interchangeability clinical study, to ensure thorough risk assessment.

In Europe, guidance from the EMA separates the drug from the delivery device, allowing for differences in the administration device, as long as there is no impact on safety and efficacy. Clinical switch studies for biosimilar drugs are not required in the EU, but prescribers and policymakers may assume that they are necessary and hesitate to make decisions without clinical data. This may be reflected in attitudes to device switching, especially as there is a lack of extensive guidance and existing evidence on this aspect of interchangeability.

| General Information | DAI® | Aidaptus® |
|---|---|---|
| **Device Type** | Single-Use Disposable Autoinjector | Single-Use Disposable Autoinjector |
| **Activation Type** | Combined Pressure and Button | Pressure |
| **Needle Insertion** | Automatic | Automatic |
| **Needle Removal** | Manual | Manual |
| **Geometry** | | |
| **Total Device Length (pre use)** | 153 mm | 162 mm |
| **Evidence Device Diameter** | 18 mm | 18 mm |
| **Weight (incl fill volume)** | 34.4 g | 35.3 g |
| **Activation** | | |
| **Activation Force** | 8.6 N (button) | 15 N (shroud) |
| **User Hold Force** | 2.8 N | 4 N |
| **End Of Dose Indication** | | |
| **Visible** | Yes | Yes |
| **Audible** | Yes | Yes |
| **Tactile** | No | No |
| **Dication** | | |
| **Delivered time** | 1.8 s | 1.8 s |
| **Delivered dose*** | 0.49 mL | 0.49 mL |
| **Exposed needle length** | 5.3 mm | 6.5 mm |

Table 1: Technical data comparison between DAI and Aidaptus.

## A DEVICE SWITCHING STUDY

Recognising the need for a greater evidence base and to support pharmaceutical companies in de-risking their choice of device, Owen Mumford commissioned an independent study assessing patients' ability to switch between two different autoinjectors. Biologics suitable for subcutaneous administration are now routinely delivered using autoinjector devices, in large part because they offer convenience and allow patients to self administer medication in their own homes without a healthcare professional. The study aimed to determine whether regular users of a market-leading three-step autoinjector can switch to a two-step autoinjector and perform the injections successfully at first and second time of use.

The three-step autoinjector used in the study was SHL Medical's (Zug, Switzerland) DAI®, a button-activated device that was one of the first modern autoinjectors to be commercialised for home injection.[15] Study participants switched between the DAI and Aidaptus®, a two-step autoinjector manufactured by Owen Mumford Pharmaceutical Services.[16] With two-step devices such as Aidaptus, it is not necessary to push a button as injection is activated through pressure, i.e. when the device is pressed onto the injection site. The key features of the two autoinjectors are summarised in Table 1.

> "The study aimed to determine whether regular users of a market-leading three-step autoinjector can switch to a two-step autoinjector and perform the injections successfully at first and second time of use."

## STUDY PARTICIPANTS

An independent research agency conducted the study. A total of 52 tests were conducted, with 26 participants in the UK and 26 participants in the US. All participants had been using the DAI device for at least three months.

Figure 1 (next page) shows the breakdown of participants by gender and age. The average age was 51 years. In the research conducted in September and October 2021 in the UK, 18 women and eight men, aged 16–65 years, participated. In the research conducted in April 2022 in the US, 16 women and 10 men, aged 41–75 years, participated.

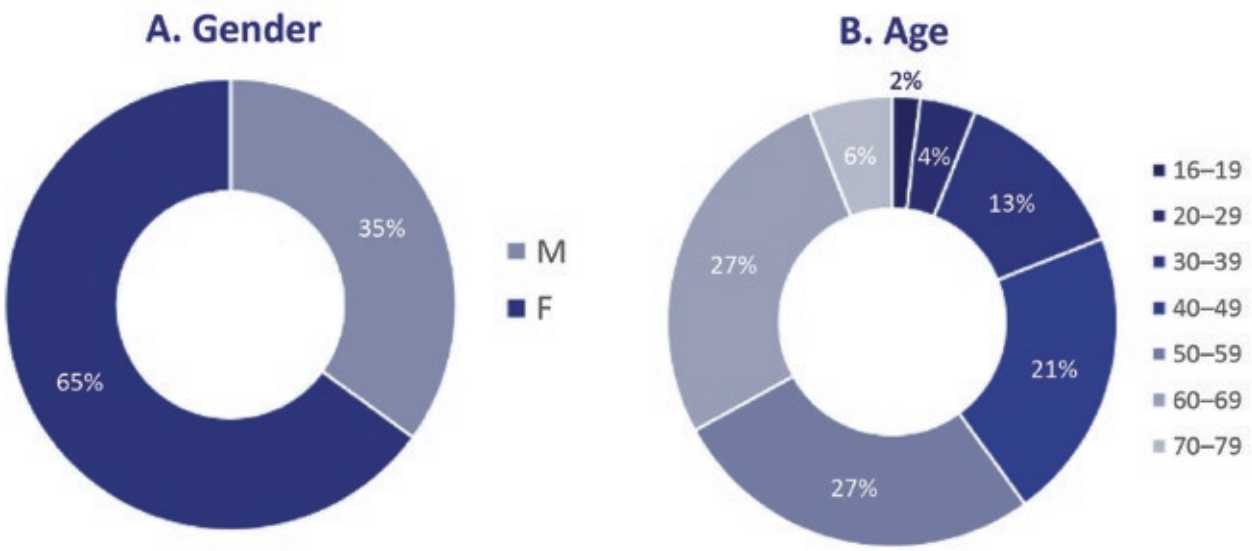


Figure 1: Breakdown of participants based on (A) gender and (B) age.

## METHODOLOGY

The study followed the FDA guidance document published in May 2019: "Considerations in demonstrating interchangeability with a reference product".[17] Participants were asked to complete four injections, alternating between DAI and Aidaptus autoinjectors (Figure 2). This study was not intended to be a direct comparison between the DAI and Aidaptus autoinjectors, as all participants were already familiar with the DAI. Rather, it tested participants' ability to learn how to use the new Aidaptus autoinjector, to switch from a familiar to a new device, and to successfully complete injections with a new autoinjector.

Each participant was provided with the following:

- Two Aidaptus devices in individual boxes (i.e. one device per box) containing instructions for use (IFU): 0.5 mL sterile water for injection in a prefilled syringe
- Two DAI provided in individual boxes (i.e. one device per box) containing IFU: 0.5 mL drug volume in a prefilled syringe
- One injection pad
- Two sharps bins (one on the table for the devices, one on the floor for the injection pad)
- Gloves (the option of wearing gloves was given due to covid-19 concerns).

This was the first time participants had been presented with Aidaptus and they did not receive training, a demonstration or coaching. Participants were provided with the devices in unopened original boxes (containing their respective IFUs) and asked to administer injections into an injection pad placed on a table. Facilitators were briefed to intervene only in instances where there was a risk to the participant.

The primary measure was injection success. Injections were considered successful if the participant correctly delivered the injection into the pad, as described by the IFU, and allowed the contents of the autoinjector to be fully delivered into the injection pad before removing it. Aside from injection success, other measures were calculated by analysing videos of participants throughout the test. Ease of use was calculated by watching how participants handled and examined the device, as well as the time taken for injections. To calculate time taken, an injection was considered to have begun once the participant placed the injector on the injection pad and initiated the injection process, and to have ended after the participant removed the injection device from the injection pad.

> "Ease of use was calculated by watching how participants handled and examined the device, as well as the time taken for injections."

## RESULTS: EASE OF SWITCHING

The user tests had a 100% success rate for both devices, meaning that each injection in the sequence was delivered and completed successfully.

### Injection Time

Although participants were familiar with the three-step autoinjector, DAI, they took more time for the initial injection than

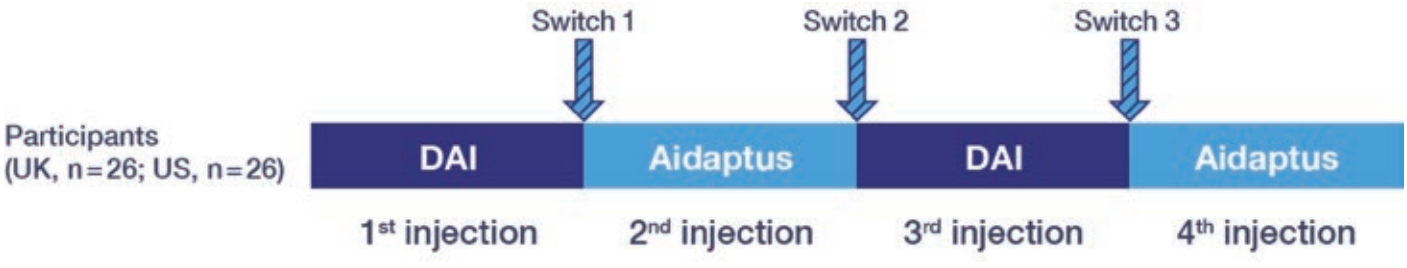


Figure 2: Study design – alternating autoinjection device.

with the two-step autoinjector (Figure 3). On average, the first Aidaptus injection times were 1.2 seconds faster than the first DAI injection times. For the second injection, mean times of both the three-step (DAI) and the two-step (Aidaptus) autoinjectors were similar, at 8.8 and 7.9 seconds, respectively.

### Further Observations

- **Geography:** US participants were, on average, 4.6 seconds faster than UK participants in delivering the first Aidaptus injections; however, times were similar for the second injections.
- **Sex:** the average time taken for injections for women across Aidaptus injections was 30% longer than for men (Figure 4). There was only a very small difference (one second) between the total time taken across both DAI injections.
- **Handedness:** for left-handed participants, the time taken to deliver both Aidaptus injections (27.5 seconds) was similar to the time taken to deliver both DAI injections (28.4 seconds).
- **Age:** older participants (over 40 years old) took marginally longer to deliver their injections for both devices but still completed injection successfully.

### IFU and Device Examination

Since participants did not receive training or a product demonstration, but did have access to an IFU, the study observed how they approached the injection process.

> "Since participants did not receive training or a product demonstration, but did have access to an IFU, the study observed how they approached the injection process."

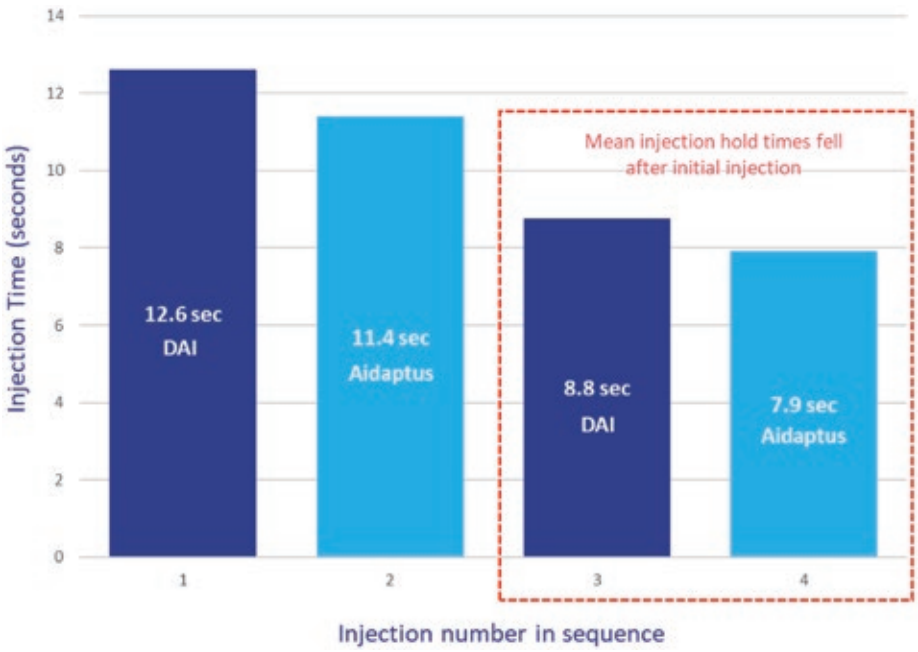


Figure 3: Mean time taken for each injection with DAI and Aidaptus (n = 52).

A total of 23% of participants were labelled as "cautious", as they examined the device and/or IFU before every injection. The study environment and the fact they were being observed may explain why participants took the time to examine both the familiar and new device. Across all injections, cautious participants spent longer examining the device and delivered their second injections more quickly than their first injections. Meanwhile, "impulsive" participants (8%) delivered their second injections faster than non-impulsive participants and in the same average time across the two devices. Impulsive participants were those who never examined the device or IFU across all four injections.

### Further Observations

- **Ease of use:** most participants needed to examine the device only once to deliver injections successfully.
- **Geography:** a higher percentage of US participants (92%) than UK participants (85%) examined the IFU and device before their first Aidaptus injection. Before the second Aidaptus injection, 73% of UK participants examined neither the device nor IFU, compared with 54% in the US.
- **Sex:** for the first injections using the DAI and Aidaptus, more men examined the IFU and/or device than women. Before the second injections, a greater proportion of women examined the IFU and/or device than men. However, gender did not impact the success of injections or the ability to switch between the two devices.
- **Age:** the percentage of participants who looked at the IFU and/or device prior to injecting across all four injections increased with age.

## SUMMARY

The results of this study clearly showed that all participants were able to switch successfully from the three-step autoinjector, DAI, to the two-step autoinjector, Aidaptus, with no impact on injection success. Participants used the two devices in a

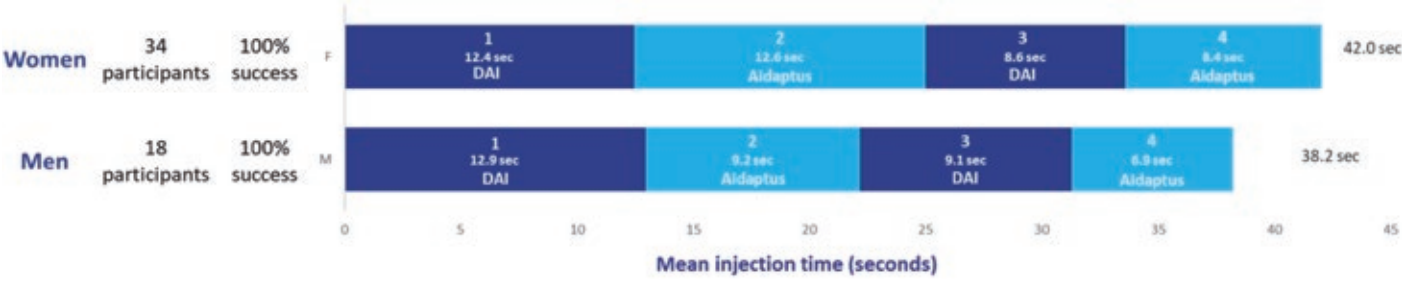


Figure 4: Mean time taken to deliver injections for women and men (n = 52).

similar way, with injection times falling after each injection, indicating familiarisation. When first given Aidaptus, most participants examined the device or looked at the IFU (or both) prior to beginning the injection process. After the first injection, nearly all participants were able to use a two-step autoinjector as easily as a three-step autoinjector, with no additional need to refer to the IFU or device to achieve very similar injection times. Mean injection times were similar for both devices. Demographic factors such as age, gender or handedness, and behavioural factors such as impulsiveness or cautiousness did not impact injection success.

## CONCLUSION

The choice of injectable drug delivery devices can help pharmaceutical manufacturers to differentiate their combination products, especially as the market becomes increasingly crowded with biosimilars. However, switching of drug delivery devices should maintain (and ideally improve) the patient experience and have a limited impact on patient behaviour.

Multiple factors may be at play in the switching process, and more studies are needed for a thorough understanding of these. One study on this topic assessed patient experiences in a switch from Humira to one of its biosimilars in Iceland.[9] It revealed the impact of requiring patients to switch to a biosimilar, of modifying drug formulation, of changing the type of needle and of a lack of training uptake. However, unlike the user test described in this article, the Icelandic study was based on telephone interviews rather than a formalised switching trial according to FDA guidelines. Other similar trials focusing on the patient experience after switching are underway.[18,19]

The user study discussed in this article focused on the device itself, decoupling the drug delivery device element from the combination product. All of participants switched devices successfully, without external intervention, effectively de-risking the choice of a two-step autoinjector in place of a three-step device.

## ABOUT THE COMPANY

Owen Mumford is a major healthcare company and device manufacturer that commercialises pioneering medical products in its own brand and custom device solutions for the world's major pharmaceutical and diagnostic companies. Owen Mumford's goal is to enhance access to diagnostics, encourage adherence to treatment and reduce healthcare costs, making a world of difference to a world of people.

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## ABOUT THE AUTHOR

**Alex Fong**, Head of Insight at Owen Mumford, is an experienced senior manager in the insight, analytics and strategy fields. He has applied these skills in a broad range of industries, including the FMCG/CPG, retail, telecoms and management consulting sectors. Mr Fong has lived and worked in several international markets throughout his career, including Hong Kong, the US, South Africa and France.

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# PICCOJECT – USING HUMAN FACTORS TO FULFIL PATIENTS' NEED FOR INJECTION CONFIDENCE

Here, Thomas Thueer, PhD, Program Lead AI and Syringe Technology, Chris Muenzer, Vice-President Innovation and Development, and Ines Schlenker, Product Manager, all at Haselmeier, discuss the development of the enhanced usability features of PiccoJect, Haselmeier's novel autoinjector.

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## INTRODUCTION

Injection, especially self-injection, can be a daunting prospect for patients. It is therefore critical for injection devices to emphasise features that enhance usability and instil confidence in their users. To achieve this, human factors studies are a crucial element of the development process. By undertaking such studies, drug delivery device developers can access invaluable feedback from patients on their needs, preferences and desires, which can then be incorporated into their device design to improve its usability and reduce the risk of use errors.

In recent years, device developers have refined the techniques for establishing what patients will accept and incorporating real user feedback into the device design. Regulators, too, have recognised the value of human factors studies, with many regulatory agencies now expecting human factors studies to be included as part of any new combination product submission.

## PICCOJECT – USABILITY AT THE FOREFRONT OF DESIGN

To meet the needs of patients, Haselmeier has developed PiccoJect (Figure 1) – a compact, fully-featured two-step


Figure 1: Haselmeier's PiccoJect is a compact, fully-featured two-step autoinjector designed for subcutaneous delivery of drug products, compatible with any standard 1 mL long or 2.25 mL PFS.

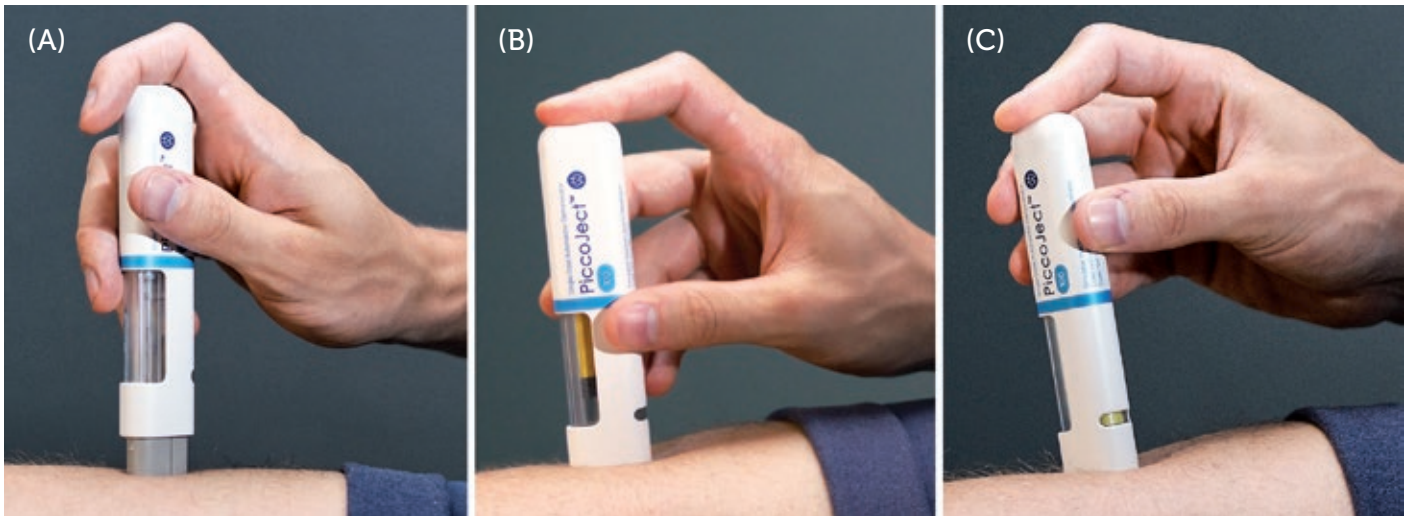


Figure 2: (A) PiccoJect directly before injection with the cap already removed. (B) PiccoJect during injection – the yellow plunger moves down in the large wrap-around drug window. (C) PiccoJect immediately after the injection is finished – the status indicator shows that injection is completed.

> "PiccoJect was developed according to the guiding principle of 'excellence through simplicity', which is embodied throughout its design."

autoinjector platform for subcutaneous drug delivery that can be easily adapted to customers' needs. PiccoJect was developed according to the guiding principle of "excellence through simplicity", which is embodied throughout its design.

Human factors and patient-centricity have played a key role in the development of PiccoJect, with patient needs placed firmly at the heart of its design. PiccoJect's design has been also recognised for excellence by the industry, winning the Good Design Award 2022 and the Red Dot Award 2023. To maximise usability, the device has a flat, compact design that improves the device's ergonomics for a broad patient population, as well as keeping it small and easily portable. PiccoJect also features a large wrap-around viewing window for patients to observe the progress of their injection, as well as a coloured status indicator to provide clear information about its use status (Figure 2). Furthermore, PiccoJect's shape and internal layout enable the use of larger-diameter springs, allowing Haselmeier to better optimise the spring force to match the injection time to the drug properties.

PiccoJect has been designed as a full-service platform, with support from early-phase combination product development through design verification up to final assembly, packaging, labelling and serialisation. In keeping with the guiding principle of "excellence through simplicity", PiccoJect has an extremely low part count, consisting of only eight parts in total, which significantly lessens the challenges associated with manufacturing and scale-up. Also, in accordance with this principle, PiccoJect is compatible with any standard 1 mL long or 2.25 mL prefilled syringe (PFS).

In keeping with the industry-wide push towards greater sustainability, PiccoJect has been developed using plastic materials from sustainable feedstocks and low-carbon electricity during manufacture. Additionally, PiccoJect's design has been future-proofed, with multiple connectivity options in development.

## UNDERSTANDING WHAT PATIENTS WANT FROM PICCOJECT

Haselmeier partnered with DCA (Warwick, UK) to ensure that the lived experience of patients was kept at the

Figure 3: PiccoJect has a number of features specifically developed to provide patients with confidence in their treatment, including excellent visibility of the injection's progress through its large wrap-around viewing window, and audible clicks at the start and end of injection to ensure that the device is held in place until the full dose has been injected.

heart of PiccoJect's design. The combined development team has extensive design experience developing injection devices, covering a wide range of therapies. This breadth of experience was invaluable for conducting a series of human factors studies on PiccoJect, both in formal user studies and more free-form conversations. In Haselmeier's experience, patients prioritise one overarching quality in a drug delivery device – confidence (Figure 3). PiccoJect's features are specifically designed to provide patients with confidence throughout the injection process, helping them to physically interact with the device and to understand:

- When to use the device
- That the drug inside is safe to inject
- How to use the device
- That the device is working as intended
- That delivery has been successful.

## FIRST HUMAN FACTORS STUDY

After initial prototyping, the first study investigated five autoinjector models, covering both 1 and 2.25 mL variants. Three of the functional models were PiccoJect prototypes and two were representative of an existing marketed autoinjector as a benchmark. All of the models were visually representative and contained no drugs or needles, with the intent being to assess patient responses to a simulated injection, including handling and visual feedback features.

This study set out to explore potential sources of use errors and handling issues, as well as to investigate patient preferences, which could then be used to inform the next phases of PiccoJect's design. Across a total of 24 participants, the study contained an even split of experienced and injection-naive users aged between 25 and 67 years. No training or assistance was provided except for a simplified instructions for use (IFU), with half of the participants performing self-injections and half performing the injection on a mannequin. All users performed an injection with each of the five autoinjector models. PiccoJect matched the marketed device in terms of task performance.

To investigate user preferences, participants were initially asked for their first impressions of the devices before handling them. For this purpose, a 2D image was shown to the participants. After performing the injection, the participants were asked again for their feedback.

"Participants noted that PiccoJect offered them greater usability, in particular due to the comfort and security of PiccoJect's wide cross-section (18 out of 24) and its large viewing window (20 out of 24)."

The initial impressions generally favoured PiccoJect, with a majority of participants naming one of the PiccoJect models as the one that they were instinctively drawn to, as they found it the most attractive and the easiest to use.

Notably, a shorter model of PiccoJect included in the study proved polarising, with study participants frequently taking either a strong like or a strong dislike to the smaller size. Interestingly, a number of participants who chose it as their favourite of the 2D images then revised their selection to one of the standard-length PiccoJect models after handling and using them.

After completing the study, participants were asked which of the five models was their favourite. Overall, 92% of participants (22 out of 24) chose one of the PiccoJect models. Participants noted that PiccoJect offered them greater usability, in particular due to the comfort and security of PiccoJect's wide cross-section (18 out of 24) and its large viewing window (20 out of 24). This was highly encouraging feedback for the design team, as it demonstrated that PiccoJect's usability features successfully offered participants the confidence they desired.

## SECOND HUMAN FACTORS STUDY

The second study was conducted once a fully functional prototype of PiccoJect had been developed, with the aim of confirming the value of PiccoJect's advanced usability features using these more realistic devices.

"The mean score across all participants was 6.6 (between 'Happy' and 'Very Happy'), with 23 out of 24 participants giving either a 'Happy' or 'Very Happy' rating."

As with the first study, the second study had 24 participants, all adults, with a mixture of experienced and injection-naive users, half of whom had dexterity issues. Again, participants were provided with no instruction or assistance beyond a simplified IFU. Across a total of 96 injections, the task performance matched expectations for a two-step autoinjector and the findings of the previous study.

After completing the study, participants were asked to rate PiccoJect on a Likert scale (1–7) to indicate how willing they would be to use the device on a daily basis. The mean score across all participants was 6.6 (between "Happy" and "Very Happy"), with 23 out of 24 participants giving either a "Happy" or "Very Happy" rating. All 12 experienced users stated that they would be willing to replace their current injection device with PiccoJect.

## THIRD HUMAN FACTORS STUDY

The most recent study further demonstrated the value of PiccoJect's usability features using devices manufactured with components from the commercial injection moulds. The third study followed the same format as the first and second, with 24 adult participants, of whom some were experienced with injection devices and some were injection-naive users. Again, several of the participants had dexterity issues, including at least one with fairly severe impairments. Participants were asked to rank individual features on a Likert scale, and nearly all features were scored between six and seven on average (Figure 4).

One study participant with severe dexterity impairment (Cochin score of 63) stated "I really like the shape – it's not like anything I've used before. How natural it feels." They went on to say that "I think I might be able to use this myself, and unsupervised, which is a really massive thing for me". This shows the potential significance of the confidence and independence that a feature as simple as PiccoJect's flat cross-section can offer patients with dexterity issues.

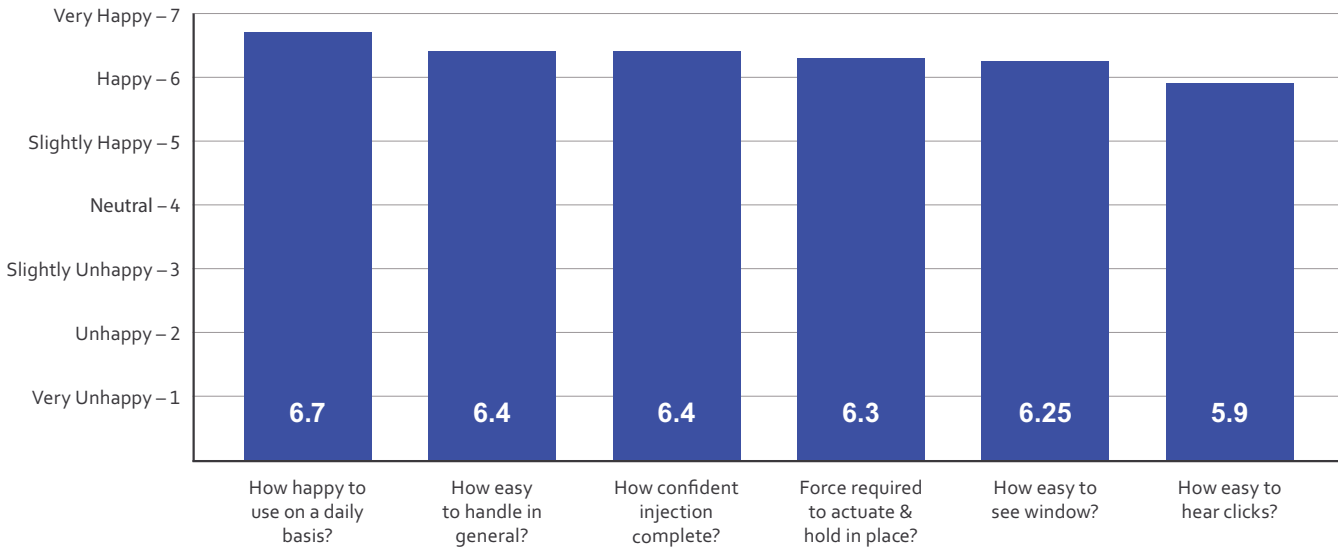


Figure 4: Summary of the third human factors study conducted in 2023. Users provided subjective feedback on different usability aspects of PiccoJect on a Likert scale, with seven being highest and one being lowest. Nearly all aspects achieved ratings between six and seven.

## CONCLUSION

When designing an injection device, it is imperative to pay close attention to the needs of patients, incorporating their desires and needs into the design as early as possible. Formative human factors studies, conducted throughout the development cycle, can allow developers to keep the patient at the heart of the design, resulting in an injection device with usability features that can instil patients with confidence. Firmly believing in this principle, Haselmeier has developed the PiccoJect autoinjector, designed with the guiding principle "excellence through simplicity" at its core.

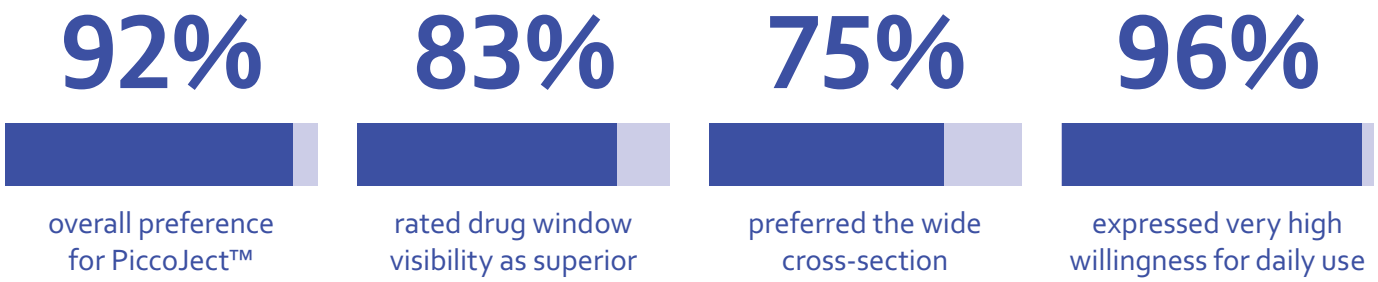


Figure 5: Summary of patients' preference for PiccoJect from across the first two human factors studies.

Across three formative usability studies, participants were highly positive about PiccoJect. In particular, patients valued its usability features, including the large wrap-around viewing window, flat cross-section and clear feedback, with nearly all study participants stating that they would be happy to use PiccoJect on a daily basis to inject their medications (Figure 5).

With simplicity set as the core requirement, PiccoJect is easy to manufacture, adaptable to the specific needs of a given drug and compatible with all standard 1 mL long and 2.25 mL PFSs. With PiccoJect, Haselmeier offers a fully featured device platform with a strong focus on usability that is favoured by users, who have provided very positive feedback in several human factors studies.

## ABOUT THE COMPANY

Haselmeier, the drug delivery device business of medmix, designs, develops and manufactures advanced drug delivery systems, including pen injection systems and autoinjectors, with a central focus on patient comfort and customers' needs. The company has a broad portfolio of technologies and services, delivering user-friendly injection systems that enable patients to self-administer their medication reliably and accurately. Haselmeier is known for its long-standing track record in providing innovative drug delivery devices, collaborating closely with its customers in the pharmaceutical and biopharmaceutical industries. With more than 100 years of expertise in the development and manufacture of drug delivery devices, a global footprint, nearly 250 distinguished and motivated experts and more than 200 granted patents, Haselmeier remains committed to developing innovative solutions that support its customers and help improve the health of millions of people worldwide.

## ABOUT THE AUTHORS

**Thomas Thueer** is the Program Lead at Haselmeier for the PiccoJect autoinjector. He started his career in the field of medical devices at DCA on the design of insulin pens. He then transitioned to pharma and gained substantial experience in combination product development from design input all the way to product launch as a device team leader at Roche, where he was also a founding member of the Autoinjector Technology Centre. Dr Thueer holds a Master's degree in Mechanical Engineering, as well as a PhD in Robotics from ETH Zurich in Switzerland.

**Chris Muenzer** is the Vice-President of Innovation and Development at Haselmeier. He leads a team of experts that create customised drug delivery systems for pharmaceutical and biotechnology companies. He has over 18 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, engineering development, 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 is a frequent contributor to industry conferences and ISO standards.

**Ines Schlenker** is a Product Manager at Haselmeier, responsible for all PFS-based products and contributes to the needs and requirements from the market side to the company. She is trained as a medical engineer and holds a Master's degree in Technical Physician. She has several years of professional experience in the management of medical devices as a product manager and worked for Implant Systems before she joined Haselmeier.

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DRUG DELIVERY

# GAS-POWERED AUTOINJECTOR PLATFORM ENABLES BIOLOGICS DRUG DELIVERY

In this article, Matt McCawley, Chief Technology Officer, and Albie Lavin, Technical Advisory Consultant, both at Altaviz, discuss the company's universal biologics autoinjector platform, highlighting how its gas-powered drive system, based on Pico-Cylinders, provides numerous benefits over legacy spring-powered autoinjectors.

The AltaVISC universal biologics autoinjector platform is designed to address the performance needs for patient delivery of high viscosities and large dose volumes in the rapidly evolving biotherapeutics market. As large molecule therapeutics drive viscosities into the hundreds, or even thousands, of centipoise range,[1] and enzymatic adjuncts[2] enable subcutaneous injections well above conventional 2 mL delivery volumes, it is necessary to reinvent the legacy spring-powered autoinjector platform to enable the self-administration of these truly revolutionary therapies. Simply put, these new, game-changing therapies require new, game-changing delivery systems.

The AltaVISC (Figure 1) is a two-step, low-force activation autoinjector with an actuation mechanism that is configurable to allow buttons, levers, push-on-skin or squeeze triggers. The core drive mechanism is powered by compressed gas cylinders called Pico-Cylinders (Picocyl, CO, US) that pressurise an expansion chamber, which then drives a plunger into standard size glass syringes, including 1.0 and 2.25 mL.

> "Because the gas is contained within the device, drug delivery is effectively silent – there is no loud click or snap like that from the springs found in legacy autoinjectors."

The gas is entirely contained in the expansion behind the plunger and does not make direct contact with the stopper or primary drug container surfaces. Because the gas is contained within the device, drug delivery is effectively silent – there is no loud click or snap like that from the springs found in legacy autoinjectors. Pico-Cylinders can be filled with vapour-phase ($N_2$, Ar) or dual-phase ($CO_2$) gases to a wide pressure range (5–350 bar), allowing plunger force and delivery time to be configurable without requiring spring swaps or housing design changes.

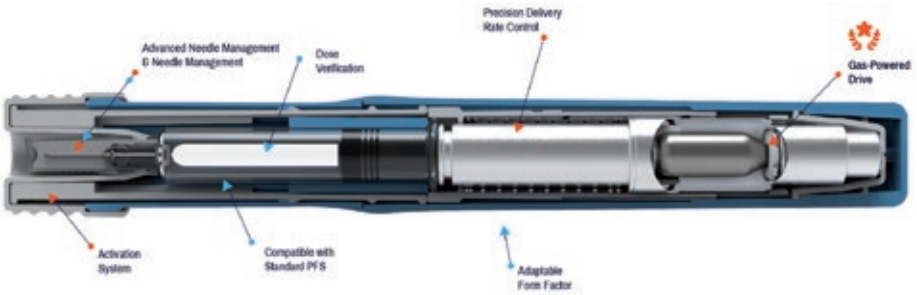


Figure 1: The AltaVISC universal biologics autoinjector platform by Altaviz.

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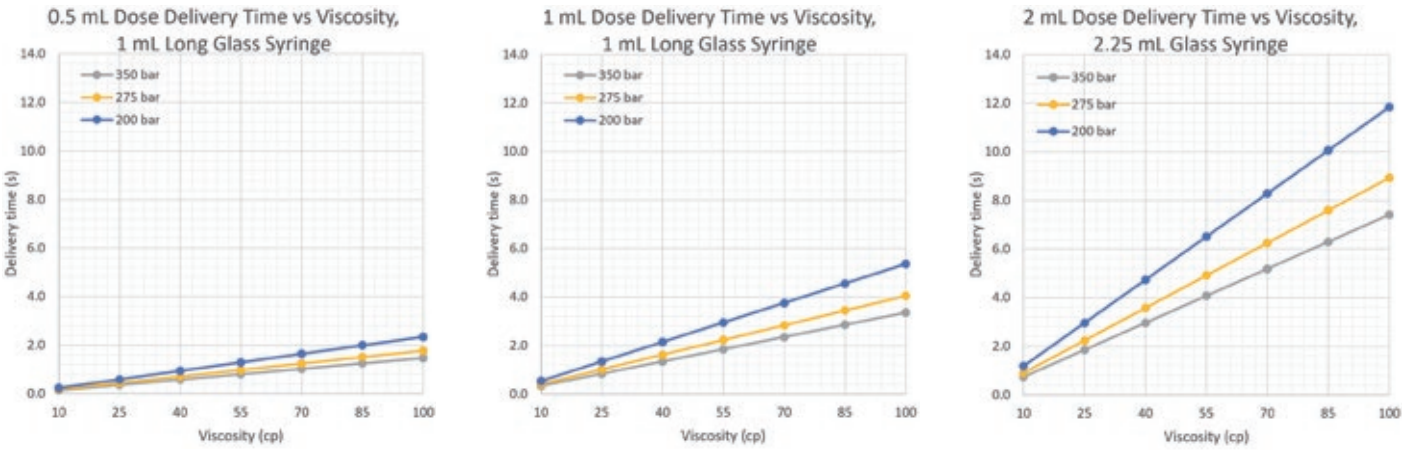


Figure 2: Dose delivery time versus viscosity model data.

## KEY PERFORMANCE ADVANTAGES

The AltaVISC delivers several significant performance advantages over the current state-of-the-art autoinjectors, making the platform suitable for the coming wave of biologic therapies that will require high-viscosity and large-dose delivery.

### Soft Start and Low Force Drop-Off Enables Faster, More Consistent Drug Delivery

The AltaVISC exhibits a relatively constant force profile relative to a spring-driven system. This yields a higher average force over the entire actuation stroke, which, in turn, yields a higher average stopper velocity and a reduction in delivery time. Furthermore, there is no large force spike when the device is actuated, as there is with legacy spring-powered autoinjectors, and this "soft start" makes the delivery force curve very consistent.

### Higher-Pressure Capacity Enables High-Viscosity Drug Formulation Delivery

The Pico-Cylinders used in the AltaVISC can be filled to pressures up to 350 bar in a very small form factor. This high pressure capacity, along with the faster delivery time enabled by the low force drop-off, allows for delivery of high-viscosity drug formulations. Dose volumes between 0.5 and 2 mL with viscosities up to 100 cP can be delivered through a ½" 27G thin-wall (TW) needle in under 8 seconds. The results shown in Figure 2 were calculated using a numerical integration model designed to track plunger motion inside an autoinjector, given a 27G TW needle and a 1.0 mL long and 2.25 mL glass syringe. This model was verified using 100 cP silicone oil in an AltaVISC prototype technology demonstrator.

Ultra-high viscosity (>1000 cP) drug delivery is also possible with the AltaVISC.[3] The numerical integration model data shown in Figure 3 represents different dose delivery time projections using 100–3000 cP formulations through a 25G extra-thin-wall needle.

> "This high pressure capacity, along with the faster delivery time enabled by the low force drop-off, allows for delivery of high-viscosity drug formulations."

### Gas Power Enables Delivery Through Small Gauge Needles

AltaVISC's combination of high-pressure capacity and faster delivery time enables the use of smaller gauge needles, which improves patient tolerability. The numerical integration model data in Figure 4 shows that 1 mL of 100 cP formulation can be delivered through a 30G TW needle in a 1 mL long glass syringe in less than 15 seconds.

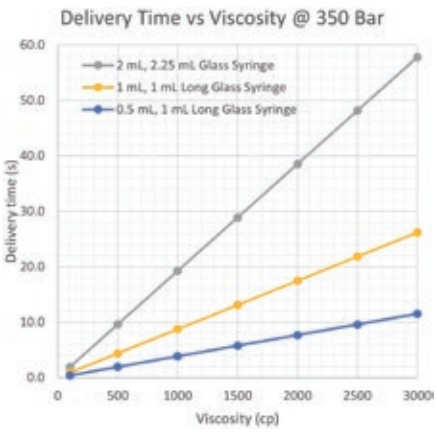


Figure 3: Ultra-high viscosity delivery time model data.

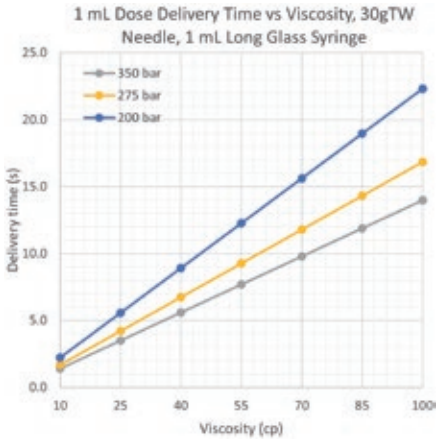


Figure 4: Small needle gauge delivery model data.

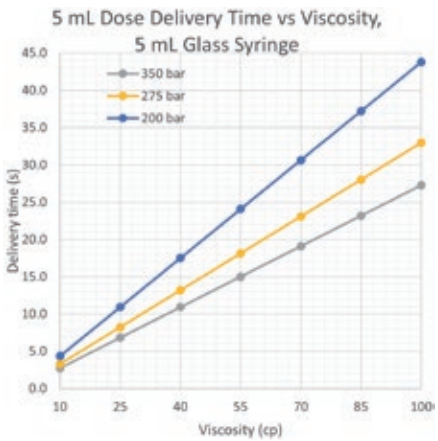


Figure 5: High-volume dose delivery model data.

### Improved Delivery Time Allows for High-Volume Doses

Legacy spring-powered autoinjectors require lower viscosity formulations or larger needle gauges to deliver high-volume doses. The AltaVISC has enough energy to deliver 5 mL through a 27G TW needle in under 30 seconds and could potentially deliver even higher doses if desired (Figure 5, previous page).

## PATIENT EXPERIENCE IMPROVEMENTS OVER CURRENT MARKETED AUTOINJECTORS

Altaviz's AltaVISC uses the same two-step dose delivery workflow as current state-of-the-art autoinjectors, allowing patients and healthcare professionals to keep their current training and use procedures. Additionally, the AltaVISC provides several improvements over the current state-of-the-art autoinjectors with respect to the patient experience. For example, because the AltaVISC uses compressed gas for actuation with a soft start, there is no loud click or snap from a heavy spring extending. Loud noises during actuation can cause significant apprehension in patients when taking their medicine,[4] and the silent delivery profile of the AltaVISC allows them to feel more comfortable complying with their dosing regimen.

The AltaVISC also allows for the use of smaller needle sizes than is typical for biologics injections, due to the increased force available from the high-pressure Pico-Cylinder drive. One of the largest complaints patients have about biologics autoinjectors is the pain experienced during injection and extraction of the needle; this pain is directly proportional to needle size. Enabling smaller needle sizes opens the door to products that reduce the pain experienced by the patient, thereby reducing anxiety around taking medication and improving dosing compliance.

> "Altaviz's AltaVISC uses the same two-step dose delivery workflow as current state-of-the-art autoinjectors, allowing patients and healthcare professionals to keep their current training and use procedures."

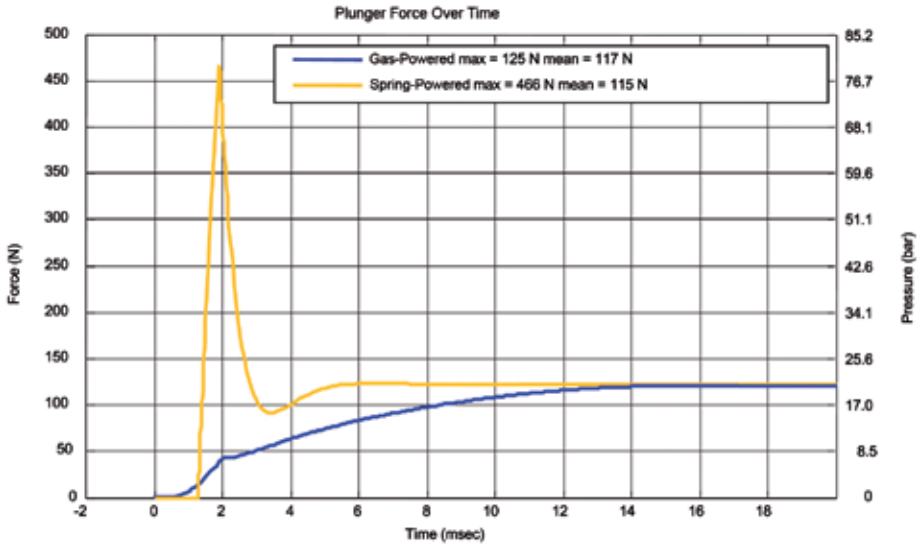


Figure 6: Force and pressure comparison between gas- and spring-powered autoinjectors.

## RELIABILITY BY DESIGN

Legacy spring-powered autoinjectors are the standard for delivering small molecule therapies in the 1–10 cP range, but quickly reach their limits when applied to high-viscosity and large-volume injections. In typical autoinjectors, the plungers are powered by the potential energy stored in a preloaded stainless steel spring. At time of use, the spring is released and the potential energy is converted to kinetic energy that drives the autoinjector plunger to deliver the drug. In most autoinjectors, there is an intentional gap between the plunger and the stopper to accommodate drug fill tolerances, bubbles and volume changes due to temperature excursions during filling, transportation and final use.[5]

Upon the release of the spring, the spring and plunger accelerate until the plunger impacts the stopper, and an impulse force (Figure 6) is created as the velocity of the moving spring mass is rapidly decelerated. This impulse force is significantly higher than the force required to deliver the drug and can contribute to syringe flange breakage. The impulse force also creates increased pressure in the syringe that can lead to syringe container failures. Both failure modes are well known in the industry.[3]

Higher viscosity and larger dose volumes require higher spring forces to administer these drugs in a patient-acceptable delivery time. With higher spring forces come higher spring mass, the impact forces are exacerbated and the probability of syringe breakage increases. A dynamic model was created in MATLAB/Simulink® to simulate the AltaVISC delivering 100 cP silicone fluid from a 2.25 mL glass syringe using a staked 27G TW ½" needle in 10 seconds. There is an initial gap of 5 mm between the plunger and the stopper.

> "The Soft Start feature of gas power now allows the safe delivery of higher viscosities and larger dose volumes in standard glass prefilled syringes."

In contrast, the AltaVISC plunger is driven by gas pressure only, eliminating the high mass drive spring. The plunger rod is initially biased so that it comes in full contact with the stopper to eliminate any gap between the plunger and the stopper. Eliminating the gap eliminates the force spike and resulting pressure spike, so the peak force of the system is limited to the delivery force. The force and pressure comparisons are shown in Figure 6.

The results for the spring-powered autoinjector show a peak force of 466 N, with a 115 N mean delivery force. The peak pressure is 79.4 bar. In contrast, the AltaVISC does not exhibit a peak force spike. Rather, the force ramps up to a mean delivery force of 115 N. The peak pressure is 21.3 bar. As glass syringe breakage is the direct result of the peak force for flange breakage and peak pressure

Figure 7: AltaVISC assembly rendering.

for container rupture, the glass syringe in the AltaVISC would only experience 27% of force and pressure compared with the spring-powered autoinjector, significantly increasing reliability.

The Soft Start feature of gas power now allows the safe delivery of higher viscosities and larger dose volumes in standard glass prefilled syringes. The safety margin taken up by the peak force spike in spring-powered autoinjectors can be converted to useful delivery force, meaning the AltaVISC could potentially provide three times the delivery force of a spring-powered autoinjector while maintaining current standards for reliability.

In addition to designing out primary drug container breakage, the Pico-Cylinder drive system in the AltaVISC has shelf life and shelf stability benefits over spring-powered systems. Pico-Cylinders can maintain pressure for over five years, much longer than the shelf stability of typical drug formulations. Typical spring-powered systems require a very heavy spring to be loaded, which runs the risk of stress relaxation in the spring and plastic creep in the polymer components. The performance of spring-powered systems will consistently degrade over the shelf life of the product. The Pico-Cylinder drive system in the AltaVISC is not loaded during storage, so there is no risk of creep or device integrity loss over a shelf cycle.

## SUSTAINABILITY

The AltaVISC can provide a smaller carbon footprint than alternative autoinjector technologies. The Pico-Cylinders that drive the AltaVISC use inert atmospheric gases, such as $N_2$, Ar or $CO_2$, that can be sustainably sourced and managed. They provide a solution that complies with the Kigali Amendment (2019) of the Montreal Protocol on substances that deplete the ozone layer, unlike many gasses that are widely used as propellants in the cosmetics and pharmaceuticals industries.[6] Furthermore, the activation spring, cylinder and deep-drawn stamped components that comprise the Pico-Cylinder drive system used in the AltaVISC require 66% less stainless steel compared with typical drive springs used in legacy autoinjectors (15 g vs 45 g).

> "Configuring the device to output more or less force for different viscosity formulations or different dose volumes does not require any change to the device mechanism or components."

## PLATFORM FLEXIBILITY

The AltaVISC also provides unparalleled flexibility in the product development and manufacturing process.

### Same Gas Cylinder Form Factor Delivers 5–350 bar

The Pico-Cylinder used in the AltaVISC can be filled with various gases to a wide range of pressures without requiring a size or form factor change. This means that configuring the device to output more or less force for different viscosity formulations or different dose volumes does not require any change to the device mechanism or components. The same component manufacturing equipment is used to fill the Pico-Cylinder from 5 to 350 bar.

### Accommodates all Drug Formulations

The AltaVISC can be tuned to deliver any drug formulation, including high-viscosity biologics and shear-sensitive molecules. The high-pressure capacity of the Pico-Cylinder and the soft start force profile enable significantly higher delivery forces, in turn enabling short delivery times for high-viscosity drug formulations. For shear-sensitive molecules, the gas pressure inside the Pico-Cylinder can be reduced, and the combination of the soft start force profile and the low force drop-off enables smooth delivery without any potentially harmful pressure fluctuations.

### No Loaded Spring During Component Handling and Assembly

The Pico-Cylinder that drives the drug delivery mechanism requires a septum to be opened to release the gas and, prior to actuation, the cylinder is in a completely unloaded state. This means all the components in the device are not experiencing any load during their shelf life or the assembly process, and device assembly is a very simple snap-in operation shown in Figure 7.

### Many Gas Options

The Pico-Cylinder used in the AltaVISC can be filled with vapour-phase or dual-phase gases. Vapour-phase gases, such as Ar or $N_2$ exhibit excellent pressure consistency across the typical use case temperature range of 0–40°C, ensuring consistent delivery rates for drug products intended for community use. Dual-phase gases, such as $CO_2$, allow for extremely high expansion ratios, and thus enable larger volumes to be achieved in cases where temperature is more consistent, such as in a clinic or operating room.

### Human Factors Experience is Equivalent Across Products

Since the same Pico-Cylinder can be used to deliver different dose volumes or viscosities, the user actuation force and

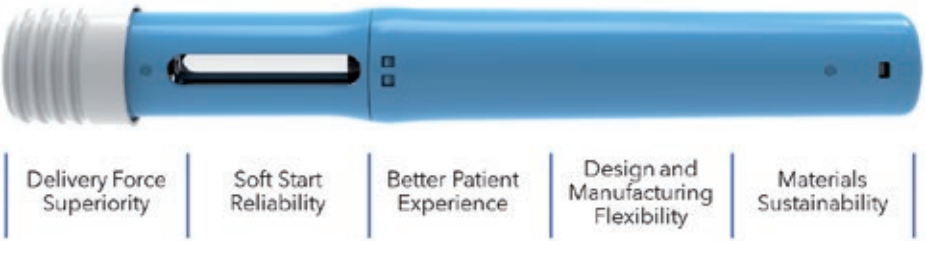


Figure 8: AltaVISC advantages.

user workflow does not change across different products. Therefore, the human factors development risk is minimal when bringing new products to market.

## CONCLUSION

The AltaVISC (Figure 8, previous page) elegantly harnesses the high energy density of compressed gas to deliver significantly higher viscosities and larger dose volumes in a patient friendly, reliable, safe, sustainable and flexible platform that is easily adaptable to the current and future needs of the biologics market.

## 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's clients may engage to leverage existing platforms and application accelerators or develop custom solutions.

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## ABOUT THE AUTHORS

**Matt McCawley** is the Chief Technology Officer at Altaviz, a company founded to conceptualise, design, develop and commercialise innovative delivery platforms and solutions for next-generation drugs, implants and specialised applications. Mr McCawley has over 15 years of experience in ophthalmic device and drug delivery, with 16 US and 60 international patents. Mr McCawley's passion is finding innovative device solutions for novel implant and drug therapies. 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.

**Albie Lavin** is the inventor of the Impel Pharmaceuticals I143 device, the first nasal spray developed around the use of a single-use compressed gas cylinder. Mr Lavin has spent the last five years developing novel nasal spray devices designed to achieve precision olfactory delivery, including combination products indicated for acute agitation, Parkinson's disease and migraine. He currently serves as a Technical Advisory Consultant to Altaviz and remains passionate about developing novel device solutions for the drug delivery space.

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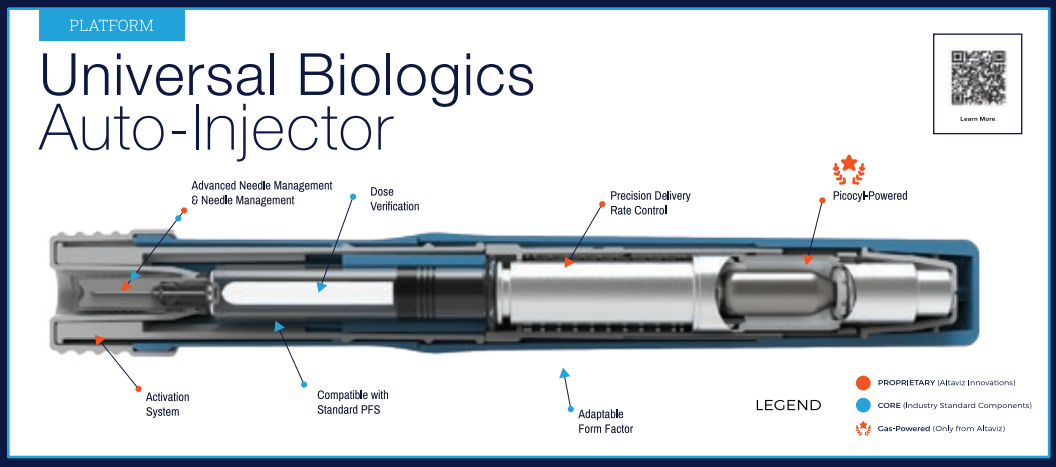
PLATFORM

# Universal Biologics Auto-Injector

- **High Viscosity Biologic Delivery**
- **High Volume Delivery**
- **Subcutaneous Delivery**
- **Intramuscular Delivery**




Newer classes of biologic drugs have higher viscosities and require delivery of larger volumes outside of the capability of traditional spring-powered devices. Attempting to deliver these new treatments with spring-powered devices can result in larger, less ergonomically friendly injector devices with long delivery times and large needles whose noise and vibration levels are frightening to the end users.

With the power to deliver high viscosity, large volume formulations in short or programmed periods of time, new biologic drug-compatible auto-injectors and wearable bolus injectors benefit from the power of Pico-Cylinders. The high energy density coupled with the smooth, silent delivery of drugs can reduce syringe breakage and ease patient concerns leading to higher compliance and a better user experience.

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Recipharm

# TECHNOLOGICAL ADVANCEMENTS TO OVERCOME VISCOSITY CHALLENGES FOR INJECTABLE DEVICES

**In this article, Joe Neale, Head of Innovation, Development and Programme Management at Recipharm, explores injectable drug development, delving into the intricacies of how technology is advancing to meet the challenges of administering complex formulations, enabling a more positive patient experience, promoting dosing compliance and maximising the benefits of these essential medicines.**

Injectable drug delivery stands as a cornerstone of modern medical practice, being essential for numerous medical interventions. From vaccinations to intricate biologic therapies, parenteral administration and injectable devices have revolutionised patient care, allowing for precise dosing and targeted treatment strategies.

A notable trend in the pharmaceutical industry in recent years is the surge in the number of therapeutics in development that require parenteral delivery. More than 50% of new chemical entities in the drug development pipeline are now parenterally administered biologics.[1] Although the rising demand for biologics holds promise to produce innovative and life-changing medicines, their large molecular composition, and therefore high viscosity, presents potential complications for their injectability.

Complications in administering viscous formulations are frequently due to traditional injectable devices being unable to deliver these medicines through a needle fine enough to be acceptable to the patient. This issue not only affects patient comfort, but also risks inaccurate dosing, low adherence and poor treatment efficacy when delivering high-viscosity therapeutics.

Challenges surrounding high-viscosity parenteral administration are further intensified by a rising preference for self-administered therapeutics and the usability advantages of autoinjectors. The healthcare landscape is continuously shifting to develop medicines and treatments that cater more effectively to patient needs, manifesting in an increased demand for self-administered therapeutics. This is further reflected in the significant growth of the global self-injection devices market, which is predicted to increase from USD$6.6 billion (£5.3 billion) in 2021 at a compound annual growth rate of 5.7% to 2030.[2]

> "The healthcare landscape is continuously shifting to develop medicines and treatments that cater more effectively to patient needs, manifesting in an increased demand for self-administered therapeutics."

Addressing the growing desire for patient-centric administration options and overcoming challenges surrounding high-viscosity formulation requires a delicate balance of innovation and scientific understanding to provide a solution that ensures accurate and consistent dosing, as well as patient compliance.

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"Synergy between technological innovation and pharmaceutical ingenuity is needed to redefine the administration of viscous formulations."

## ADMINISTRATION CHALLENGES OF VISCOUS FORMULATIONS

Viscosity refers to the internal resistance of a liquid to flow. Highly viscous liquids have a higher resistance to flow due to the presence of large, complex molecules that entangle with each other, leading to stronger intermolecular forces within the liquid. Injectable drug formulations can vary in viscosity depending on factors such as the nature of the API and solvents used; for example, larger API or solvent molecules increase viscosity. Currently, high-viscosity formulations are being developed at an increasing rate – so the technology being developed to facilitate their administration must meet their intricate needs.[3]

Conventional injection devices consist of short-gauge needles (commonly referred to as standard-gauge needles) and a spring-powered plunger. These devices are effective for administering small molecule medicines but have limitations when administering viscous formulations. The high resistance of the formulation and the thin needle diameter require significant pressure to be applied to the plunger, risking breaking the syringe container, especially when it is made from glass.

Instead, the standard for viscous drug administration has been the use of traditional injectables with broad-gauge needles. These needles enable the delivery of viscous formulations with a force equivalent to non-viscous formulations via a standard-gauge needle. This approach reduces the risk of shattering the syringe container under pressure.

However, despite their effectiveness in preventing breakage, broad-gauge needles can cause significant patient discomfort and pain due to the size of the needle piercing the skin and underlying tissue. Additionally, the emotional distress caused to people with needle phobia can be significantly exacerbated by the large needles needed for injecting highly viscous formulations. Therefore, there is a clear need to devise a solution for the administration of viscous formulations that overcomes the challenges of traditional methods, while also meeting the demand for broader self-administration options.

## OVERCOMING THE HURDLES OF VISCOUS DRUG ADMINISTRATION

Synergy between technological innovation and pharmaceutical ingenuity is needed to redefine the administration of viscous formulations. Advancements in injection device technology must aim to overcome the various issues posed by viscous formulations and be designed and developed with the following considerations in mind.

### Minimised Variability in Dosing

As these formulations resist flow due to internal friction, precise measurement and uniform delivery to ensure that each patient receives the intended dose can be a tough task. Inconsistency in dosing can impact the treatment's efficacy, raising concerns about whether it achieves desired therapeutic outcomes.

When specific formulations demand a controlled or precise injection speed to optimise absorption or maintain therapeutic levels, even minor deviations in injection speed can result in inconsistent dosing. The potential for injection speed variability is increased with high-viscosity formulations, as non-Newtonian flow and clogging characteristics can complicate administration. Further to this, variation arising from both individual techniques and the requirements of the specific formulation can affect the rate at which a medicine enters the bloodstream within a given timeframe.

This potential inconsistency warrants a closer examination of more refined solutions. By addressing the contributing factors and considering refined strategies, such as standardised injection protocols or technologies that regulate injection speed, the impact on dosing accuracy can be alleviated.

### Increased Patient Comfort

Increasing the spring force and using a broad needle gauge are ways to improve the consistency of injection speed, but these solutions also increase the discomfort felt by the patient. Addressing this uncomfortable experience is crucial, as it discourages patients from adhering to their prescribed treatment regimen. This potential non-compliance casts a shadow on the therapeutic effectiveness of the drug, compromising the benefits that could be reaped from the treatment.

As companies look to differentiate their biologic products from one another within the same indication, any benefits that can be achieved through developing a treatment that is more appealing to patients can prove to be commercially advantageous. The development of novel and patient-centric delivery device technologies will be pivotal for meeting both patient and market demands.

### Improved Ease of Use

The high pressure required to push the plunger of traditional devices is often impractical for elderly patients or those with dexterity issues, impacting ease of use. The intricacies of achieving accurate dosing and minimising discomfort during administration will often necessitate the expertise of healthcare professionals, adding to the burden on healthcare systems and taking away patient control over their treatment. This dependency on professional intervention makes the administration process more inconvenient and costly, as well as limiting patient autonomy, making self-administration an appealing proposition if the challenges to ease of use can be overcome.

### Solutions from Innovation

Innovations in injection device technology are proving to be pivotal in addressing the challenges posed by viscous drug solutions, enhancing patient comfort and ensuring accurate dosing. These advancements not only alleviate the limitations of conventional methods but also open the door to a more patient-centric approach that encourages independence and fosters a positive treatment experience.

"Recipharm's VapourSoft® technology addresses the need for an administration solution that facilitates the passage of viscous formulations through narrow gauge needles without subjecting the broader device to excessive pressure."


Figure 1: Autoinjectors powered by VapourSoft technology.

## VAPOURSOFT® TECHNOLOGY: RESHAPING THE MECHANICS OF DRUG DELIVERY

Developed with these considerations in mind, Recipharm's VapourSoft® technology addresses the need for an administration solution that facilitates the passage of viscous formulations through narrow gauge needles without subjecting the broader device to excessive pressure. VapourSoft is a novel and innovative technology that uses liquefied gas to power drug delivery devices, such as autoinjectors (Figure 1). It introduces altered pressure profiles, fundamentally reshaping the mechanics of drug delivery and overcoming the administration challenges of viscous formulations by enabling smooth and gentle delivery of high-concentration biologics through fine needles.

This advanced technology offers a more evenly distributed pressure application, providing a critical advantage in enabling the administration of viscous formulations with enhanced precision, while also reducing pain and discomfort to patients when injected with conventional syringes. This can improve the patient experience and thereby improve adherence to these therapies by providing a compact, flexible and easy-to-use device.

This departure from the norm has profound implications for drug delivery. Central to the success of this advancement is the noteworthy enhancement of patient comfort. The combination of altered pressure profiles and finer needles culminates in an experience that not only minimises discomfort during the injection, but also alleviates the psychological unease that needle-phobic patients often encounter. This increased comfort level is an important step towards patient-centric care that encourages individuals to take an active role in their treatment journey.

## THE IMPORTANCE OF WORKING WITH EXPERTS IN DEVICE DEVELOPMENT

Collaborating with specialist third-party device experts enables drug companies to develop more user-friendly and patient-friendly injectable treatments. The value of these experts lies in their ability to provide comprehensive support in surmounting the multifaceted challenges associated with both the administration and manufacture of viscous injectable drug formulations. Their expertise can help navigate the complex terrain of these formulations, ensuring that the final product not only meets technical benchmarks but also aligns seamlessly with patient needs and comfort.

The importance of this collaborative approach cannot be overstated. Pharmaceutical companies can receive considerable benefit from the insights and experience these experts bring to the table, gaining a deeper understanding of the intricacies involved in optimising drug delivery. While technological solutions like VapourSoft® technology are a major facet of addressing the administration of high-viscosity formulations, the expertise of third-party specialists provides a holistic perspective that considers variables beyond technology alone.

## HARNESSING INNOVATIONS TO OVERCOME VISCOSITY CHALLENGES

Viscous formulations present unique challenges in the field of injectable drug development. However, technological advancements in injection device technology and container design have paved the way for improved patient experiences and enhanced drug delivery. By overcoming the limitations of traditional devices and optimising the manufacturing process, drug companies can ensure precise and reliable delivery of viscous drugs.

The effect of these technological advancements extends across the dimensions of patient care. From fostering a more comfortable and less distressing injection experience to encouraging patient autonomy through self-administration options, the impact is profound. Moreover, the underlying enhancement in dosing precision and therapeutic efficacy underpins the ultimate objective of patient-centric care – improving the lives and wellbeing of those in need.

Collaboration with third-party device experts is crucial in developing user-friendly injectable treatments that can address the administration and manufacturing challenges associated with viscous formulations. By prioritising patient-

"Collaboration with third-party device experts is crucial in developing user-friendly injectable treatments that can address the administration and manufacturing challenges associated with viscous formulations."

centricity and leveraging advancements in technology, drug developers can deliver a better experience for patients, improve dosing compliance and maximise the benefits of these effective medicines.

## ABOUT THE COMPANY

Recipharm is a leading contract development and manufacturing organisation in the pharmaceutical industry, with almost 9,000 employees. The company offers manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and APIs, pharmaceutical product development and development and manufacturing of medical devices. Recipharm manufactures several hundred different products for customers, ranging from big pharma to smaller research and development companies. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US, and is headquartered in Stockholm, Sweden.

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## ABOUT THE AUTHOR

**Joe Neale** is a biochemist by training, with a Master's degree in Translational Medicine. He has more than 25 years of experience developing products within the diagnostic, medical device and combination product fields.

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windgapmedical

# IN THE THICK OF IT: ACCELERATING THE MIXING AND DELIVERY OF HIGH-VISCOSITY INJECTABLES

In this article, Brent Buchine, PhD, Chief Business Officer, Miriam Silton, Business Development Associate, Jameson Woods, Senior Design & Development Engineer, and Andrew Ryan, Senior Design & Development Engineer, all at Windgap Medical explore how the combination of gas power and a side-by-side cartridge configuration increases the working viscosity range for the mixing and delivery of complex injectable formulations.

High-viscosity and difficult-to-mix injectables are becoming more prevalent as pharmaceutical pipelines fill with novel biologics and incorporate a long-overdue focus on patient experience through less frequent, self-administered treatments. While increasingly promising, complex injectables – including biologics, long-acting injectables, lyophilised formulations and other advanced therapies – present challenges throughout the value chain, from formulation to filling to administration.

One particularly difficult challenge is handling the significantly increased viscosities inherent to many of these formulations. As pharmaceutical companies work to bring their molecules to market, they are faced with a difficult trade-off: extend development timelines to investigate lower-viscosity formulations that may be compatible with existing autoinjectors (not good for commercial success) or revert to large-volume doses administered via on-body devices or intravenous (IV) infusions (not good for patients). Some pharmaceutical companies may even choose to defer or cancel development programmes due to viscosity challenges despite significant unmet patient needs. Windgap Medical has a solution to this conundrum with its proprietary large-volume dual-chamber (LVDC) autoinjector platform that enables subcutaneous (SC) and intramuscular administration of high-viscosity injectables.

"As pharmaceutical companies work to bring their molecules to market, they are faced with a difficult trade-off: extend development timelines to investigate lower-viscosity formulations that may be compatible with existing autoinjectors or revert to large-volume doses administered via on-body devices or IV infusions."

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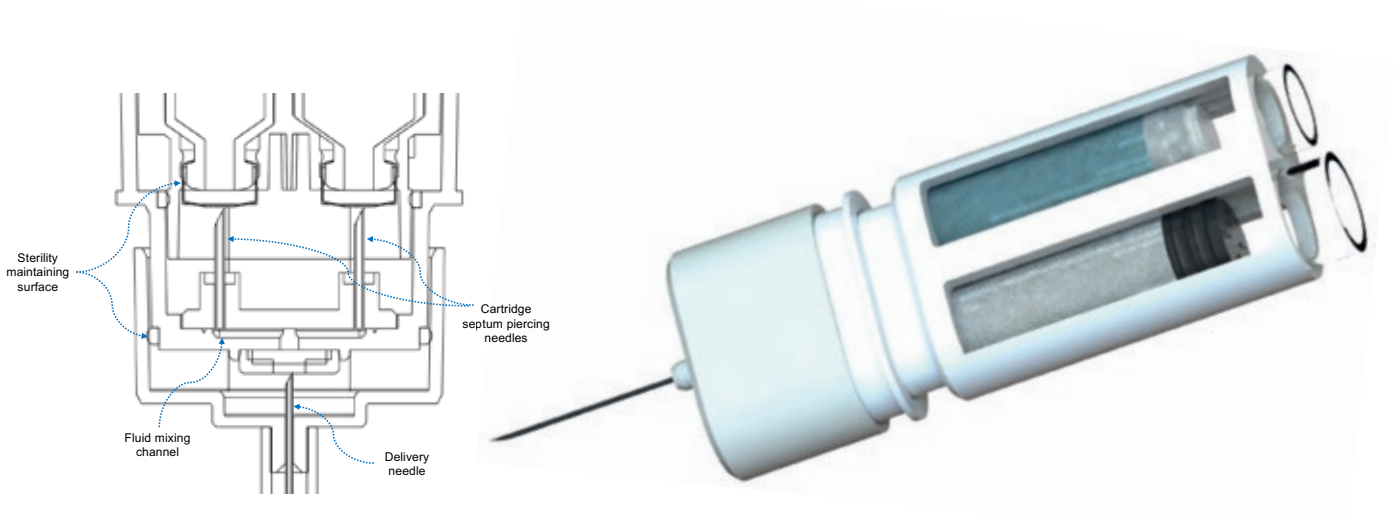


Figure 1: On the left, a cut-away schematic of Windgap's proprietary mixing and delivery hub. On the right, the novel side-by-side configuration of standard, single-chamber cartridges.

## THE CASE FOR – AND CHALLENGE OF – SELF-ADMINISTRATION

Patients and caregivers often prefer SC injections over IV injections due to a lower risk of infection and other adverse reactions, as well as an increased ability to self-administer, reducing time spent in clinical settings.[1]

To achieve the 1–2 mL administration volumes typically required for SC injection, biologics must be formulated at high concentrations, which exponentially increases protein-protein interactions and, therefore, formulation viscosity.[2] These high concentrations may also lead to stability challenges, such as aggregation and denaturation, when in solution. One method of addressing this issue is lyophilisation, which keeps the drug product in a more stable powdered form until the time of injection.

Long-acting injectables (LAIs) come with additional viscosity challenges. LAIs offer patients convenience and safety compared with traditional injectables, as fewer treatment sessions are required and the pharmacokinetic profile between treatments may be more uniform.[3] These formulations often use high-molecular-weight carriers to achieve successful delivery and controlled release, which naturally increases the viscosity of the combined solution. LAIs are commonly lyophilised to minimise the stability concerns that stem from fragile molecules, carrier aggregation and premature drug release.

The good news is that pharmaceutical companies are not alone in this effort. As they work on novel drug formulations to address the viscosity challenges of mixing, dosing and injecting, device companies such as Windgap Medical are designing solutions from a different angle.

## A BETTER PATIENT EXPERIENCE LEADS TO BETTER PATIENT OUTCOMES

Patient adherence can be a significant challenge for high-viscosity drugs. Readying viscous drugs for administration often demands complex preparation routines. As these drugs are frequently left in, or converted to, powdered form for storage and transportation, mixing is required to reconstitute them at the point of care. This may be done via manual shaking, swirling, tapping or a combination of these methods. User instructions often specify extended preparation times to overcome natural human variability in speed, vigour and movement, which presents a significant barrier to adoption and access.

In the case of highly viscous formulations, it becomes impractical to consider mixing a solution that behaves like a syrup or honey. For example, UCB's (Brussels, Brussels) Cimzia® (certolizumab pegol), a commercial treatment for Crohn's disease, can take up to 30 minutes to fully reconstitute.[4] Even in the simplest cases, there is a risk of incomplete reconstitution due to orientation dependencies and lack of a well-defined endpoint. Incomplete reconstitution can have severe consequences for patients, including immunogenicity and incomplete dosing.[5]

Once ready for injection, these thicker doses require more time, larger needle diameters or even both to deliver the same volumes. This increase in time and discomfort can decrease a patient's willingness to take the injection again. However, a BD & Eli Lilly study showed that, when controlled for needle dimensions and flow rate, perceived injection site pain was lower at higher viscosities.[6] This is a promising finding, suggesting that a device design capable of accommodating high viscosities without changing the needle gauge improves patient comfort over low-viscosity formulations.

As viscosities increase, higher forces are required to maintain tolerable delivery times. However, many devices on the market today are still spring-based systems, which are prone to breakage and malfunction if too much force is applied. The working range of these systems is further limited by the decreasing force output of spring power over the duration of the injection.

## A PROMISING SOLUTION TO A LONG-TERM CHALLENGE

With thousands of new therapies entering clinical trials each year, it is ever more critical to design novel delivery devices that simplify the administration of these life-changing drugs for both pharmaceutical companies and patients.

The novelty of Windgap's LVDC platform stems from its innovative arrangement of off-the-shelf primary drug containers (PDCs), as shown in Figure 1. The architecture features side-by-side nesting of two single-chamber cartridges with Windgap's proprietary mixing and delivery needle hub. The side-by-side nesting permits the use of readily available, ISO-compliant cartridges compatible with industry-standard filling methods for powder and liquid products while maintaining a compact, easy-to-handle form factor. Cartridge sizes from 1 to 5 mL can be accommodated. Windgap's LVDC products are gas powered to enhance functionality when managing both high viscosities and large-volume injections.

The device platform is currently being used to develop solutions for automated mixing and delivery of lyophilised compounds or co-therapies in three (or fewer) steps. To achieve this, device

activation causes septum-piercing needles to puncture both cartridges simultaneously. This dual puncture creates a closed fluidic connection between the two chambers, transferring the liquid to the powdered drug cartridge for initial mixing. The device automatically regulates the release of stored gas to reciprocate the solution back and forth between the two cartridges and complete the mixing process, removing the need to shake or swirl. The device-controlled mixing reduces the number of user steps and effort required to prepare and administer a lyophilised or powdered drug.

In a recent feasibility study conducted in partnership with a top-five pharmaceutical company, Windgap evaluated the LVDC platform's performance across a range of viscosities. This study tested mixing times for 1, 2 and 3 mL fluid volumes across a range of viscosity standards using off-the-shelf 3 mL cartridges; the standards were then delivered through 27G, 29G and 31G needles. The reported time for one reciprocated mixing cycle is the time required for the plunger of one cartridge to be fully depressed and then returned to its starting position as the fluid travels back and forth via the mixing hub.

Figure 2 highlights the LVDC's ability to mix formulations up to and beyond 500 cP. When driven at 100 psi, the device completes a mixing cycle for 3 mL of 500 cP test fluid in less than two seconds, with faster times possible for smaller volumes and lower viscosities. If managing shear stress is more critical than minimising mixing time for a given application, the mixing rate can be tuned to mix the product more gently and prevent shear-related degradation.

Table 1 provides a glimpse of what is possible at smaller volumes and lower, more common viscosities. The mixing time in seconds is reported for the full range of tested volumes and viscosities at set pressures. A 1 mL volume of 10 cP liquid can be mixed in less than half a second per cycle with 50 psi and, more impressively, one mixing cycle for 3 mL of 100 cP liquid can be completed in less than a second with 75 psi.

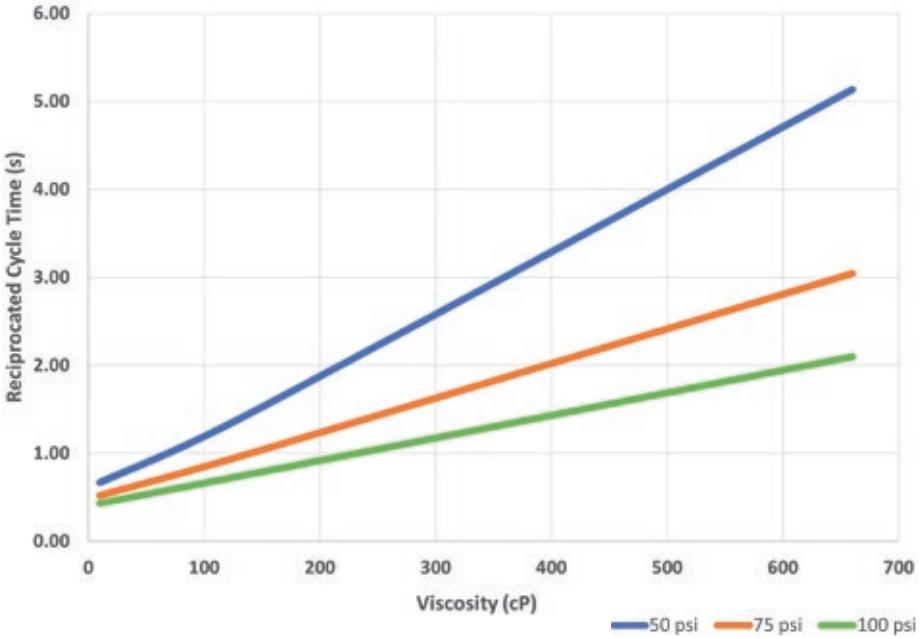


Figure 2: The time in seconds to complete one mixing cycle for a 3 mL dose is shown with respect to applied pressure for a range of viscosities. Data include the time required to actuate valving and pressurise the system at the beginning of each test.

> "The gas pressure can be customised with minimal design changes to meet the force requirements for different target injection volumes, times and viscosities."

Previous feasibility studies with other pharmaceutical partners have indicated that the LVDC system continues to function effectively when operated at the higher pressures required to administer formulations beyond 5,000 cP. In all studies, the mixing hub did not inhibit the delivery flow path and injection times were similar to those demonstrated by other gas-based devices for a given needle gauge, applied pressure and dose; for example, the LVDC delivers 3 mL of 10 cP liquid through a 29G SC needle in 9.9 seconds at 100 psi of pressure. This expanded working range makes the platform a reliable and efficient choice for future drug pipelines. The gas pressure can be customised with minimal design changes to meet the force requirements for different target injection volumes, times and viscosities.

| | 10 cP (@ 50 psi) | 100 cP (@75 psi) | 500 cP (@100 psi) |
|---|---|---|---|
| **1 mL** | 0.4 sec | 0.4 sec | 0.7 sec |
| **2 mL** | 0.5 sec | 0.6 sec | 1.3 sec |
| **3 mL** | 0.7 sec | 0.8 sec | 1.7 sec |

Table 1: Time in seconds to complete a single mixing cycle given a fluid volume and viscosity (applied gas pressure shown in parentheses for each viscosity). Data includes the time required to actuate valving and pressurise the system at the beginning of each test.

## PUTTING FORMULATION DEMANDS AND PATIENT NEEDS SIDE BY SIDE

The Windgap team incorporates a patient-centric approach to device development, prioritising human factors engineering early in the design process to develop a robust patient experience while also solving technical challenges. With the push of a button, LVDC users – patients, caregivers and healthcare professionals – can activate the internal gas-powered mechanisms that then regulate mixing and administration of the contained therapy.

When the device is in its fully automatic configuration, treatment may be delivered in just three steps – initiate mixing,

> "The controlled, reciprocated mixing between the side-by-side cartridges presents an exciting opportunity to shift…to device-controlled mixing with a quantifiably validated endpoint."

| Simplify | Automate | Accelerate |
|---|---|---|
| • Eliminate the need for shaking, swirling and tapping with reciprocated mixing<br>• Administer in three (or fewer) steps<br>• Compatible with standard industry cartridges from 1 mL to 5 mL. | • Activate with the push of a button<br>• Enable device-controlled mixing and/or delivery to minimise risk<br>• Validate number of cycles to reach mixing endpoint. | • Speed up mixing of high-viscosity and large-volume therapies<br>• Reduce formulation challenges for a faster path to market<br>• Customise the optimal solution with LVDC platform technology. |

Table 2: Key benefits of the LVDC autoinjector platform.

remove cap, inject – with little human force required. Furthermore, the LVDC platform has demonstrated acceptable injection times without the need for a painfully large needle. Its performance with higher concentrations and viscosities opens the door for lower-volume injections and a broader range of therapies to be converted from IV to SC injection.

Additionally, the controlled, reciprocated mixing between the side-by-side cartridges presents an exciting opportunity to shift from manual mixing with subjective evaluation of completion to device-controlled mixing with a validated, quantifiable endpoint after a pre-determined number of mixing cycles. Whether reconstituting a dry powder or mixing two liquids, such a shift promises more consistent mixing outcomes and reduces the risk of error from ill-defined instructions to "shake", "swirl" or "tap" at the point of care. This is just one example of how Windgap empowers patients by designing with both the end use and end user in mind.

As shown in Table 2, the LVDC platform is well-suited to adapt to the rising tide of challenges, viscosity or otherwise, flooding through the industry's drug pipelines.

## CONCLUSION

Windgap Medical is on a mission to inject simplicity into complex drug delivery. Its LVDC platform addresses the challenges of traditional autoinjector approaches and large-volume, high-viscosity formulations. The company seeks to "solve beyond the

solution" to develop highly innovative drug delivery devices that leverage its patented technologies. Windgap Medical welcomes partnerships with the pharmaceutical industry for custom development programmes based on the LVDC platform or its rescue medication (ANDI®) platform.

*Some statements are forward-looking. Unless specifically stated, these devices are not approved for sale in the United States or the European Union.*

## 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 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 (epinephrine) 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.

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## ABOUT THE AUTHORS

**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 over 100 patents based on his inventions. As Chief Business Officer of Windgap Medical, Dr Buchine oversees business development, corporate partnerships, and pipeline strategy. He received his PhD in Materials Science & Engineering from Georgia Tech (US).

**Miriam Silton**'s expertise lies at the intersection of product development and life science innovation. At Windgap Medical, she is responsible for identifying and pursuing new business opportunities for Windgap's growing portfolio of drug delivery technologies and capabilities. Ms Silton holds a BS in Materials Science & Engineering from the University of Maryland (MD, US) and MBA from Harvard Business School (MA, US).

**Jameson Woods** is a Senior Design and Development Engineer at Windgap Medical. He has eight years of experience in quality, manufacturing and R&D in the medical device industry. At Windgap Medical, Mr Woods is responsible for developing next-generation autoinjectors. He holds a BS in Mechanical Engineering from Wentworth Institute of Technology (MA, US).

**Andrew Ryan** is a Senior Design and Development Engineer at Windgap Medical. He has eight years of engineering and design experience, with a focus on early-stage medical device design. Mr Ryan is currently focused on advancing Windgap's next generation of autoinjectors to enable delivery of high-viscosity and difficult-to-mix drugs. He holds BS and MS degrees in Mechanical Engineering from Northeastern University (MA, US).

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# CCBio's Omega & Salus Pen Injectors

## THE ROLE OF PEN INJECTORS

According to the WHO's definition, drug adherence refers to "the degree to which the person's behaviour corresponds with the agreed recommendations from a healthcare provider". When it comes to clinical treatment and managing chronic diseases, it is common for patients to experience a decline in their drug adherence, often due to the disease being asymptomatic or symptoms improving. This leads to prolonged illness, increased healthcare costs and increased disease complexity, creating a vicious cycle.

> "There is clear evidence to suggest that self-injection is an effective strategy for improving medication adherence in gastrointestinal therapy."

Currently, leading pharmaceutical companies provide clinical recommendations for the treatment and management of chronic diseases using drug delivery systems, such as pen injectors. There is clear evidence to suggest that self-injection is an effective strategy for improving medication adherence in gastrointestinal therapy, as these pen injectors, compared with traditional hospital-administered injections, reduce discomfort and enhance user-friendliness.[1]

Starting with a focused design and progressing through development to practical market cases, CCBio has developed a solution that balances performance, robustness and usability, drawing inspiration from the patient-centric usage patterns of pen injectors. CCBio offers two optimised pen injectors designed in

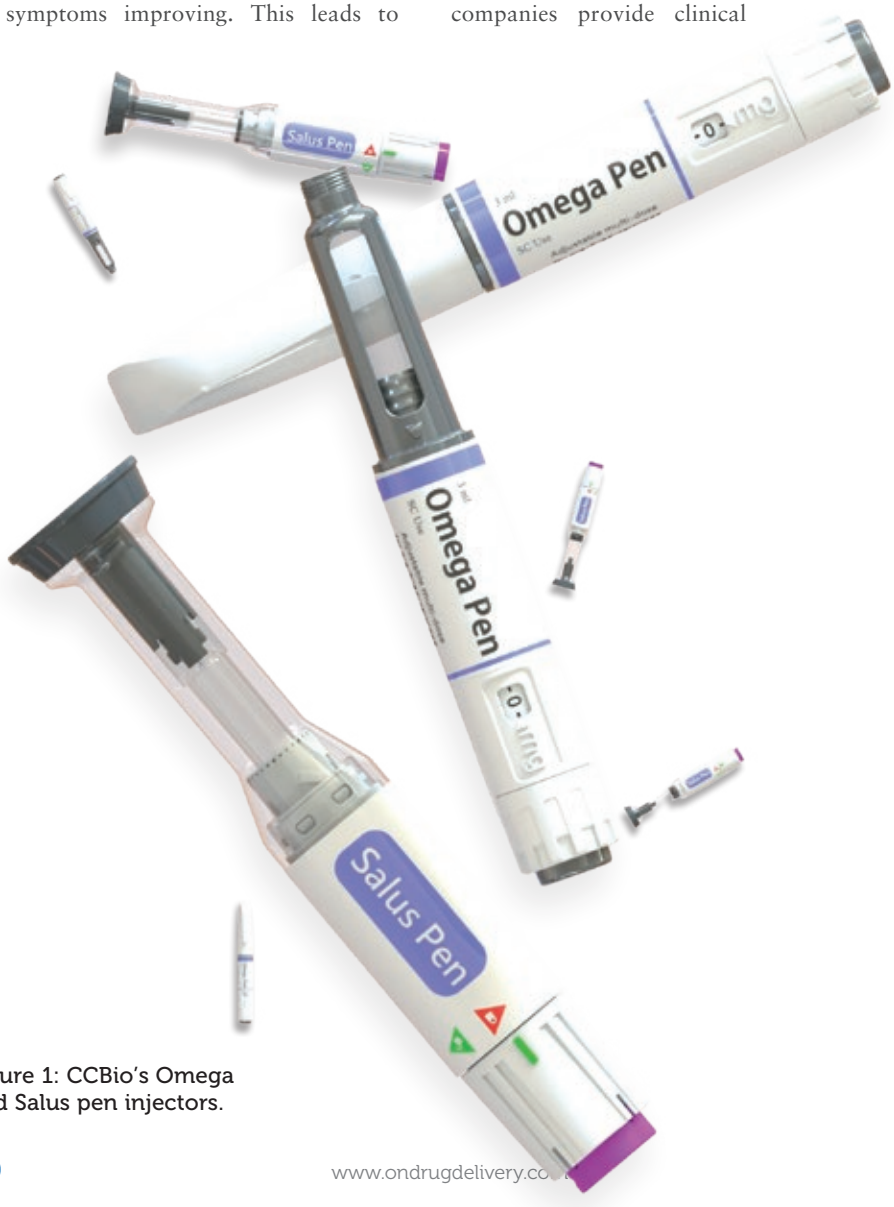


Figure 1: CCBio's Omega and Salus pen injectors.

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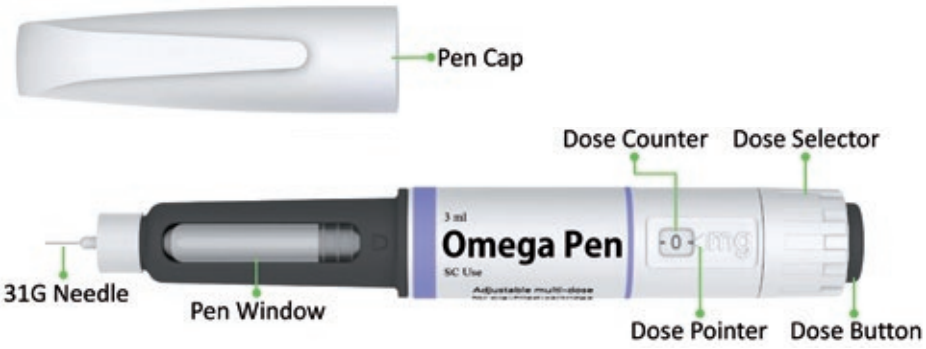


Figure 2: The Omega multidose pen injector.

response to the concerns of both pharmaceutical companies and patients – Omega and Salus (Figure 1). These two modern pen injectors from CCBio aim to provide pharmaceutical partners with a better choice.

## OMEGA

CCBio's Omega pen injector is a multidose injection device with a non-replaceable container (Figure 2) that has been successfully developed based on the needs from insights of pharmaceutical partners. Omega incorporates all the essential elements of a successful multidose injection device, for example, device length has been optimised in terms of user ergonomics, dexterity concerns, comfort and convenience for all use steps. Omega features a novel mechanical energy storage mechanism based on compression spring mechanics – rotating the dose selector recharges and stores energy every time the user dials in a dose setting.

## SALUS

Likewise, CCBio's Salus, a single-dose injection device with a non-replaceable container (Figure 3), has been developed based on key unmet needs communicated by pharmaceutical partners and incorporates all the essential elements of a successful autoinjector device. CCBio leverages simple mechanical capabilities based on compression springs to facilitate one-time injection. After injection, the device provides passive needle protection, allowing patients with needle phobia to self-administer comfortably. The user-centric design includes an activation key for easy differentiation between pre-use and post-use. CCBio has also carefully designed the assembly process for integrating the drug-containing prefilled syringe into the autoinjector body, taking the pharmaceutical company's perspective into consideration, making the assembly of Salus pen a straightforward two-step process. This minimises assembly errors and reduces the cost of assembly equipment.

## CONCLUSION

In anticipation of the expiration of numerous drug patents within the next five years, particularly for combination product series, CCBio has identified a demand for a pen injector that can be paired with biosimilar drugs. Focusing on a response to this demand, CCBio has introduced two self-injection pen injectors, Omega and Salus (Table 1), with the hope of providing a valuable choice to customers in need.

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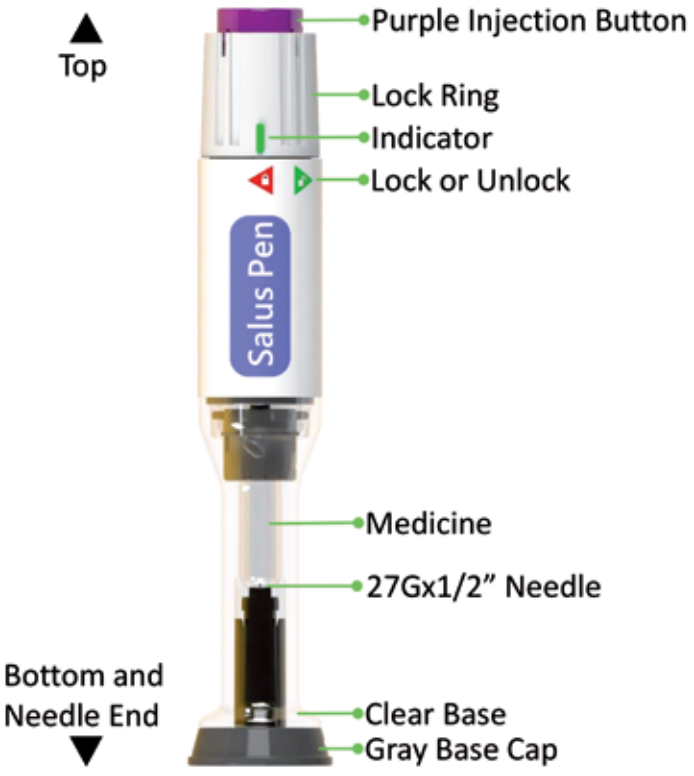


Figure 3: The Salus single-dose autoinjector.

| Property | Omega | Salus |
|---|---|---|
| Key Needs Addressed | Consistent with the usage model of the Ozempic® (semaglutide, Novo Nordisk) injection pen | Consistent with the usage model of the Trulicity® (dulaglutide, Eli Lilly) injection pen |
| Device Type | Mutidose injector | Autoinjector |
| Administration Route | Subcutaneous | Subcutaneous |
| Primary Container Format | 3 mL drug cartridge | 1 mL prefillable syringe; drug cartridge |
| Primary Container Material | Glass | Glass |
| Usage | Mutidose; disposable | Single dose; disposable |
| Dose Volume | 1.5 / 3 mL | 0.5 mL |
| Priming & Dose Setting | Priming or dose setting by the dose selector | N/A |

Table 1: Properties of the Omega and Salus autoinjectors.

Roncadelle Operations

# NEEDLESTICK INJURY RISKS: SAFEGUARDING HEALTHCARE WORKERS AND PATIENTS

**In this article, Fred Metzmann, PhD, Chief Business Officer at Roncadelle Operations, discusses how using safety syringes can be a cost-effective measure to reduce the risk of injury to healthcare personnel and patients, and introduces the company's devices designed for safer drug administration.**

Needlestick injuries (NSIs) are a risk to healthcare workers and patients that can lead to dangerous and potentially life-threatening infections, including hepatitis B, hepatitis C and HIV. In EU countries alone, more than one million cases occur annually.[1] In the UK, compensation for NSIs between 2012 and 2017 cost the NHS more than £4 million.[2] The economic burden of NSIs in Italy, for example, is estimated at €72 million (£61 million), only including direct costs for diagnostics, prophylaxis and post-exposure monitoring.[3]

In many EU countries, despite the so-called "Sharps Directive" (Directive 2010/32/EU), there is still suboptimal adoption of safety syringes. A survey by HOSPEEM (European Hospital and the Healthcare Employers' Association) and the EPSU (European Federation of Public Services Union) investigated the concerns associated with poor compliance with the Directive. Among them, they noted a lack of adequate resources, training programmes and effective data collection systems.

It is essential that institutions and healthcare organisations facilitate consistent interpretation and widespread implementation of the Directive, as well as the ISO 23908 standard, which defines the safety requirements for the design and manufacture of devices to ensure compliance with the EU regulation.

Currently, there are medical devices available on the market that guarantee full compliance with the quality and safety standards established by the Directive. Roncadelle Operations' syringes are simple to use, require a minimal amount of force to activate and include an automatic safety mechanism to avoid any potentially harmful actions by the operator.

> "NSIs and sharps injuries represent the most common occupational injuries among healthcare workers, with an incidence of approximately 41%."

## AN UNDERESTIMATED HEALTH PROBLEM

While approximately 50% of injuries go unreported, in Italy alone, around 100,000 percutaneous exposures occur each year.[4] NSIs and sharps injuries represent the

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most common occupational injuries among healthcare workers, with an incidence of approximately 41% (Figure 1).[5]

Accidental NSIs are the most common and can occur during a wide range of procedures, including blood sampling, suctioning, drug administration, inserting catheters and handling clinical waste. These injuries occur most commonly among nurses, and the physical and emotional impact of such incidents can be severe and long-lasting.

The economic burden of NSIs, only considering the direct healthcare costs for diagnostics, prophylaxis and post-exposure monitoring, is estimated at about €850 per event,[3] and this is excluding any indirect costs incurred due to loss of productivity and workers' compensation.

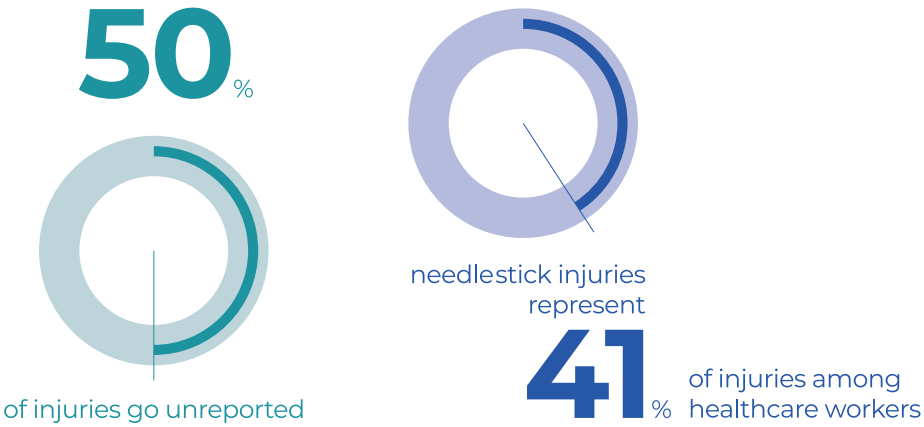


Figure 1: Sharps and NSIs represent the most common occupational injuries among healthcare workers, accounting for approximately 41% of all injuries.

## A SERIOUS BUT AVOIDABLE RISK

NSIs primarily result from the misuse of safety syringes, which incorporate protective mechanisms that, upon activation, create a lasting barrier between the hands and the needle until proper disposal.

Studies conducted in the EU have demonstrated that the use of safety syringes with integrated protection mechanisms, together with training programmes to educate staff appropriately and the improvement of working conditions, could prevent 80% of NSIs (Figure 2).[6,7] Such measures would significantly reduce healthcare costs and stress, enhance workers' productivity and improve the patient's experience.

In the current healthcare situation – characterised by continuous growth in pharmaceutical innovation alongside an increase in chronic conditions, such as diabetes, cardiovascular diseases and autoimmune diseases – it is important to consider the growing role of prefilled safety syringes for subcutaneous administration. The relevance of these devices relates to the use of new drugs that require special dosing accuracy and are frequently administered or self-administered at the patient's home.

One study estimated that by 2027, the global value of the prefilled syringe (PFS) market will surge from its current $5.9 billion to about $9 billion at an annual growth rate of 9%.[8]

> "Over the last decade, the prevention of sharps injuries has become a high priority topic across the EU, which has led to the adoption of the Directive 2010/32/EU10 for the prevention of sharps injuries in the hospital and healthcare sector."

## THE REGULATORY FRAMEWORK

Over the last decade, the prevention of sharps injuries has become a high priority topic across the EU, which has led to the adoption of the Directive 2010/32/EU10 for the prevention of sharps injuries in the hospital and healthcare sector. The aim is to provide "the safest possible working environment through the prevention of injuries caused by all types of medical sharps devices."

The Directive introduced the framework Agreement negotiated by the sector's European social partners HOSPEEM and EPSU. For example, in Italy, the Directive was incorporated through Legislative Decree No. 19 of February 19, 2014,[9] which amended Legislative Decree No. 81/2008 to enhance health and safety in the workplace. In Germany, the EU Directive 2010/32/EU on protection against sharp injuries in the health sector is implemented through the TRBA 250. This guideline mandates employer responsibilities in Section 4.2.5, building on the BioStoffV's regulation for mandatory safety devices. The regulatory framework specifies the minimum requirements that must be adopted by the member states to protect workers.

The requirements include:

- Risk assessment – mapping of all work areas and situations where the potential for injuries exists
- Adoption of appropriate preventive measures – with particular attention to the use of medical devices with integrated safety and protective mechanisms, and the elimination of unsafe devices
- Reporting in case of accidents and injuries – currently, 50% of cases are unreported
- Information and training programmes to raise awareness and provide practical instruction on the correct use of devices with integrated protective mechanisms.

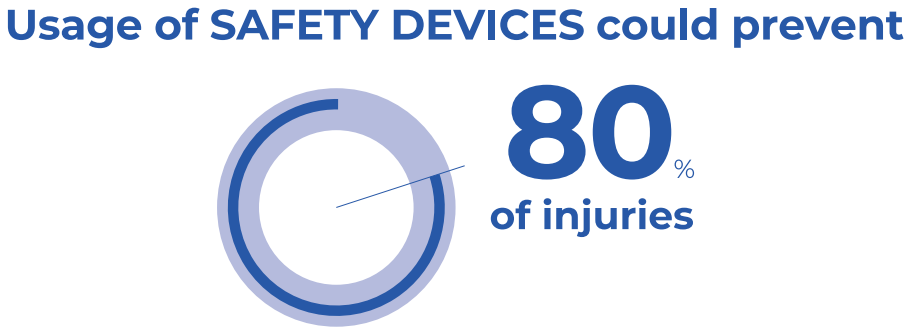


Figure 2: Safety devices could prevent 80% of injuries.

## CRITICAL ISSUES AND POSSIBLE AREAS FOR ACTION

In February 2017, HOSPEEM and the EPSU adopted a joint work programme for the period 2017–2019 with the aim of monitoring the implementation of the Directive in the EU member states and, above all, implementing the measures stipulated in the legislation.[10]

A survey, directed to HOSPEEM and EPSU national affiliates,[11] was conducted to examine the areas where adoption of the Directive has produced positive benefits in preventing sharps injuries and to identify the existing challenges with the implementation of the legislation in order to identify ameliorative solutions that could be be applied in the different national contexts.

The suboptimal adoption of safety-engineered protection mechanism devices, which mainly affects Southern European countries (Italy, Spain and Greece), was among the most critical issues that emerged from the survey. A lack of sufficient financial resources, with the consequence that many hospitals are still buying equipment without safety mechanisms, thereby disregarding the regulatory provision, was cited as one of the main problems by respondents from Spain and Norway. In these countries, the need for hospitals to restrict spending puts facilities at risk of incurring much higher costs for the management of occupational incidents.

A second challenge highlighted in the survey relates to difficulty within the workforce of adopting new, more innovative devices, as reported by 68% of Italian nurses (Figure 3). Another issue is the non-comprehensive coverage of training programmes by all categories of staff who are potentially at risk. In particular, this relates to temporary workers, such as trainees, students and interns, as highlighted by respondents from Spain and Austria.

The lack of an effective data collection system for percutaneous exposure incidents at the national level does not facilitate the identification and rectification of the causes and corresponding corrective measures. The issue of underestimating the number of cases due to the non-reporting of sharps injuries emerged as particularly relevant in Italy, Spain, Germany and Norway.

The working group has drafted recommendations aimed at protecting healthcare personnel and patients from the risk of injury, thereby preventing the transmission of dangerous infectious diseases:

1. The allocation of adequate resources for the purchase of quality medical devices equipped with safety-engineered protection mechanisms as part of a broader strategy aimed at eliminating occupational risk, which has a net positive impact on healthcare facilities' budgets
2. The adoption of common procedures for the procurement of medical devices and materials
3. Revision of the national regulation on reporting percutaneous exposures with the aim of reducing the number of unreported injuries and facilitating the sharing of best practices at the European level
4. Funding for training activities for healthcare workers that focuses on the use of the latest generation of medical devices.

"Promoting a safe working environment is a priority for modern healthcare systems, despite a shortage of doctors and nurses in Europe."

## SAFETY SYRINGES: A SAFE AND EFFECTIVE WAY TO REDUCE NSIs

The World Health Organization (WHO) recommends the use of safety-engineered syringes with a reuse prevention feature to eliminate or reduce the risk of infection as much as possible for workers and patients.[12]

Promoting a safe working environment is a priority for modern healthcare systems, despite a shortage of doctors and nurses in Europe. EN ISO 23908:2013 outlines the requirements and test methods for evaluating the performance parameters of sharps injury protection features for medical devices containing hypodermic needles for single use, introducers for catheters and lancets, and other needles used in blood sampling.

As part of the EC's proposal for standardisation of the Medical Devices Regulation 2017/745 (MDR) and the In Vitro Diagnostic Medical Devices (IVDM) Regulation 2017/746, EN ISO 23908:2013 is listed among the "existing harmonised standards to be revised" by May 27, 2024, concerning "technical solutions for safety mechanisms to be applied in the design and manufacture of devices to ensure compliance with Sections 11.1 and 22.2 of Chapter II of Annex I of Regulation (EU) 2017/745. The standard applies to devices intended to be used for the administration and/or extraction of body/blood fluids and/or medicinal substances."

Given the importance of addressing the issue of NSIs, it is imperative that there should be no gaps in the interpretation of the MDR regarding general safety and performance requirements. This is crucial for manufacturers and to avoid disparities in protecting the safety of healthcare workers, patients and the community. The key elements are that safety syringes should be as simple as possible to use, require a minimal amount of force for activation and should include an automatic safety mechanism to avoid any potentially dangerous intervention from the user.

Highlighting the real risk of uneven implementation of the regulation, the Spanish General Nurses Council and

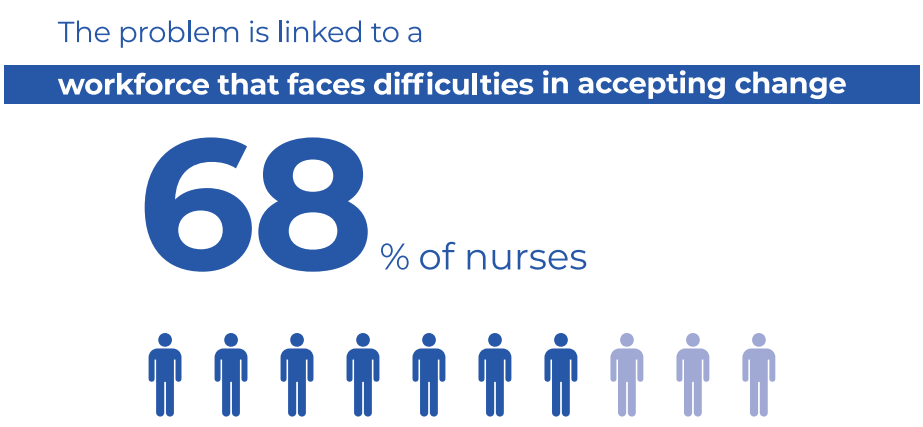


Figure 3: There is difficulty amongst healthcare workers when it comes to adopting new, innovative devices, as reported by 68% of Italian nurses.

European Biosafety Network have published an Interpretation Guide aimed at ensuring consistency in the implementation and interpretation of the MDR about the requirements defined in Annex 1, Sections 11.1 and 22.2.[13]

## TECHNOLOGICAL INNOVATION FOR THE PREVENTION OF NSIs

There are medical devices already on the market that guarantee full compliance with the quality and safety standards established by the regulations. Roncadelle Operations has been developing minimally invasive and safe devices for the administration and self-administration of drugs for more than two decades, making use of state-of-the-art technologies and production facilities.

### SafeR® Syringe

The SafeR® passive safety syringe with retractable needle has several safety features that ensure accurate dosing of the drug, allow the needle to automatically retract at the end of the injection, avoid contact between the operator and the patient and prevent reuse of the device (Figure 4).[14]

### SafeR® Shield for Prefilled Syringes

Similarly, in the SafeR® Shield PFS, the needle is fully covered by the shielding system on completion of the injection. Additionally, as the drug does not come into contact with anything but the syringe, there is no need for drug stability studies (Figure 5).[14]

### SafeR® Reverse for Prefilled Syringes

In the SafeR® Reverse PFS, the shielding system automatically activates after the injection, and the needle is fully covered. The design eliminates the need for stability studies as the drug does not come into contact with anything but the syringe (Figure 6).[14]

### SafeR® Car-GO for Cartridges

In the SafeR® Car-GO syringe, the entire cartridge and needle retract on completion of the injection. As the drug only touches the cartridge until the injection, the syringe does not require drug stability studies (Figure 7).[14]

## CONCLUSIONS

To minimise the risk of NSIs and protect healthcare workers and patients from potentially serious infections, the following


Figure 4: Roncadelle SafeR® syringe.


Figure 5: Roncadelle SafeR® Shield for Prefilled Syringes.


Figure 6: Roncadelle SafeR® Reverse for Prefilled Syringes.

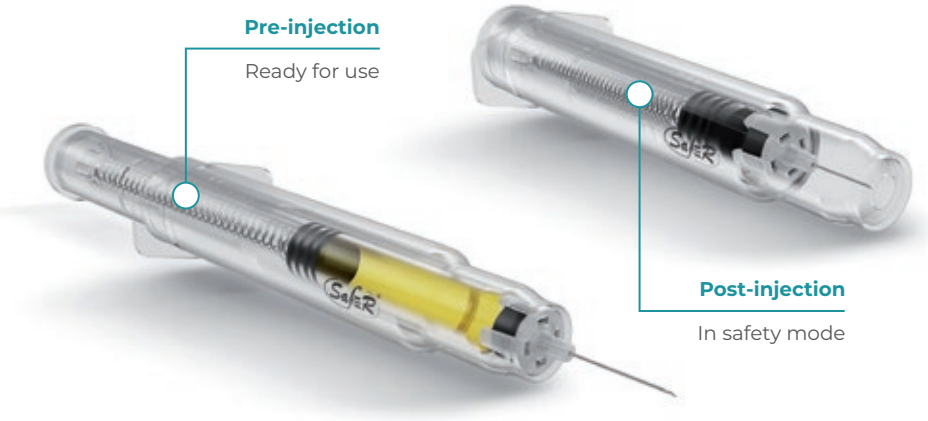


Figure 7: Roncadelle SafeR® Car-GO for Cartridges.

recommendations are desirable. Firstly, the consistent interpretation and universal implementation of the Medical Sharps Directive 2010/32/EU and the Medical Devices Regulation (EU) 2017/745, as well as the updated ISO 23908 standard (by May 2024). Secondly, the rigorous implementation of syringes that adhere to the highest safety standards, specifically those with passive safety mechanisms and automatic needle retraction, is essential. It is equally crucial to phase out and eliminate devices that do not meet these safety benchmarks. Furthermore, the introduction of nationwide surveillance to guarantee the purchase and use of safety devices, monitor accidental exposures and collect up-to-date data on NSIs.

## ABOUT THE COMPANY

Roncadelle Operations, located near Milan (Italy), operates as both an original equipment manufacturer and a contract development and manufacturing organisation. Roncadelle specialises in crafting safe and user-friendly delivery and secondary packaging solutions for injectables. Leveraging engineering expertise and high-quality industrial standards, the company's products serve as either standalone medical devices or components of combination products. Guided by a "just do it faster" philosophy and a "value-for-money" focus, Roncadelle delivers swift, economical solutions. Its core aspiration is to safeguard people from infection, creating safer injection solutions based on sound engineering performance. Roncadelle forges strategic partnerships with its customers and is committed to serve as an investment partner, strategically allocating resources to facilitate its clients' focus on innovation and market leadership. The company's strategically located facility with state-of-the-art cleanroom manufacturing embodies its commitment to innovation, efficiency and safety in healthcare.

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## ABOUT THE AUTHOR

**Fred Metzmann** holds a PhD in Polymer Chemistry and boasts over 25 years of expertise in the MedTech sector, notably within drug delivery devices. He has cultivated a deep understanding of the medical device market through various leadership positions in sales, marketing and product management. In his current role as Chief Business Officer of Roncadelle Operations, Dr Metzmann is responsible for the market launch and growth of passive safety syringes, as well as innovative needle protection systems for PFSs and cartridges. His publications, notably those concerning injection pen systems, underscore his ongoing commitment to propelling advancements in the drug delivery devices technology. Combining in-depth technical expertise with pragmatic market knowledge, Dr Metzmann has become a valued expert on injection devices. In the ever-changing healthcare industry, he advocates advanced safety strategies for injection devices, underscoring his deep commitment to protecting healthcare workers from infection.

# SAFEGUARD PEOPLE FROM INFECTIONS

INNOVATIVE & SMART SOLUTIONS
FOR SECURE, MORE SUSTAINABLE,
RELIABLE ADMINISTRATION
OF INJECTABLES

## SAFER® SYRINGE

Passive safety syringe
with retractable needle

## SAFER® SHIELD

Passive needle-guard
for pre-filled syringes

## SAFER® REVERSE

Passive syringe retraction
for pre-filled syringes

## SAFER® CAR-GO

Passive cartridge & needle
retraction for cartridges

**Product portfolio based on proprietary IP**

**Smart platforms easy and flexible to customise**

**Fast development cycle with short time to market**

**Smart, Efficient & Sustainable solutions**

Roncadelle Operations

Roncadelle Operations is dedicated to revolutionising the safety of liquid drug injections and improving the well-being of patients and healthcare professionals. As a Contract Design and Manufacturing Organisation (CDMO), we provide expertise and tailored solutions to primary packaging and pharmaceutical companies.

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# ACQUIRING A LIQUID BIOPSY INCIDENTAL TO INTRAVITREAL INJECTION

In this article, Alexandre Tumlinson, PhD, Product Lead at Twenty/Twenty Therapeutics, introduces the VitreoDx injection system to address emerging trends in intravitreal therapeutics.

## NEW INTRAVITREAL THERAPIES HIGHLIGHT UNMET NEED

Any fluid injected into the closed space of the eye results in a short-term spike in intraocular pressure (IOP), which then resolves over the next minutes or hours.[1] If the spike is large enough, the patient may lose light perception in the eye until the pressure normalises and adequate perfusion returns. In this case, the doctor will carefully monitor IOP, and may perform paracentesis (i.e. using a 30G needle to relieve excess fluid through the cornea of the eye) if the patient does not recover sight within a few minutes.

The 50 µL dose typically delivered with traditional anti-vascular endothelial growth factor (anti-VEGF) therapies for wet age-related macular degeneration (AMD) and diabetic retinopathy rarely results in a pressure spike of clinical significance.[2] However, two recently approved therapies for geographic atrophy (GA) are both formulated with a 100 µL dose volume; injection volumes of this size result in a larger number of high IOP events, requiring careful pre-injection coaching of patients, and often require post-injection management.[3,4] A greater challenge looms, however, as many patients suffer concurrent GA and wet AMD,[5] especially as modulation of the complement pathway may increase the incidence of neovascular events.[6]

High-viscosity, large-molecule biologics increase the time and physician effort required to deliver a therapy through a small gauge needle. One of the GA drugs mentioned previously is recommended for delivery with a 29G or larger needle. However, in clinical trials, the other drug was delivered in two separate doses (at the same appointment) due to its high viscosity.[7]

Reports of rare, vision-threatening occlusive vasculitis have plagued several recently approved and pipelined therapeutics. Sharma *et al* (2022) warn that inflammatory effects are not new, but these cases represent a vision-threatening extreme of side effects that are actually common for intravitreal therapies, going on to recommend vigilance in the use of all new intravitreal biologics.[8]

As blockbuster anti-VEGFs lose patent protection, the intravitreal injection (IVI) space is predicted to fill with new entrants promising identical results at lower cost.[9] Biosimilars will drive adoption against an established preference for reference drugs, while established drugs will struggle to defend market share against lower-cost alternatives.[10]

> "As blockbuster anti-VEGFs lose patent protection, the IVI space is predicted to fill with new entrants promising identical results at lower cost."

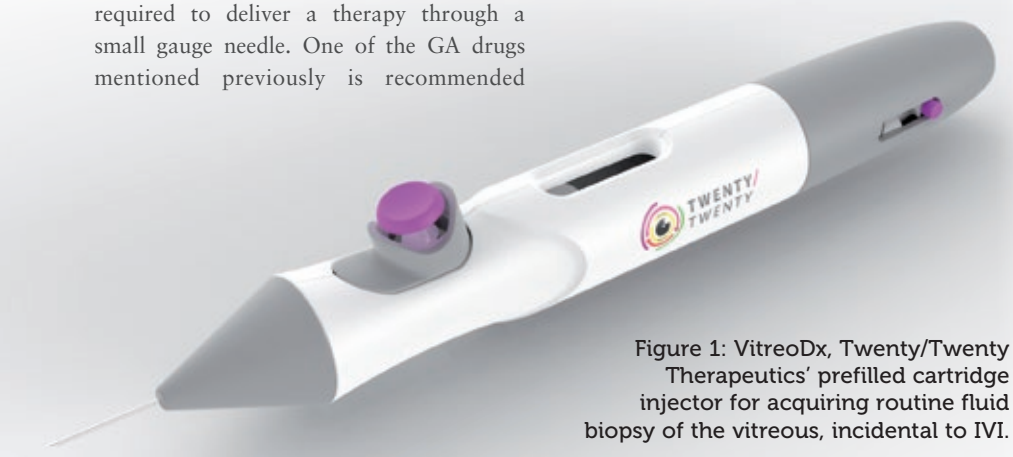


Figure 1: VitreoDx, Twenty/Twenty Therapeutics' prefilled cartridge injector for acquiring routine fluid biopsy of the vitreous, incidental to IVI.

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Future pipelined drugs acting on novel pathways promise benefit to individuals whose disease is driven primarily via those pathways.[11] On the other hand, retina care decisions are currently driven by what the specialist can see via structural imaging. While optical coherence tomography, fluorescence angiography and direct or photographic visualisation of the fundus can tell healthcare professionals if a patient has GA or swelling associated with neovascularisation, it cannot tell them the degree to which various pathways contribute to disease in a particular patient. Faced with this lack of information, doctors will generally choose the first line drug that works best for most patients, and then potentially trial an alternative if some criteria of observable change are not observed in response.

## VITREODX ENABLES ROUTINE LIQUID BIOPSY OF THE VITREOUS HUMOUR

Acquiring a liquid biopsy directly with a 25G needle "tap" procedure prior to a normally indicated IVI has been shown to be effective approximately 90% of the time. Twenty/Twenty performed a similar experiment *ex vivo* using non-vitrectomised human eyes, aged 76–91 years, suggesting that 30G needle taps may perform similarly in this cohort, in which the vitreous is significantly liquefied.

Following this evidence, Twenty/Twenty designed a device to perform the "tap and inject" procedure with an optimised workflow and minimal trauma to the patient – VitreoDx (Figure 1). The device is a prefilled, disposable, cartridge-based injector, with a novel aspiration mode. The key technical challenges it addresses include long term storage of 50–100 µL evacuated volumes, reliably switching between aspiration and injection modes in a smooth single motion, and easily removing the acquired sample for analysis. Twenty/Twenty also packages the system in an attractive industrial design that should be intuitively familiar to a retinal surgeon. The final surgical workflow is simple (Figure 2):

- After opening the sterile package, the needle of the device is inserted through the pars plana as per normal
- The surgeon presses a "button" to begin acquiring the sample

> "VitreoDx has the potential to mitigate problems currently facing intravitreal therapy."

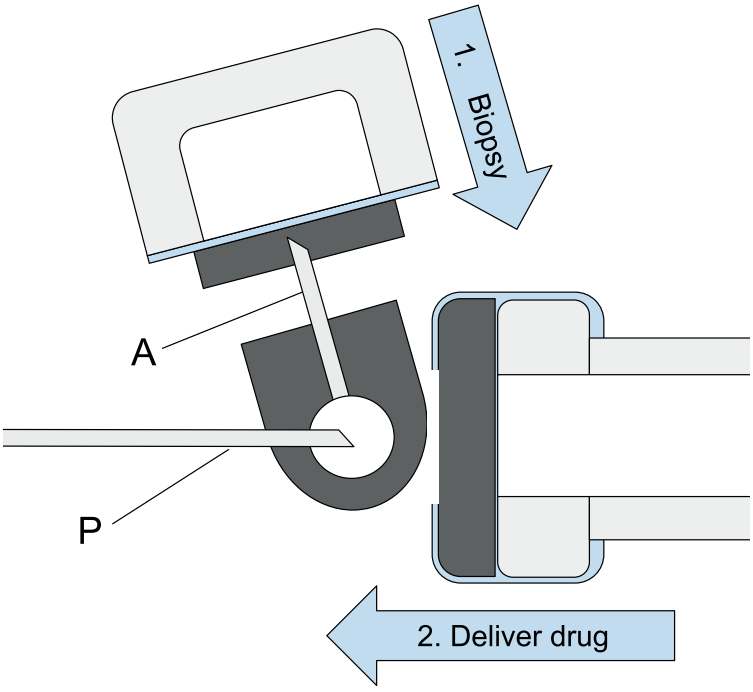


Figure 2: Schematic illustrating VitreoDx's unique fluidic system for acquiring a neat biopsy of vitreous fluid prior to injecting the drug. Arrows indicate the lateral pressing motion of the button to impale the evacuated biopsy chamber on the accessory needle (A), followed by the axial sliding motion of the button to impale the drug cartridge on the primary needle (P).

- After two seconds, the surgeon slides the "button" forward to initiate delivery of the drug
- After removing the needle from the eye, the surgeon can easily remove the sealed "button" containing the biopsy from the disposable contaminated sharps to be sent for analysis.

Microlitre fluid biopsies from *ex vivo* human eyes collected with VitreoDx prototypes have been analysed for over a hundred proteins related to angiogenesis and inflammation using a proximity extension assay from Olink (Uppsala, Sweden). Consistent with academic work on surgical vitreous specimens,[12] using the same proteomics assays, 90% of the assayed proteins were quantifiable in at least 25% of the submitted samples.

VitreoDx has the potential to mitigate problems currently facing intravitreal therapy. By removing liquid volume prior to injecting drug, VitreoDx prophylactically protects the eye from an IOP spike.[13] Because the acquired volume is similar to the injection volume and injection occurs directly after sampling, the eye is only briefly hypotonic, and need not be manipulated as a "soft" eye. When used with paired drugs during the same appointment, VitreoDx is best used with the largest injection, delivered first, to best equilibrate pressure and avoid aspiration of either drug. For a large majority of patients, the necessity of a post-injection paracentesis should be avoided. Because a preloaded spring automatically forces the drug from the cartridge, the surgeon does not lose dexterity struggling to extrude a high-viscosity drug through the needle.

The sample collected by VitreoDx presents a further opportunity for development and value creation (Figure 3). A sample analysis report describing a longitudinal history of the observed protein concentration in known angiogenic and inflammatory pathways, including anti-drug antibodies, can offer the surgeon an alternative viewpoint to supplement structural imaging,[12,14] and may aid in appropriately timing the next dose or flagging potential side effects.[8] The sample analysis may also help to identify patients who may benefit from highly specific drugs acting on novel pathways, such as by identifying patients who express the drug target at higher than typical levels.

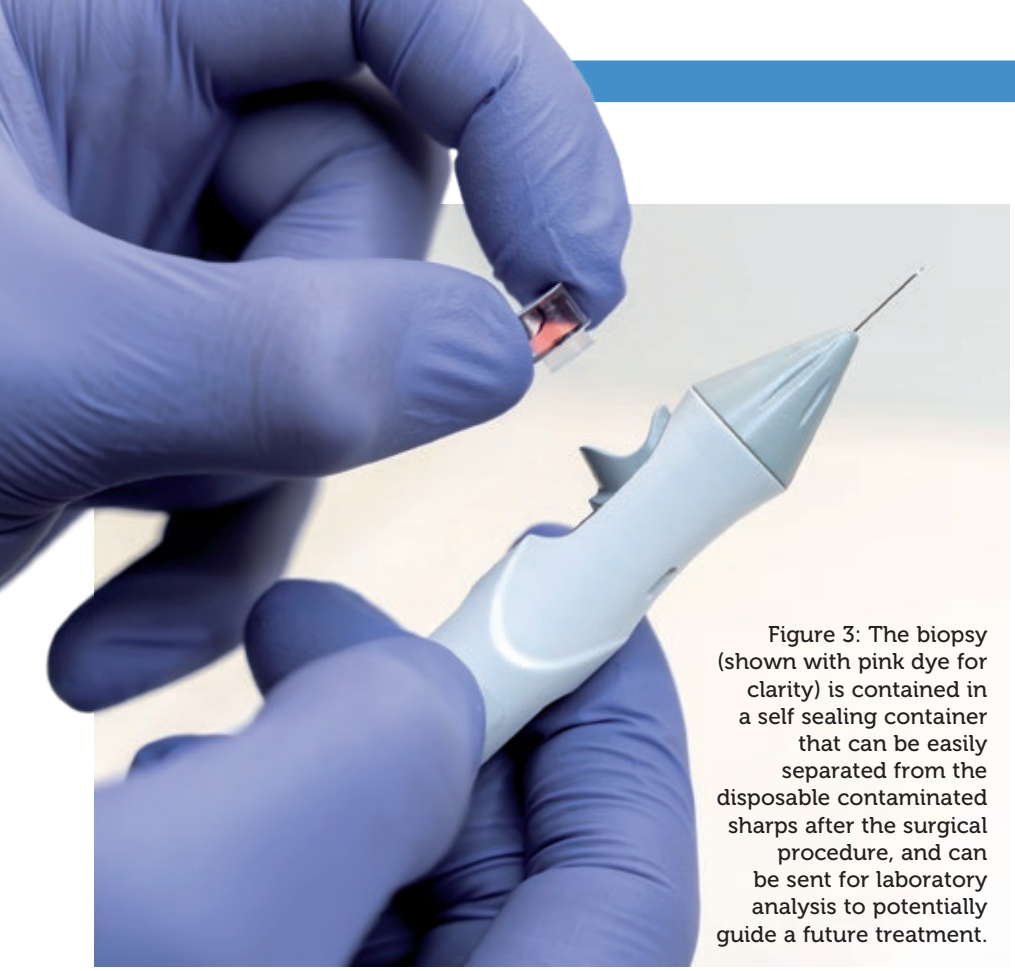

Figure 3: The biopsy (shown with pink dye for clarity) is contained in a self sealing container that can be easily separated from the disposable contaminated sharps after the surgical procedure, and can be sent for laboratory analysis to potentially guide a future treatment.

Doctors using this device and analysis may be able to take advantage of procedure codes describing in-office "tap-and-inject" for greater reimbursement. Taken together, the workflow, patient advantages and increased procedure compensation represent an opportunity for a differentiated product, even when packaged with first-line medications that may be pharmacologically similar to competitors.

In addition to benefits in clinical practice, pharmaceutical developers stand to gain from routine liquid biopsy in research activities. For example, clinical trial success is likely to be improved by enriching the study population by selecting subjects who express a drug target protein above a specific threshold.[15,16] Companies that engage in routine vitreous liquid biopsy in trials or in clinical practice will have access to large libraries of rich data from which to discover novel drug targets.[17]

> "In addition to benefits in clinical practice, pharmaceutical developers stand to gain from routine liquid biopsy in research activities."

The VitreoDx device described in this article has completed feasibility testing and design for manufacturing is in process. This product in development has not been evaluated by the US FDA and is not available for sale in the United States. Twenty/Twenty Therapeutics is now actively seeking device and pharma partners who are interested in participating in validation activities to discover the value of routine vitreous liquid biopsy.

## ABOUT THE COMPANY

Twenty/Twenty Therapeutics is a joint venture between Verily Life Sciences, an Alphabet company, and Santen Pharmaceutical, a leading Japanese ophthalmology company. VitreoDx is a central pillar of Twenty/Twenty Therapeutics' mission to develop transformative innovations to prevent and halt vision loss in patients with macular degeneration.

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## ABOUT THE AUTHOR


**Alexandre Tumlinson**, PhD, leads the engineering programme at Twenty/Twenty Therapeutics, creating devices to improve intravitreal therapy. Prior to working on drug delivery systems with the ability to perform interesting diagnostic functions, he worked as a Senior Staff Scientist with ZEISS Meditec, developing the kind of structural imaging that he is now trying to supplement. Dr Tumlinson received his PhD in Biomedical Engineering from the University of Arizona (US) and undertook his postdoctoral research at the Cardiff School of Optometry (UK). Prior to his doctoral work, Dr Tumlinson earned a BSE in Optical Engineering and a MS in Optical Science from the University of Arizona (US).

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# "A CHILD IS NOT A SMALL ADULT": CHALLENGES AND SOLUTIONS IN DEVELOPING DRUG DELIVERY DEVICES FOR CHILDREN

In this article, Tom Oakley, Director of Drug Delivery Device Development, and Heather Jameson, Senior Engineer, both of Springboard, consider the main differences in developing therapies and drug delivery devices for children and babies when compared with adults.

Paediatricians have been known to say, "a child is not a small adult!" Why do they say this, and what does it mean for developing therapies and drug delivery devices?

This article itemises the main differences between adults and children and the implications, including:

- Anatomical development
- Metabolism and pharmacokinetics
- Patient ability and usability
- Patient preference and adherence.

## ANATOMICAL DEVELOPMENT

The anatomical development of the child is critical when considering therapies and devices. Apart from the obvious changes in height and weight over time, there are more subtle changes that occur as the child grows. For example, the sitting height of a newborn infant represents about 70% of total body length but, by the age of three years, this typically reduces to 57% and, as an adult, typically 50%. In newborn infants, muscle mass constitutes approximately 25% of body weight compared with 43% in adults.[1]

Growth and development are not constant processes for the individual, and they vary greatly between individuals of the same age. For newborn children, gestational age (age since conception) can be more meaningful than age since birth.

Nasal anatomy is an example where key differences exist between children and adults. Infants under two years old also have more diffuse lymphoid follicles throughout the nasal cavity in addition to the nasal-associated lymphoid tissue areas found in the adult nasal cavity.[2] Infant nasal anatomy has a greater degree of similarity to rodents than that of adult humans, meaning that the results of studies with rodent models could be more applicable for human infants. This could theoretically help to accelerate development of infant nasal vaccines; however, in practice safety and efficacy are generally established in adults before any infant studies commence for reasons we will cover later.

> "The differences in anatomy between children and adults, as well as between anatomical ages, have many implications for drug delivery devices."

The differences in anatomy between children and adults, as well as between anatomical ages, have many implications for drug delivery devices. For example, emergency autoinjectors that inject into the muscle need to account for the difference in fat and muscle distribution in children, and inhalers need to be appropriate for the smaller lung capacity and inspiratory flow rates in children. Some injection sites that are suitable for adults might be unsuitable for young children.

## METABOLISM AND PHARMACOKINETICS

Children have a reduced ability to maintain homeostasis compared with adults due to their greater metabolic and nutritional requirements (relative to their body mass). Most of the first year of life is characterised by immaturity of kidney and liver function, so younger children are more susceptible to dehydration,

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"When most new medicines are licensed or receive their marketing authorisation, they are only licensed for use in adults."

fever and other conditions. Therefore, drug delivery devices may need to allow for more regular delivery of smaller doses than for adults, or even quasi-constant drug administration, possibly under the supervision of a clinician. Dose increments may need to be smaller for children than adults.

The reticuloendothelial system, composed of macrophages found in the lymph nodes, spleen and other lymphatic tissues, is comparatively more active in childhood. Lymphatic tissues, such as tonsils and adenoids, swell rapidly in response to minor infections. Antibody production is different in infants compared with older children or adults. Thus, drugs that influence the immune system, such as immunosuppressant monoclonal antibodies, may need to be given in different doses, to different parts of the anatomy (for example, multiple injection sites), with different pharmacokinetic modifiers (such as sustained-release formulation or even implants).

When most new medicines are licensed or receive their marketing authorisation, they are only licensed for use in adults. This is because, on the whole, the manufacturer only investigates their safety and efficacy in the adult population. This could be due to a lack of commercial incentive for conducting studies in children or an inability to recruit enough children for clinical trials. In 2004, the UK government recognised the need for high-quality research in children and young people and resolved to establish a national research network to study medicines for children.[3]

## PATIENT ABILITY AND USABILITY

There is a widespread trend across healthcare to move treatments from the hospital to the general practitioner, and from the general practitioner to self-administration. Reasons for this are well documented and tend to focus on patient convenience and reduction of healthcare costs.

However, there are additional considerations when treating children compared with most adults.

The ability of the child to self-administer drugs is likely to be limited, especially for younger children. In the first few years of life, "the user" is going to be an adult, for example, a parent, other carer or clinician. The separation of "user" from the "patient" means that device design might need to be modified. Imagine an on-body delivery system where the user interface is designed for the patient to operate but, in this case, somebody else must operate it. A display or icon designed for the patient to see when they look down at their stomach will be upside down when viewed by a user who is facing the patient (Figure 1).

Training and instructions for use can be more complicated for treating children because multiple people (child, parent, clinician, etc) may need to be involved, each having different roles and varying levels of life experience and learning needs. A study of the readability of manufacturers' patient information leaflets for commonly used medicines for children showed that nine out of 10 could not be read at a reading age of 13. Indeed, many adults would not be able to use those instructions because 9% of adults have a reading age of 13 or lower.[3]

Figure 1: Child positioning a wearable injector on his stomach, ready for use.

Young children may find it more difficult to alert adults to adverse events such as pain, nausea or swelling, and so extra care must be taken to ensure that the drug delivery device and drug are not causing excessive side effects.

Co-ordination of movement can be harder to achieve for children than adults. Several studies have shown that adults struggle to co-ordinate the activation of a pressurised metered dose inhaler with their inhalation manoeuvre. The smaller lung capacity and inspiratory flow rate of children mean that the optimal activation window is even smaller. Therefore, many children need to use a spacer with a pressurised metered dose inhaler.[4] Even then, around 20% of children under two years old cannot generate the inspiratory pressure to open a unidirectional valve of a valved holding chamber (Figure 2).[5]

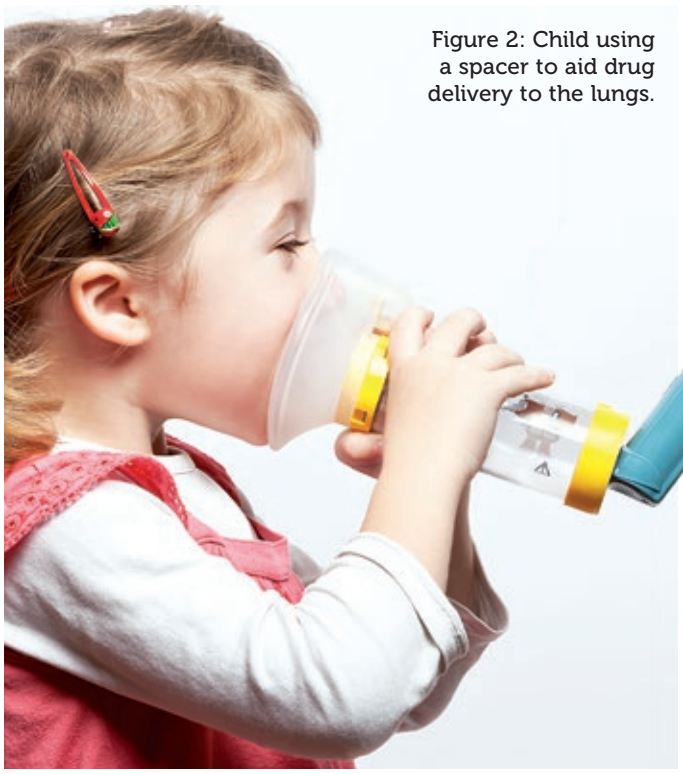

Figure 2: Child using a spacer to aid drug delivery to the lungs.

## PATIENT PREFERENCE AND ADHERENCE

Medical devices for adults are tending to look increasingly like consumer products due to patient preference (such as fitting with their lifestyle image) and user interface expectations.

Children are likely to have different preferences and values from adults. Some pharmaceutical and medical device companies have made progress in adapting devices to appeal to children, for example, by having superhero or other graphic themes on the device.

Some companies have considered adding fun or engaging features to drug delivery devices that could motivate children to adhere to the instructions for use, for example, adapting an inhaler to play a sound when inhaling correctly. Others have added "gamification" to devices so that children feel more engaged, motivated and positive about interacting with their therapy regime.

There is evidence of adverse consequences because of low compliance in children in prophylactic treatments, especially in antibiotics, asthma, epilepsy and lymphoblastic leukaemia. Adolescence poses a special challenge concerning treatment compliance: the evidence shows low rates of adherence in cystic fibrosis, diabetes and asthma.[3]

> "The ability of the child to self-administer drugs is likely to be limited. In the first few years of life, 'the user' is going to be an adult, for example, a parent."

## SUMMARY

We have seen how the differences in the anatomy, metabolism, ability and preferences of children demand customisation of drug delivery devices to meet their needs. Deep understanding of the patients and users (who are often different people) is necessary when delivering drugs to children and babies. Research and formative studies need to be conducted early and throughout device development, and the treatment regime and device characteristics may need to be different depending on patient age.

## ABOUT THE COMPANY

Springboard is an engineering consultancy that specialises in developing devices from concept to manufacture for regulated markets. The company is an expert in creating innovative yet robust designs and solving difficult technical problems quickly. Springboard does not have internal projects, so is as fast and cost effective as possible, and the intellectual property entirely belongs to its clients.

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## ABOUT THE AUTHORS


**Tom Oakley** leads engineering and scientific teams developing new injection devices, pumps and inhalers. He has been the named inventor on dozens of patents throughout his 20 years' experience in industry. Mr Oakley is a regular speaker at various international conferences on innovation and medical device development, and mentors engineering and MBA students on innovation and device development at the Cambridge University Engineering Department and the Judge Business School (Cambridge, UK). He read Engineering at Cambridge University before becoming the Choate Fellow in Human Physiology and Pathology at Harvard University (MA, US).

**Heather Jameson** is a Senior Engineer at Springboard, taking a leading role in planning and executing both design and test projects and has worked on the design and development of several drug delivery devices. She read Engineering at Cambridge University (UK), before completing a PhD in Fluid Mechanics at the distinguished Whittle Laboratory. She continues to play an active part in university relations in addition to her public speaking engagements on STEM and outreach.


2023 PDA

# THE UNIVERSE OF PRE-FILLED SYRINGES AND INJECTION DEVICES CONFERENCE

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# COMBINING PLASTIC BAG FLEXIBILITY WITH GLASS STORAGE STABILITY – NEXT-GENERATION PACKAGING FOR SENSITIVE PREMIXED DRUGS

In this article, Pauline Koyanagi, Global Business Development, Pharmaceutical & Medical Packaging, and Atsushi Mio, Technical Advisor, both at ZACROS, look at the benefits of flexible drug packaging and discuss the benefits of the company's MediTect™ packaging for sensitive liquid parenteral formulations.

Intravenous (IV) drugs are most easily administered using a premixed, ready-to-use bag. Unlike injectables that require admixing, these are essentially a closed system, mitigating the risk of exposing patients and medical workers to harmful chemicals and avoiding the risk of human error in drug preparation. Premixed bags eliminate the time needed for drug reconstitution and provide the ideal grab-and-go solution, which may be crucial in emergency situations when every second counts to save a life.

Additionally, flexible plastic packaging is lightweight, robust and easy to handle, with a lower carbon footprint than glass. Lighter and more compact, it requires less material for manufacture than rigid containers and takes less space for transport, storage and disposal.

> "Conventional IV bags are not suitable for many sensitive drugs due to stability problems, and injectable drugs known to be unstable in plastic are still typically packaged in glass bottles or vials."

However, conventional IV bags are not suitable for many sensitive drugs due to stability problems, and injectable drugs known to be unstable in plastic are still typically packaged in glass bottles or vials. The provision of stable, next-generation IV bags promises to solve these problems by helping to ensure the purity of drugs administered to patients, thereby improving patient safety and outcomes and reducing the burden on medical staff.

## REDUCING THE RISK OF INTERACTION

When changing a dosage form from a concentrated solution in a glass container, such as a vial or an ampoule, to a ready-to-use plastic bag, the chief concern is the interaction of the drug formulation with the bag's plastic surfaces. Primary containers are designed to prevent all interaction between the drug contents and the packaging material, including extractables migrating into the formulation and sorption of the API into or onto the bag itself. This is vital to preserve the intended potency of the contained drug.

Conventional IV bags are recommended for IV infusion of stable drugs that have a low level of interaction. However, these are not suitable for several small molecules and biologics, including those with highly diluted APIs such as large-volume parenterals.

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Established in 1914, ZACROS is a Japanese company that converts flexible films into a range of packaging solutions. It has created unprecedented functionality in flexible plastics, with core competencies in film casting/co-extrusion and bag-making. This is backed by extensive research into cyclo-olefin polymers and copolymers (COP/COC), which are important engineering plastics with many useful properties.

For parenteral container applications, COP/COC were initially used for prefilled syringes and vials – rigid containers made from injection moulding. ZACROS was the first company to succeed in making COP into a flexible film, and the company has spent seven years developing and refining non-interactive (NI) films that prevent elution and sorption. This has enabled the production of IV bags that offer ultimate stability for sensitive drug contents, combining glass-like storage stability with the flexibility of plastic bags. The NI resin used for the layer in contact with the contained drug enables historically unstable drugs to be packaged in plastic and immediately administered to a patient (Figure 1).

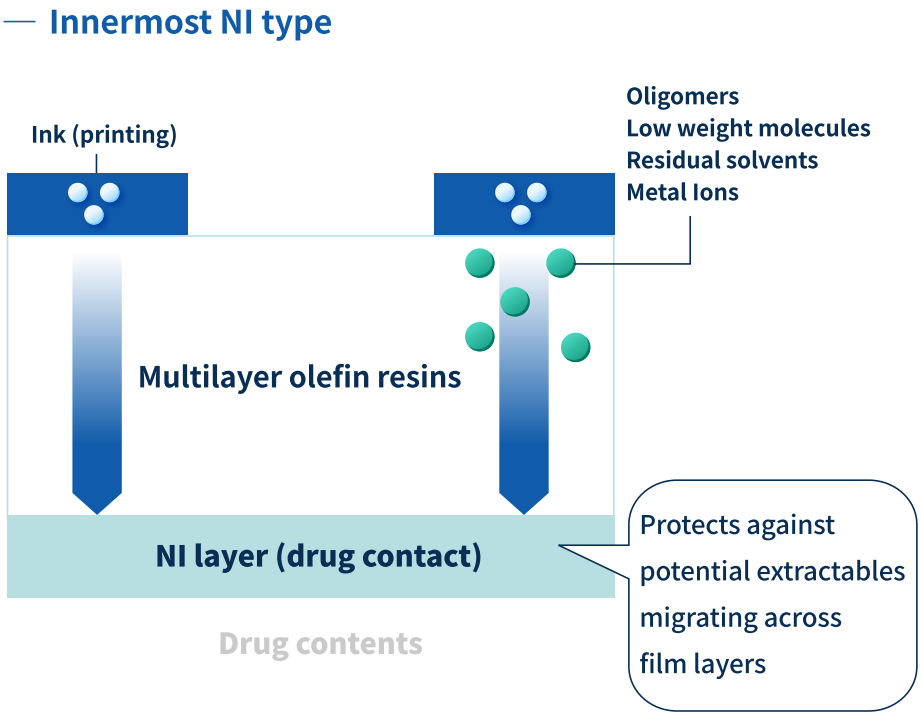


Figure 1: The NI layer acts as the ultimate defence against potential extractables.

## MEDITECT™ TECHNOLOGY

MediTect™ packaging has been created by ZACROS specifically for sensitive liquid parenteral formulations, and is dedicated to maintaining sensitive liquid pharmaceuticals in their original state from formulation to administration. It offers a variety of material options and properties, making it ideal for premixed bags. Its main applications are neurological drugs, angina treatments and osteoporosis treatments.

Product features include:

- NI properties, enabling glass-like drug stability performance
- US FDA drug master file (DMF) registered, and compliant with EP, USP and JP regulations
- High level of safety, hygiene and functionality ensured by multilayer co-extrusion technology
- Manufactured in a ISO 15378 & 13485-compliant site (ISO Class 6 cleanroom).

The proprietary NI technology combines an unparalleled level of chemical compatibility and sorption resistance with an ultra-low extractables profile. The multilayer olefin resin minimises extractables of all kinds, including polyolefin oligomers, residual solvents, additives, adhesives and inactive ingredients volatilised from ink. Such extractables cause drugs to become unstable and can compromise the quality of the IV solution.

The properties of the NI film provide product integrity and help to maximise the shelf life for the most demanding applications. Performance data show that the bags maintain the potency of APIs over time by the prevention of sorption effects comparable with glass container controls (Figure 2).

MediTect™ IV bags have many different construction options. Table 1 provides information about ZACROS's standard bag options compatible with hydrophobic APIs.

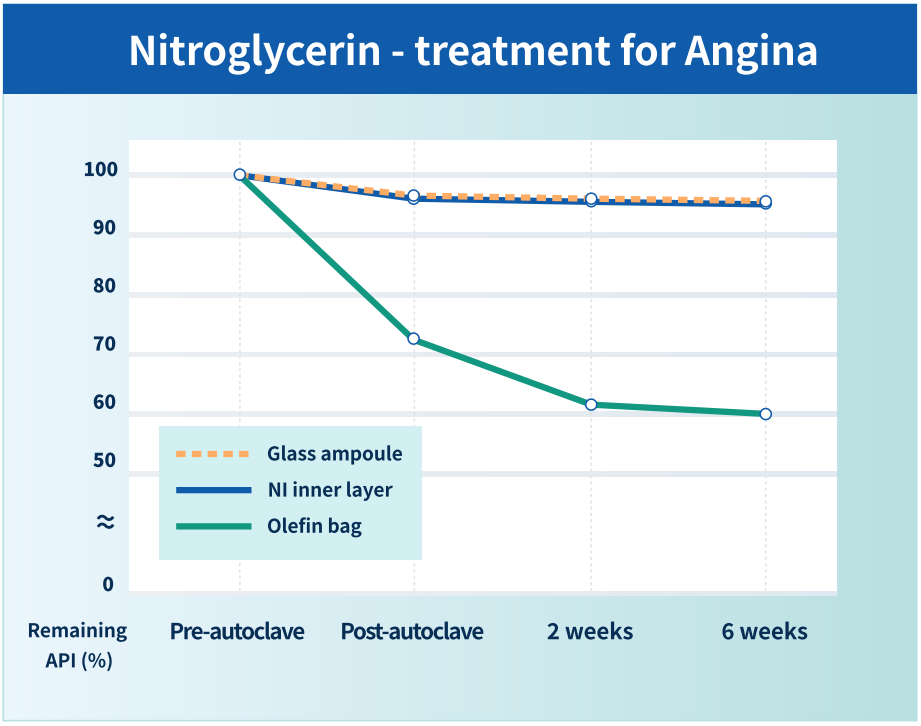


Figure 2: MediTect™ bags maintain the potency of APIs over time comparable with glass container controls.

| | NI-PP (inner NI) | NI-PP (inter NI) |
|---|---|---|
| **Film layers** | PP/AD/NI | PP/AD/NI/AD/PP |
| **Fill volumes** | 50–300 mL | 50–300 mL |
| **On-bag printing** | Yes | Yes |
| **MVTR (g/m²/day)** | 1.1 | 1.5 |
| **Heat resistance** | 121°C compatible | 121°C compatible |

Table 1: ZACROS's standard bag options compatible with hydrophobic APIs.

## WORKING IN PARTNERSHIP TO DELIVER NEXT-GENERATION FLEXIBLE PACKAGING

ZACROS has an integrated manufacturing process for MediTect™ products from start to finish. It can develop products to meet specific requirements and can work directly with companies or introduce experienced contract manufacturing organisations for filling. ZACROS's liquid medicine primary packaging has been sold in the US and Japan for over 30 years, and some products are DMF registered. Staff are well versed in major regional regulations and guidelines and can help with submissions to the FDA and other regulatory authorities.

MediTect™ IV bags have been commercialised in Japan for over ten years. For example, ZACROS has worked with one of its partners to develop premixed bags for the administration of nitroglycerin to treat heart failure. All infusion bags are compliant with ISO standard 15747 (covering plastic containers for IV injections) and can keep the drug stable after autoclave terminal sterilisation and long-term storage. Bags come in a variety of shapes, sizes and labelling and can be made with various materials of construction. All are non-PVC and DEHP-free. ZACROS is currently broadening its portfolio by including aseptic-filling compatible IV bags that are focused on biologics.

Testing facilities are available for MediTect™ products, and ZACROS's R&D centre in Japan offers opportunities for joint development. Prototypes and samples are readily available, and bags may be customised to multiple sizes and configurations. The R&D centre offers powerful evaluation equipment to customers, who can make use of the prototype workshop and small-scale modular equipment for quick sample creation. The machinery room has filling machines for each type of packaging, sterilisation systems, handling systems and other semi-automated machines that are available for testing and assessing customer-tailored packaging and contents.

The experimental factory is intended for joint-development and in-house experimenting, where quick testing and assessing is possible. Isolators make it possible to handle and perform tests with a wide range of pharmaceutical contents directly on the premises.

For additional barrier properties, overwrap secondary packaging is also available. Overwraps are an economic way to add barrier properties to primary packaging as desired. For example, for products that are sensitive to oxygen, wraps are available that have very high oxygen barrier properties – these have been tested and developed and are already on the market. These pouches come in a variety of shapes, sizes and colours, and can be made with various materials of construction (VM-PET, aluminium, etc).

Increasing interest from overseas means that ZACROS is now working with a range of pharma and biotech companies to develop products for specific applications and create differentiated, novel containers. The platform is expanding from small molecules and terminal sterilisation to include biologics and aseptic filling, with more formats in development. The bags have proved compatible with all drugs that have been tried so far.

As the technology develops further, ZACROS believes that it will become a key enabler for modern healthcare, allowing safe, regular drug administration in a home setting and therefore fewer hospital visits.

## ABOUT THE COMPANY

ZACROS, also known as Fujimori Kogyo, is a Japanese converter of flexible films and packaging that was established in 1914. ZACROS as a brand has reliably and effectively provided support to the pharmaceutical industry with all forms of flexible packaging for all kinds of solutions, including for injectables, oral and transdermal drug delivery. Besides healthcare, the ZACROS Group also supplies the business fields of personal care, electronics, IT and infrastructure.

## ABOUT THE AUTHORS

**Pauline Koyanagi** is responsible for the global business development of ZACROS's pharmaceutical and medical packaging. Her main role includes the promotion and identification of new market opportunities for the MediTect™ technology. Prior to joining ZACROS, Ms Koyanagi worked in marketing and international business development in various industries for nearly seven years.

**Atsushi Mio** is a technical advisor for ZACROS's pharmaceutical and medical packaging. He was previously widely involved in the development of parenteral drug containers as an R&D engineer and manager. Mr Mio has more than 16 years of professional experience in this area and contributes to enhancing relationships with worldwide pharmaceutical industries.

ZACROS

# MediTect™ - achieve glass-like packaging performance combined with the flexibility of plastic for next-generation drugs


**MediTect™** is designed specifically for sensitive pharmaceuticals for IV infusion. The Non-Interactive (NI) film minimises potential extractables and sorption effects, and achieves the required shelf life for ready-to-use products.

**ZACROS's** differentiated containers will set your product apart from the rest.

Contact us today for an initial assessment

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Stevanato Group

# BIOLOGIC INTEGRITY: MEASURING AND MANAGING THE HIDDEN LEACHABLES RISK FROM PFS ADHESIVE

**Here, Enrico Barichello, Syringe Product Manager at Stevanato Group, considers the often-overlooked influence of adhesive in the assembly of prefilled syringes and how the hidden risks can be managed and overcome.**

The growing prevalence of biologic drug products witnessed in recent years has been matched by a parallel increase in demand for prefilled syringes (PFSs) as the delivery mechanism of choice.

These innovative systems offer numerous key benefits, providing a precise pre-measured dose of a particular medication within a ready-to-use secure container. Beyond this, PFSs offer the advantages of reducing the risk of dosage errors, avoiding the potential for contamination caused by repeatedly inserting and withdrawing a syringe into a vial, and enhancing patient convenience in self-administration or autoinjector applications.

However, when it comes to biologics and biosimilars, the benefits of PFSs can only be realised if specific factors around safety and efficacy are considered. Generally, drug products of this nature present challenges around integrity and stability due to their sensitive nature. For example, in injectable form, the liquid formulation can be susceptible to degradation or contamination through interaction with the critical components that make up the primary packaging of the PFS.

In light of this, pharma companies and their delivery partners naturally put significant focus on the various elements that present a threat to the container closure system and have the potential to compromise the purity of the drug product within. Among these elements, however, there is one that remains relatively unexplored and uncharacterised in terms of its influence on drug integrity – the adhesive used in the assembly for staked-needle syringes.

> "The presence of the adhesive introduces a potential contamination risk, as it is an additional substance in direct contact with the drug product."

## CHALLENGES IN UNDERSTANDING SYRINGE GLUE LEACHABLES

With staked-needle PFSs, patient convenience and safety is increased as there is no requirement to attach a needle prior to delivery, which means time-consuming steps that could otherwise introduce human error are removed. To facilitate this, the adhesive plays a vital role in securing the needle to the glass in the cone of the syringe barrel. However, at the same time, the presence of the adhesive introduces a potential contamination risk, as it is an additional substance in direct contact with the drug product. In particular, it could result in leachable compounds migrating from the adhesive into the dose over time under normal storage conditions.

Adhesive leachables, such as acrylates, are problematic because they can potentially react with proteins and pose a risk to the integrity of the drug product. Given the sensitivity and complexity of biologic drug molecules, a comprehensive assessment of leachables is therefore essential to

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avoid undesirable interactions that could compromise drug quality or patient safety. This demands close control over the formulation, application and curing process of the needle adhesive, with a clear understanding of the interaction between the adhesive and the individual characteristics of the specific biologic formulation in question.

It might be assumed that such challenges can be overcome in large part through knowledge of the raw materials that constitute the adhesive, and suppliers are indeed likely to be able to provide preliminary extractable data relating to the ingredients used to form the adhesive compound. However, while this information should form part of the overall assessment, it does not account for the parameters associated with the final gluing and curing process, which, critically, can introduce new compounds that could impact the extractables profile and pose a risk to the purity of the drug product over time.

## ADDRESSING SYRINGE-GLUE COMPATIBILITY

Pharma companies therefore face a situation where they must, in the interests of efficacy and patient safety, interrogate their choice of syringe platform in its market-ready state for the risk of extractables. Furthermore, the evaluation of syringe-glue compatibility should ideally be carried out early in the development process to avoid the possibility of subsequent complications and delays. In following this path, crucial questions emerge – What testing process should be followed? Does the chosen syringe platform allow for customisation to address any concerns that might be identified? Where should the process begin?

Stevanato Group undertook a project on behalf of one customer that provided important responses to these challenges based on a comprehensive assessment of the parameters involved in the gluing process. This work encompassed anticipation and management of potential issues that may arise in relation to leachables, including a tailored approach to resolving interaction-related concerns.

> "The evaluation of syringe-glue compatibility should ideally be carried out early in the development process to avoid the possibility of subsequent complications and delays."


Figure 1: Both processes, industrial and bench top, employ a system using LED lights for the core task of curing the adhesive.

The project employed the design of experiments approach and method development in order to evaluate the influence of relevant variables and identify specific glue-derivative compounds that may interact with the drug product. This resulted in the creation of a series of experiments that accurately recreated the conditions being assessed and allowed for high-impact process parameters to be tested using varying values.

## ENSURING PRECISE TESTING AND ANALYSIS

In any scientific approach to testing and analysis, precision is critical to the quality of the results. In this case, Stevanato Group's in-house manufacturing equipment was used to develop a dedicated bench-top unit, upon which all experimental activities were conducted with meticulous attention to methodological detail. To ensure that the findings from the test correlated with authentic manufacturing processes, the bench-top unit was also calibrated in line with the real-world machinery used for needle assembly (Figure 1).

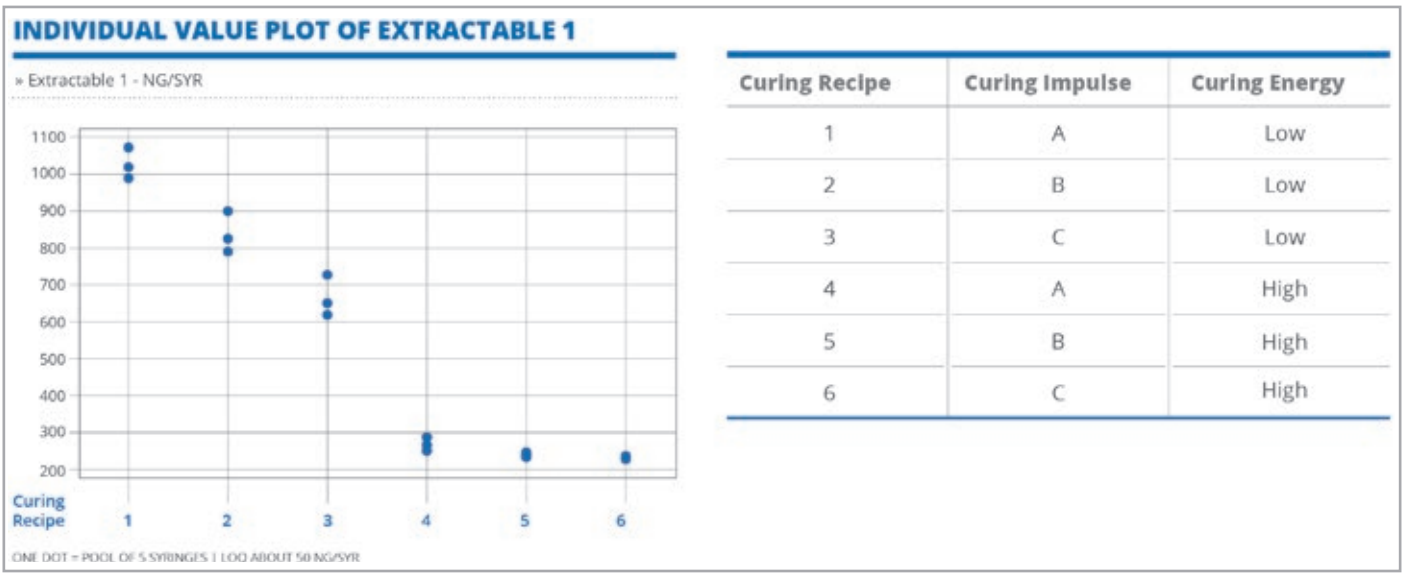
Both processes, industrial and bench top, employed a system using LED lights for the core task of curing the adhesive. This approach was designed to deliver improvements in the polymerisation process while also reducing the levels of energy consumption required.

A principal objective of the testing activities was the screening, detection and analysis of various potential extractables. As such, the Stevanato Group Technology Excellence Centers developed multiple techniques capable of quantifying the presence of glue-based compounds, such as acrylic acid, in the final cured adhesive. These techniques included high performance liquid chromatography and ion chromatography.

By optimising the parameters of the curing process through changes in curing impulse and energy, the tests allow the Technology Excellence Centers to determine the nature of the relationship between the curing method and any extractables observed. This provided the insight that is necessary for customising the adhesive curing method for a specific drug formulation, ultimately allowing adaptations to be made that minimise the risk of adverse interactions and ensure the highest level of drug product quality and patient safety.

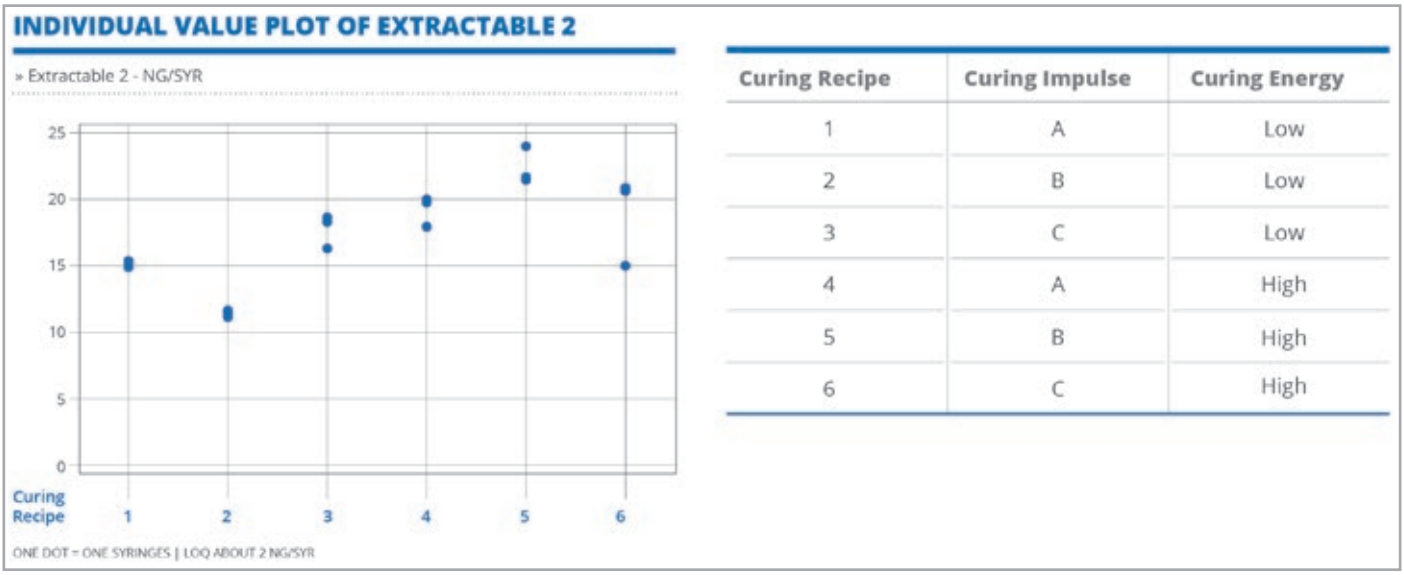
## CUSTOMISABLE APPROACH FOR OPTIMAL RESULTS

In both cases, the levels of extractables – measured in ng per syringe – varied with each of the different adhesive curing combinations (Figures 2 and 3). Generally, higher curing energy facilitates better polymerisation of the glue, resulting in lower values of extractables. However, it is noteworthy that this relationship does not apply universally to all extractables. Rather, there is the potential for certain extractables to display unique behaviours that would require specific adjustments to be made to the curing process parameters to maintain extractable levels within a desirable threshold.




| Curing Recipe | Curing Impulse | Curing Energy |
|---|---|---|
| 1 | A | Low |
| 2 | B | Low |
| 3 | C | Low |
| 4 | A | High |
| 5 | B | High |
| 6 | C | High |

Figure 2: Generally, higher curing energy facilitates better polymerisation of the glue, resulting in lower values of extractables.




| Curing Recipe | Curing Impulse | Curing Energy |
|---|---|---|
| 1 | A | Low |
| 2 | B | Low |
| 3 | C | Low |
| 4 | A | High |
| 5 | B | High |
| 6 | C | High |

Figure 3: For certain extractables, higher curing energy does not result in lower values of extractables.

> "A customised approach, based on specific drug formulation requirements, allows for the precise manipulation of curing impulse and energy to minimise the risk of adverse interactions and ensure the highest level of drug product quality and patient safety."

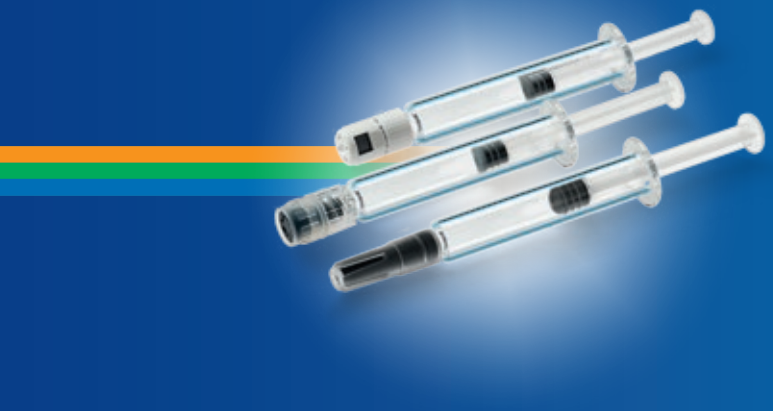
These insights emphasise the complexity of the curing process and the diverse behaviours of extractables in relation to curing. This underlines the importance of taking a nuanced and tailored approach to the management of this risk, wherein a thorough evaluation of individual extractables is necessary to refine the adhesive process for optimal results. A customised approach, based on specific drug formulation requirements, allows for the precise manipulation of curing impulse and energy to minimise the risk of adverse interactions and ensure the highest level of drug product quality and patient safety.

Stevanato Group can help drug manufacturers effectively address potential leachables issues through an approach that combines quality components with customised support as part of an integrated offering. The foundation for this approach is provided by the Alba® and Nexa® syringe platforms. Both platforms have been designed to incorporate properties that mitigate the risk from extractables. Alba® syringes have been optimised specifically for applications involving high-value sensitive injectables, thanks to the addition of a specific internal coating (Figure 4).

When employing these products, pharma customers will know that every aspect of the individual components that form the complete system has been developed with consideration not only for injectable performance, but also for supporting the stability and integrity of the drug product. This, of course, includes the adhesive used in the needle assembly.

# Alba®

## A BREAKTHROUGH SOLUTION FOR YOUR GAMECHANGER BIOLOGICS



**As pharmaceutical partners embrace the potential of biologics, we have developed our proven syringe platform, Alba®, to enable the optimisation of your opportunity.**

We know your challenges, including the increased viscosity and stability of biologics and the relative injection forces required for effective delivery. And we have responded.

The Alba® syringe meets the requirements of high-value and large volume biologics. Combining our cross-linked coating technology with dimensional, geometrical accuracy, and enhanced glide capability; this platform significantly reduces the release of sub-visible particles and inorganic extractables.

Easily integrated into automatic drug delivery devices, such as spring-based autoinjectors, and optimized for smooth self-administration, Alba® meets the needs of our pharma companies and their end users in equal measure.

Stevanato Group

MANAGING COMPLEXITY, DELIVERING VALUE

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Figure 4: Alba® syringes – Stevanato Group's breakthrough solution for biologics.

But, as the study results have shown, drug products cannot be expected to demonstrate universal properties when it comes to containment. The risk of leachables from adhesives will vary depending on the specific formulation in question. This means that a level of customisation is essential to arrive at an adhesive curing process that minimises the risk of compromising a given drug's integrity by the presence of extractables.

The testing methodology described here provides the basis for analysing this risk for an individual API, employing the skills and knowledge of Stevanato Group's in-house engineering team. This analysis opens the door to iterative development work, where the parameters of the adhesive curing process can be modified to address extractable levels. Thanks to the close integration between product teams, engineering teams and materials suppliers, as well as the ability to draw on previous experience of this process, Stevanato Group has the capabilities assist customers in arriving quickly at a compatible solution for protecting their high-value drug products.

## CONCLUSION

While it might not be an aspect of containment that attracts significant attention, consideration of leachables in syringe adhesive can be of paramount importance when it comes to PFS applications involving biologic drug products. The evidence from testing conducted by Stevanato Group shows that it has the potential to influence the levels of extractables in ways that might not be well understood, as well as in ways that will be specific to a given drug. It is only through a clear understanding of the interaction between adhesive and drug, and a focused approach to customising the curing process, that this relatively hidden risk can be managed and mitigated, avoiding any compromise to drug quality and patient safety.

## 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 Group delivers an integrated, end-to-end portfolio of products, processes and services that addresses customer needs across the entire drug lifecycle at each of the development, clinical and commercial stages. Stevanato Group'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.

## ABOUT THE AUTHOR

**Enrico Barichello** has a background in industrial engineering and a Master's degree 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 Alba® platform.

# RISING TO THE REGULATORY EVIDENCE CHALLENGE FOR HIGH-QUALITY COMBINATION PRODUCTS

In this article, Victoria Morgan, Director Strategic Marketing, Biologics, and Stacy Gates-Rector, PhD, Principal Scientist, Scientific Communications, both at West Pharma Services, explore how West is supporting pharma companies with packaging challenges through the supply of high-quality prefillable syringe plungers and provision of a highly co-ordinated technical documentation package.

When it comes to the regulation of medical devices, standards are only going in one direction. The recent revision to the medical devices requirements, which resulted in the publication of the EU Medical Device Regulation (MDR),[1] shows how the activities of pharmaceutical companies must continually adapt and adhere to ever higher regulatory thresholds, driven by an impetus to enhance quality, safety and effectiveness.

However, while all stakeholders applaud this direction of travel, there is no escaping the fact that it has made the product development journey more challenging. As well as ensuring that combination products are designed, specified and developed to meet updated regulations, pharma companies must also deliver a comprehensive dossier of data to evidence compliance. Answering the full breadth of these requirements relies on having access to the right data at the right time and presenting it in the correct form, or the process can quickly become mired in complexity, delays and unnecessary cost.

West is able to support pharma companies faced with these packaging challenges, not just through the supply of high-quality prefillable syringe plungers, but also through the provision of a highly co-ordinated technical documentation package (TDP). This service offers significant value for streamlining the gathering, assimilation and delivery of supporting data across multiple criteria, having already allowed several customers to demonstrate regulatory compliance with greater speed, efficiency and ease.

## A DEVELOPMENT BORN OUT OF TRAGEDY

In 2010, it was revealed that almost 400,000 women had received breast implants from PIP (Poly Implant Prothése) that featured unapproved industrial-grade silicone instead of approved medical-grade silicone. Many of those with industrial-grade silicone ruptured, causing serious illness and, in some cases, death (Figure 1).[2]

In September 2012, this incident, set against a backdrop of a no longer fit for purpose framework, prompted the European Commission to propose a switch to the new medical device regulations from its existing medical devices directive to ensure the safety, effectiveness and quality of medical devices in the EU. The EU's MDR (2017/745/EU) was officially published on May 5, 2017, and came into force on May 25, 2017. The MDR replaced the EU's previous Medical Device Directive (93/42/EEC) (MDD) and the EU's Directive on active implantable medical

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Figure 1: As a result of the PIP breast implant scandal in 2010, the European Commission introduced new rules for the regulation of medical devices to ensure safety, effectiveness and quality of medical devices in the EU.

devices (90/385/EEC). Compared with the EU directive it replaced (93/42/EEC), the MDR places far greater emphasis on patient safety linked to the use of a device and sets out a far more comprehensive set of enforced requirements for pharmaceutical manufacturers to follow.

The MDD had a legacy of nearly 30 years and was focused primarily on getting a product to market. The MDR, however, expands its sphere of influence to consider the full product lifecycle – development, testing, manufacturing, commercialisation, efficacy, safety and long-term use. This is not to say that the MDD ignored those elements, merely that the MDR specifies their application in greater detail.

"The new regulations impose stricter rules on product design and development, clinical evidence and post-market surveillance, among other considerations."

The implications of this update are wide ranging for both manufacturers and notified bodies as the level of rigour around required quality increases. The new regulations impose stricter rules on product design and development, clinical evidence and post-market surveillance, among other considerations.

Alongside stricter rules comes increased scrutiny by the regulatory authorities. This includes greater oversight of clinical studies and more stringent requirements for post-market surveillance, reporting of adverse events and increased transparency and traceability of products throughout the supply chain.

## ALLEVIATING THE BURDEN OF PROOF

One aspect where pharma partners are really feeling the weight of that burden and subsequent scrutiny is the creation of the relevant documentation. This includes a detailed review of technical documents to evidence a device's general safety and performance requirements (GSPRs). It also requires the interrogation of the clinical evaluation report, which contains testing data on the clinical use of a device.

"Because of its rigorous nature, the process for assessing conformity is not necessarily a straightforward one, as the process is new and notified body assessments can diverge, with room for interpretation on both the pharmaceutical company and notified body sides."

As part of a wider information-gathering process, these documents are reviewed in accordance with Annex I of the new MDR, which informs the risk-based assessment conducted by the notified body.

Because of its rigorous nature, the process for assessing conformity is not necessarily a straightforward one, as the process is new and notified body assessments can diverge, with room for interpretation on both the pharmaceutical company and notified body sides. These open areas of interpretation can potentially result in delays to the marketing authorisation applicant receiving a notified body opinion if submissions are not satisfactory. Issues such as incomplete submissions are commonplace. In such cases, there is often insufficient information provided to demonstrate compliance with the MDR, or even that the supplied technical documentation is poorly structured. All of which can complicate the notified body's already arduous task of appraising all the supplied materials.

Historically, the process of gathering such technical information has been somewhat reactive and iterative, perhaps even haphazard, as each question is addressed individually rather than approached from first principles as a whole. As a result, the gathering of data and documentary evidence has become arduous, expensive and time consuming – aspects of any process that can lead to project creep and enhanced risks. West recognises that such a fragmented approach potentially adds unnecessary time, cost and complications to an already stressful process, and the company has identified the opportunity for a smarter, more streamlined, approach.

Simply put, West embraces its Quality by Design (QbD) principles and ensures that

they are now a feature of its documentation offer. With the company's knowledge of the process, clarity around the kind of information and data required, and a deep understanding of its pharma partners, West is able to compile and co-ordinate all necessary technical information relating to the components for filing with timeliness and efficiency – all from a single point of contact. This approach further reduces the burden of accessing the right information at the right time, as opposed to navigating through several gatekeepers of data, which is often the case within the supply chain.

Following the completion of a successful pilot programme with a global top 10 pharma company, West termed this offer the "TDP". The pilot supported a pharmaceutical customer with an MDR filing for a new drug product delivered via a prefilled syringe system by addressing the recognised challenges associated with the filing process, including the need for cross-organisational stakeholder management and the co-ordination of consistent responses.

In what became a close and mutually beneficial collaboration between two assigned stakeholders within each organisation, West adopted a strategic, proactive approach to gathering, assimilating and presenting the required data at a level of detail and in a format that would satisfy scrutiny by the notified body. By focusing efforts on the "right first time" delivery of high-quality and highly relevant information connected to the specific GSPRs, the company was able to minimise requests for supplemental information, avoid complex multi-document iterations and truncate the entire certification process.

Historically, such an undertaking would have been incredibly resource heavy, with multiple stakeholders making up to 50 information requests in a three-month period. With hundreds of hours required, this would have been an expensive exercise. Under the new protocol, the TDP was presented without observations, enabling the customer to move quickly, efficiently and cost-effectively to marketing authorisation application.

> "Together with the TDP, NovaPure® plungers adhere to QbD principles featuring the tightest specifications within the West portfolio, readily applicable within today's formulation and manufacturing process."

## QbD FROM PACKAGE TO PLUNGER

Not only was the pilot programme a success for the customer, it also provided West with the TDP platform that supports applications for 1 mL long and 1–3 mL NovaPure® plungers. This comprehensive package features over 30 documents, including compliance bulletins, biocompatibility reports, quality statements, comprehensive performance data, extractables evaluations, packaging configurations and component drawings. This package is then enhanced with data specifically related to the customer and its drug product.

Together with the TDP, NovaPure® plungers adhere to QbD principles featuring the tightest specifications within the West portfolio, readily applicable within today's formulation and manufacturing process. The TDP platform is designed with functionality that makes navigating and/or extracting information from the package a clear and concise process, which helps to prevent unnecessary delays to the assessment process.

## CONCLUSION

The global prefilled syringes market size was US$7.22 billion (£5.8 billion) in 2022 and is projected to grow from $7.91 billion in 2023 to $16.32 billion by 2030 at a Compound Annual Growth Rate of 10.9%.[3] As such, increasing numbers of pharma partners will be subject to the MDR as they look to access the opportunities within the EU. With a deadline for a quality management system being set in place for May 26, 2024, pharma partners need to look towards organisations that can support them with a comprehensive TDP that not only delivers the requisite data requirements, but also saves time, money and resources.

NovaPure®

*NovaPure® is a registered trademark of West Pharmaceutical Services, Inc. in the United States and other jurisdictions.*

## 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 to ensure the safe, effective containment and delivery of life-saving and life-enhancing medicines for patients. With 10,000 team members across 50 sites worldwide, West helps to support customers by delivering approximately 47 billion components and devices each year.

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## ABOUT THE AUTHORS


**Victoria Morgan**, Director Strategic Marketing, Biologics, has global marketing responsibility for West's biologics business, which strives to develop high-quality products and services to help pharma companies serve unmet patient needs with biologic molecules. She brings a wealth of knowledge about scaling drug development through to and beyond commercialisation, predominantly in injectable drug delivery products including vials and combination products. Currently, Ms Morgan has responsibility for West's global biologics strategy development and implementation. Throughout her tenures at West, Lilly and Sanofi, Ms Morgan has served in various functions across sales and marketing, and she earned her Bachelor's degree from the University of Wales, and her MBA from INSEAD Business School in Paris.

**Stacy Gates-Rector**, PhD, has worked as a chemist and material scientist for over 10 years and has a diverse background in analytical characterisation. At West, Dr Gates-Rector works as a Principal Scientist managing various aspects of component performance projects, using the technical data gathered from these projects to generate customer documents that help promote adoption of high-value products and services. Prior to joining West, Dr Gates-Rector worked as a senior scientist characterising crystal structures of drug product. She holds a Bachelor's degree in Chemistry and a PhD focused on material science, crystallography and diffraction.

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# PRIMARY PACKAGING CONSIDERATIONS FOR SUPPORTING COMPLIANCE TO ANNEX 1 REVISION

In this article, Edouard Pagnoud, Product Line Manager for Vials Solutions, Estelle Verger, Business Development Senior Manager, PremiumCoat®, and Benjamin Brocco, PhD, Marketing Manager, all at Aptar Pharma, look at the new requirements associated with EMA GMP Annex 1 revision regarding injectable primary packaging for ensuring the sterility and safety of medicinal products and consider how Aptar's PremiumFill® can reduce the risk of contamination or product defects.

The pharmaceutical landscape is undergoing a transformative phase marked by the emergence of biotech drugs, such as monoclonal antibodies, recombinant proteins and nucleic acids, that promise to revolutionise patient care and address unmet therapeutic needs. Additionally, biosimilars, which are analogous to biologic products, are also gaining traction in the market due to their potential to provide cost-effective treatment alternatives to innovative biotech drugs. However, the sensitive nature of these drugs requires additional care when it comes to packaging and delivery. In addition to maintaining their stability and efficacy, packaging should also ensure the utmost safety for patients and promote ease of use.

The process of bringing a drug to market is intricate, demanding both time and significant financial resources. Given the high stakes, pharma manufacturers are always on the lookout for strategies to optimise their development pipelines, minimise potential risks and avoid costly scraps. This becomes even more pertinent when taking the evolving regulatory landscape into consideration. The recent updates to the European Medicines Agency's Good Manufacturing Practice (EMA GMP) Annex 1 emphasise the criticality of implementing contamination control and sterility assurance strategies, as particulate contamination and sterility are highlighted as the main causes for US FDA product recall.[1,2] While these regulatory evolutions are clearly aimed at improving patient safety, they put pharma manufacturers under pressure to meet these increasing standards of quality.

Primary packaging plays a pivotal role in this context as it is in direct contact with the drug. Any compromise in packaging quality can have direct implications on the drug's efficacy and safety. Therefore, it is imperative for drug manufacturers to recognise the significance of primary packaging early in the development process. Building partnerships with experts in pharma packaging at the initial stages can be a game-changer, helping to ensure that the drug's journey from lab to market is seamless and successful. Aptar Pharma, with expertise in rubber

> "The EMA's GMP Annex 1 emphasises the criticality of implementing contamination control and sterility assurance strategies."

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Figure 1: Aptar Pharma range of PremiumFill® closure solutions.

manufacturing and pharma grade processes, is an ideal partner to support drug manufacturers in this crucial aspect of drug development.

## DRUG DEVELOPMENT: A COMPLEX AND COSTLY PROCESS

In the pharmaceutical industry, the safety and efficacy of injectable drugs are paramount. However, one of the leading causes of recalls by the FDA for injectable drugs is particulate contamination. Such contaminants can pose health risks to patients and lead to rejection of a dose or batch on the filling lines. As the industry evolves and regulatory standards become increasingly stringent, manufacturers must ensure the purity and safety of their products.

The recent revision of Annex 1 of the EMA GMP, which came into force on August 25, 2023, aims to ensure the sterility and safety of medicinal products. This requires drug manufacturers to implement a pharmaceutical quality system that encompasses the specific requirements of sterile products manufacture, such as the control of microbial, particulate and endotoxin contamination, throughout the product's life cycle.

The establishment of a contamination control strategy (CCS) is a pivotal element that must be applied across facilities, pinpointing and mitigating potential contamination sources. However, it is not just a directive for drug manufacturers, but rather extends its influence across the entire supply chain. This ensures that every stakeholder, including primary packaging suppliers, adheres to stringent contamination control standards. By integrating the entire supply chain into its framework, the CCS ensures that every step, from initial production to final packaging, is held to the highest standards of product quality and safety.

## APTAR PHARMA'S PREMIUMFILL®: QUALITY ASSURANCE FOR YOUR PATIENTS AND OPERATIONAL EFFICIENCY

For decades, Aptar Pharma has been leading the way in developing injectables closure components, leveraging pure formulations and state-of-the-art manufacturing processes (Figure 1). As a key partner to drug manufacturers, Aptar Pharma adapts to evolutions of the market to enable successful drug development. Already a world-leader for rigid needle shields and a key player on ethylene tetrafluoroethylene (ETFE) film-coated solutions for sensitive drugs with PremiumCoat®, Aptar Pharma has been developing new strategies and solutions to meet the increasing needs of the market regarding external contaminations.

PremiumFill® solutions for vial stoppers and syringe plungers provide pharma

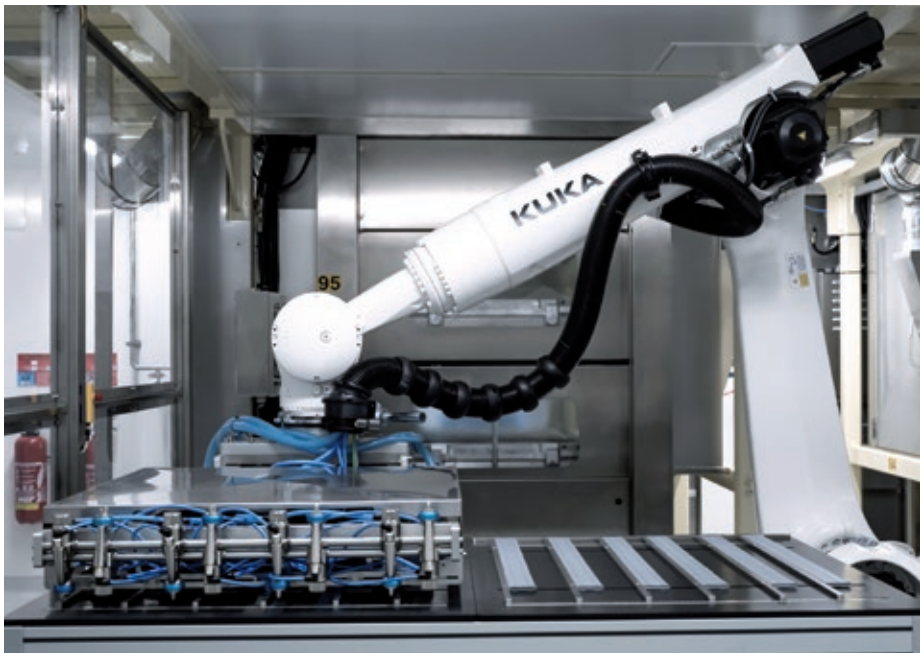


Figure 2: High-precision robot. PremiumFill® cell 8 at Aptar Granville.

partners with higher quality closure components with tighter specifications on key contamination criteria. These specifications cover contamination from biological origin, particulates (including foreign, metallic or rubber embedded) and fibres, with an overall improved particulate count index.

PremiumFill® uses the same market-proven rubber formulations and component designs, and leverages Aptar Pharma's Ultraclean 6 finishing technology. The improved specification is achieved by performing all the moulding and trimming steps in an ISO 7-classified cleanroom, thereby limiting the risk of introducing external particles onto or within the rubber. In addition to cleanroom manufacturing, the PremiumFill® process includes high-precision robotisation during the moulding steps, mitigating the risk of introducing particles through human interaction, while also enhancing reproducibility and consistency (Figure 2).

All these technologies have been integrated into PremiumFill® with one objective in mind – providing higher quality to Aptar Pharma's customers and their patients. This is part of the company's commitment to improving patient safety while also supporting regulatory compliance. The Ultraclean 6 finishing process, which is an integral part of PremiumFill®, is covered by a Type V FDA Drug Master File (DMF) to facilitate the customer's regulatory filing. Furthermore, since PremiumFill® uses the same rubber formulations, product designs and finishing process as standard products, Aptar Pharma experts have evaluated that switching to PremiumFill® would not require re-approval, making PremiumFill® a quick and easy way to further support compliance with the requirements of Annex 1. PremiumFill® products have demonstrated their benefits in the market for years. Aptar Pharma improves PremiumFill® to guarantee more stringent specifications and higher quality for its customers worldwide.

> "Aptar Pharma experts have evaluated that switching to PremiumFill® would not require re-approval, making PremiumFill® a quick and easy way to further support compliance with the requirements of Annex 1."

## CASE STUDY: PREMIUMFILL® REDUCED SCRAP LEVELS BY OVER 20% ON A CUSTOMER'S FILLING LINE

By offering higher quality with tighter specifications, PremiumFill® can also help reduce the risk associated with contamination or product defects to improve fill-finish operational efficiency by limiting the risk of rejection on the filling line. This was demonstrated through a case study performed at a customer's facility.

The pharma manufacturer switched from a standard Aptar Pharma vial stopper to the corresponding PremiumFill® vial stopper. It is important to note that upgrading to PremiumFill® did not require any process adaptation nor additional product filing. As the formulations and designs are strictly identical, the product could be processed as efficiently on existing filling lines.

Over a period of nine months of operation with PremiumFill®, Aptar Pharma's partner reported a reduction in their scrap rate of over 20%, and there were no quality complaints related to PremiumFill® products. The main defect reductions reported were for fibre contamination and rubber stains, which are both included in the PremiumFill® specifications.

In addition to helping the customer comply with stringent regulatory standards, PremiumFill® demonstrated its efficacy in improving operational efficiency. Significantly reducing scrap levels illustrates the potential for PremiumFill® to reduce the costs linked to product rejects, which, in turn, reduces the total cost of ownership for closure components, while also helping customers meet their sustainability targets.

## COMPLEMENTARY SOLUTIONS TO SUPPORT OPERATIONAL EFFICIENCY AND REGULATORY COMPLIANCE

When tackling particulate and biological contamination, the cleanliness of the primary packaging itself is only one of the levers that can be activated, as it only pertains to one of the sources of contamination. Other steps in the fill-finish process may cause external contamination, such as particles coming from the bags that contain the primary packaging, or even from the human intervention when introducing the primary packaging items into the filling line.

Another lever would be to switch from non-sterile ready-to-sterilise (RTS) closures to ready-to-use (RTU) gamma sterilised components. In addition to being the only solution guaranteeing sterility at the time of use, RTU also avoids the use of Tyvek, which has been suggested to be a source of fibres.[3] Aptar Pharma RTU solutions use only soldered polyethylene bags, with or without a rapid transfer port (RTP), which helps pharma manufacturers to meet both the sterility assurance requirements and contamination control requirements of the Annex 1 revision. Additionally, using an RTU solution can prove operationally efficient by saving the time, cost and footprint associated with sterilisation equipment and its validation (Figure 3).

When primary closure components are introduced on the filling line, there is a risk of biological or particulate contaminants inadvertently entering the restricted environment of the filling line, which could lead to potential issues. To limit the risk of contamination during this step, section 4.18 of the Annex 1 revision strongly recommends the use of isolators or the reduced access barrier system (RABS) in conjunction with RTP bags.

> "To limit the risk of contamination during this step, section 4.18 of the Annex 1 revision strongly recommends the use of isolators or the RABS in conjunction with RTP bags."

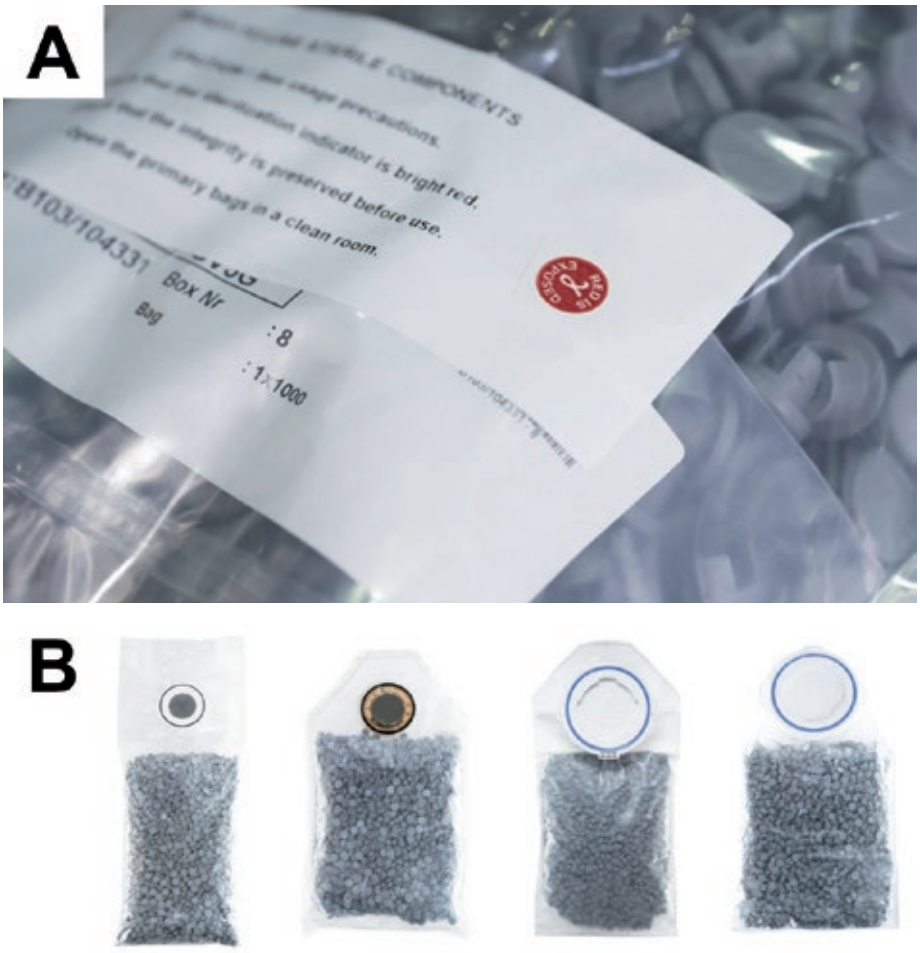


Figure 3: A. Ready-to-use lyophilisation stoppers in their packaging with irradiation indicator. B. Aptar Pharma vial stoppers and syringe plungers in four RTP bags among the models available.

To facilitate Aptar Pharma's partners' compliance with the Annex 1 revision on sterility assurance and CCS, Aptar Pharma combines various strategies:

- Limiting the risk of closure component-related particles and defects with PremiumFill® components
- Favouring RTU gamma-sterilised components to guarantee sterility at the time of use and limit the risk of particle generation potentially linked to the use of Tyvek bags
- Selecting RTPs in conjunction with isolators to avoid the accidental introduction of contaminants on the filling line.

In addition, by minimising contamination risks and supporting compliance with the Annex 1 revision, this combination of solutions has the potential to reduce both rejection rates and the operational footprint of the fill-finish operation, promoting efficiency and cost savings on equipment and validation costs.

## CONCLUSION

The pharmaceutical sector is undergoing significant changes with the promise of addressing unmet therapeutic needs, but this also brings challenges in packaging and drug delivery due to the sensitive nature of biotech drugs and biosimilars. While ensuring the stability, efficacy and safety of these drugs remains the key priority, accelerating the journey from drug development to market and ensuring a smooth production process are essential for pharma manufacturers to meet their profitability objectives.

Recent regulatory updates, such as the EMA GMP Annex 1, highlight the importance of contamination control and sterility assurance. These regulations place manufacturers under increased scrutiny to meet stringent quality standards, and the importance of partnering with primary packaging experts becomes critical to support the drug development process. Aptar Pharma, staying abreast of the latest trends, adapts its PremiumFill® solutions to align more closely with regulatory

requirements and market needs, emphasising its commitment to quality.

To further mitigate contamination risks during the fill-finish process, a comprehensive approach is recommended for ensuring compliance with regulatory standards and optimising operational efficiency. This includes the adoption of RTU gamma-sterilised components to guarantee sterility at the time of use, in conjunction with RTPs to further limit particulate contamination risks.

As the pharmaceutical landscape continues to evolve, manufacturers must prioritise both product quality and operational efficiency. Collaborative efforts with forward-thinking partners, like Aptar Pharma, can provide valuable insights to ensure the highest standards of patient safety, regulatory compliance and rapid time-to-market.

## ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, from formulation to patient, providing innovative drug delivery systems, components and active material solutions across the widest range of delivery routes including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, Aptar leads the way in developing digital healthcare devices to help improve patient adherence and compliance. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup.

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***To learn more about Aptar Pharma's PremiumFill® and PremiumCoat®, visit: www.aptar.com/pharmaceutical/delivery-routes/injectables.***

## ABOUT THE AUTHORS

**Edouard Pagnoud** is the Product Line Manager for Vials Solutions at Aptar Pharma's Injectables division. As a graduate in Chemical Engineering from the Université Technologique de Compiègne in France, Mr Pagnoud has worked in the cosmetic and pharmaceutical industry for over 10 years. Before joining Aptar Pharma in 2021, he occupied technical and industrial positions and gained a strong expertise in product development and lifecycle management for high-value solutions. In his current position, Mr Pagnoud is responsible for the vials solutions platform and is committed to support customer development projects.

**Estelle Verger** is the Business Development Senior Manager for PremiumCoat® coated solutions for Aptar Pharma's Injectables division and is responsible for the growth of the PremiumCoat® platform in the global injectable market. A graduate from ESSEC Business School and Fachhochschule Dortmund, with a Masters' degree in international business management, she joined Aptar Pharma in 2011 as a Sales Manager, Injectables. Ms Verger then moved to Aptar Pharma's Consumer Healthcare division as a product manager, where she was responsible for airless dispensing solutions for pharmaceutical applications for several years, before returning to the Aptar Pharma Injectables division in 2020.

**Benjamin Brocco** is the Global Marketing Manager for Aptar Pharma's Injectables division. Dr Brocco holds a PhD in Biophysics and is a graduate of Grenoble Ecole de Management in France. Dr Brocco worked at a world leading delivery device company, where he developed an in-depth understanding of injectables drug developers' needs. He joined Aptar Pharma in 2020 as a marketing specialist and evolved to his current position in which he co-ordinates the marketing operations of the division and aligns Aptar Pharma's value proposition with the needs of the market.

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# NEW EXTRACTABLES DATA FOR OXYCAPT™ MULTILAYER PLASTIC VIAL FOR BIOLOGICS & GENE/CELL THERAPY

In this article, Hiroki Hasegawa, MD, Researcher, and Tomohiro Suzuki, Associate General Manager, both at Mitsubishi Gas Chemical, review the properties of OXYCAPT™, the company's multilayer material for primary biologic packaging, and share the data from the latest study on OXYCAPT's extractables profile.

## INTRODUCTION

Mitsubishi Gas Chemical (MGC) is a leading company in the field of specialist polymers with oxygen-absorbing or barrier functions. In 2019, MGC launched OXYCAPT™ multilayer plastic vial & syringe, which offer excellent oxygen and ultraviolet barrier properties. Since then, a lot of biologics and gene/cell therapy companies have evaluated OXYCAPT for their products. Based on these customers' requests, MGC has conducted new extractables studies, the results of which will be discussed in the latter half of this article.

In recent news regarding OXYCAPT syringe, MGC signed a letter of intent with Becton Dickinson (BD) in May 2022 and has started earnest discussions to apply its multilayer technology to next-generation prefilled syringes for biologics. Therefore, MGC has tentatively stopped introducing the current version of OXYCAPT syringe to customers. MGC believes this collaboration will be helpful for pharmaceutical companies to develop novel and sensitive future drugs safely.

> "OXYCAPT is a multilayer plastic vial developed by MGC that offers a number of advantageous qualities as a primary drug container."

Figure 1: OXYCAPT multilayer plastic vial.

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OXYCAPT is a multilayer plastic vial developed by MGC that offers a number of advantageous qualities as a primary drug container (Figure 1). MGC continuously conducts tests to confirm OXYCAPT's excellent properties, including:

- Excellent oxygen and ultraviolet (UV) light barrier
- Strong water vapour barrier
- Very low extractables
- High pH stability
- Low protein adsorption and aggregation
- High transparency
- High break resistance
- Easy disposability
- Lightweight material.

## OXYCAPT OVERVIEW

OXYCAPT consists of three layers – the drug contact layer and the outer layer are made of cyclic-olefin polymer (COP), and the oxygen barrier layer is made of MGC's novel polyester (Figure 2). One variety of OXYCAPT, OXYCAPT-P, provides an excellent oxygen barrier. For example, the oxygen barrier of an OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial (Figure 3).

MGC recently obtained a report on the environmental impact of glass and plastic containers for medical use from a Japanese research company. The report shows that plastic containers for medical use are much more environmentally friendly compared with glass containers. For example, the carbon footprint, nitrogen oxides emissions, sulfur oxides emissions and water consumption associated with plastic containers for medical use are several times smaller than those of their glass equivalents.

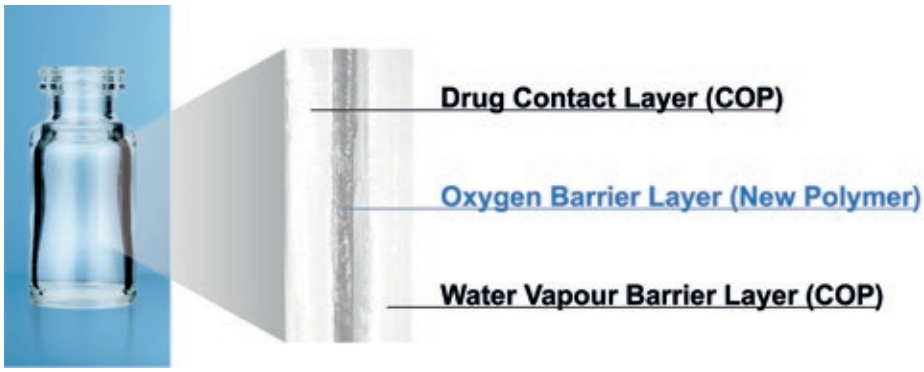



Figure 2: Multilayer structure of OXYCAPT.

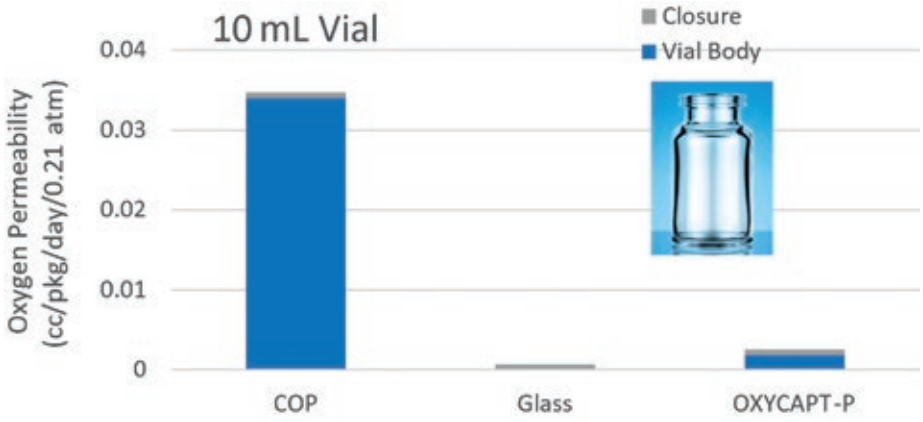



Figure 3: Oxygen permeability comparison of a typical COP, glass and OXYCAPT-P.

"While about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT."

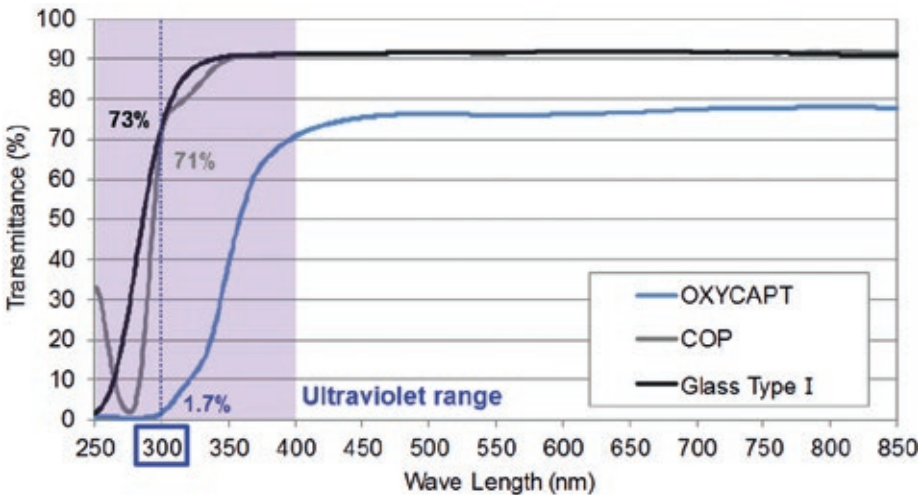



Figure 4: UV light transmittance comparison of a typical COP, Type 1 glass and OXYCAPT.

Furthermore, OXYCAPT provides an excellent UV barrier. While about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT (Figure 4). MGC has confirmed that this feature contributes to the stability of biologics.

While OXYCAPT cannot reach the performance of glass with respect to acting as a water vapour barrier, its properties are similar to those of COP, which has been used for injectable drugs for a long time. This means that OXYCAPT easily meets the requirements of a water vapour barrier set out by the International Council for Harmonisation (ICH) guidelines.

The OXYCAPT vial is produced by co-injection blow-moulding technology. MGC has also developed inspection methods for testing the oxygen barrier layer. All the containers are fully inspected by state-of-the-art inspection machinery.

Each polymer meets the requirements of US Pharmacopeia (USP) regulations USP <661>, USP <87> and USP <88>, as well as those of the European Pharmacopoeia, and has been filed in the US FDA's drug master file (DMF). The vials are also compliant with each pharmacopoeia and have been filed in the DMF.

Figure 5: OXYCAPT plastic vial in a standard nest and tub format.

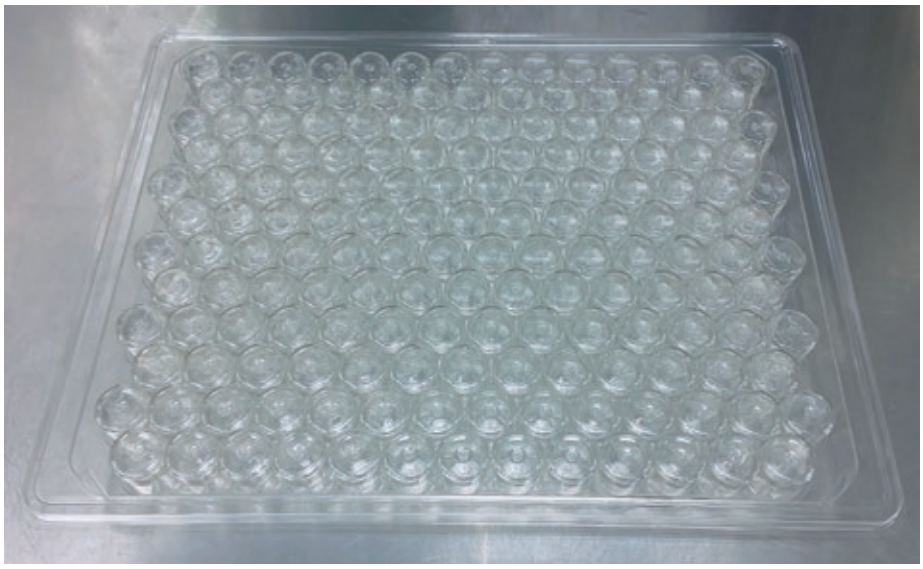


Figure 6: OXYCAPT plastic vial in a standard tray format.

MGC can offer bulk vials and ready-to-use (RTU) vials, with its RTU products provided in standard nest and tub (Figure 5) or tray (Figure 6) formats. The nest and tub are mainly sterilised using gamma rays. There are 2, 6, 10 and 20 mL variants for vials (Table 1). MGC is willing to provide samples for initial testing free of charge.

The primary target market for OXYCAPT is the therapeutic application of biologics. As mentioned in ICH Q5C (Stability of Biotechnological/Biological Products), oxidation is one of the causes of protein instability. As such, the oxygen and UV barrier properties of OXYCAPT will definitely contribute to the stability of biologics stored within. Furthermore, some drug developers have recently started evaluating the OXYCAPT vials for their gene and cell therapies; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

| ISO 8362-1 Vial | Length (mm) | Width (mm) | Outer Diameter of Flange (mm) | Inner Diameter of Flange (mm) | Packaging Option |
|---|---|---|---|---|---|
| 2R (2 mL) | 35 | 16 | 13 | 7 | Nest or Tray |
| 6R (6 mL) | 40 | 22 | 20 | 12.6 | Nest or Tray |
| 10R (10 mL) | 45 | 24 | 20 | 12.6 | Nest or Tray |
| 20R (20 mL) | 55 | 30 | 20 | 12.6 | Nest or Tray |

Table 1: MGC's OXYCAPT product portfolio.

"The primary target market for OXYCAPT is the therapeutic application of biologics."

## NEW EXTRACTABLES DATA

The latest studies conducted by MGC have shown an outstanding characteristic of OXYCAPT – extremely low levels of extractables. An organic and elemental extractables study, performed in collaboration with an outsourcing pharmaceutical company, was conducted using MGC's container closure system (CCS) comprised of a 20 mL OXYCAPT vial sterilised with 40 kGy gamma rays and a normal butyl rubber stopper.

In order to detect and quantify organic analytes, volatile compounds were measured by HS-GC-MS (headspace gas chromatography-mass spectrometry). Moreover, non-polar, volatile and semi-volatile compounds were measured by GC-MS, whereas LC-UV-MS (liquid chromatography-ultraviolet spectroscopy/mass spectrometry) was used to detect compounds with varying polarity and volatility. Furthermore, levels of the elemental impurities specified in ICH Q3D plus aluminium and tungsten were detected and quantified by inductively coupled plasma mass spectrometry (ICP-MS).

These studies were conducted by a 48-hour incubation at 50°C of the OXYCAPT CCS with four different formulations:

- 0.1% aqueous polysorbate 20 (PS-20)
- 0.1 M phosphate buffer at pH 3
- 0.1 M phosphate buffer at pH 10
- 50% ethanol solution.

These extraction solutions cover those outlined in the latest draft of USP <665>. After incubation, a sample work-up for

| Analytical method | Solution | Sample work-up | AET (ppm) | Compounds found above AET |
|---|---|---|---|---|
| HS-GC-MS | 0.1 % PS-20 | Direct | 0.015 | **No peaks were detected at levels above the AET** |
| | pH 3 buffer | Direct | | |
| | pH 10 buffer | Direct | | |
| GC-MS | 0.1 % PS-20 | Extraction | 0.3 | **No peaks were detected at levels above the AET** |
| | 50% EtOH | Extraction | | |
| | pH 3 buffer | Extraction | | |
| | pH 10 buffer | Extraction | | |
| | 50% EtOH | Evaporation | | |
| LC-UV-MS | 0.1 % PS-20 | Extraction | 0.3 | **No peaks were detected at levels above the AET** |
| | 50% EtOH | Extraction | | |
| | pH 3 buffer | Extraction | | |
| | pH 10 buffer | Extraction | | |
| | 50% EtOH | Evaporation | | |

Table 2: Organic extractables profile of OXYCAPT.

each solvent and analysis method was performed. It was then confirmed whether or not there were any organic extractables that exceeded the analytical evaluation threshold (AET). Each AET of HS-GC-MS, GC-MS and LC-UV-MS was determined by calculation with respect to the safety concern threshold (1.5 µg), filling volume of the vial, maximum number of vials administered per day and the concentration factor due to sample work-up. The results of the analyses with HS-GC-MS, GC-MS and LC-UV-MS all showed no organic compound exceeded the AET with the OXYCAPT CCS (Table 2).

> "The results of the analyses with HS-GC-MS, GC-MS and LC-UV-MS all showed no organic compound exceeded the AET with the OXYCAPT CCS."

In the study with ICP-MS, no elemental impurities exceeded their permitted daily exposure (PDE) as outlined in ICH Q3. Aluminium and tungsten, which are not listed in ICH Q3D, were also not present at a significant level (Table 3). This result indicates that OXYCAPT can contribute to a safety assessment for drugs and the pH stability of drug solution.

| Element | 0.1% PS-20 pH 10 buffer | pH 3 buffer | PDE (µg) | Element | 0.1% PS-20 pH 10 buffer | pH 3 buffer | PDE (µg) |
|---|---|---|---|---|---|---|---|
| | Amount administered with 5 vials (µg) | | | | Amount administered with 5 vials (µg) | | |
| Ag | < 1.50 | < 1.50 | 15 | Os | < 1.00 | < 1.00 | 10 |
| As | < 1.50 | < 1.50 | 15 | Pb | < 0.50 | < 0.50 | 5 |
| Au | < 30 | < 30 | 300 | Pd | < 1.00 | < 1.00 | 10 |
| Ba | < 70 | < 70 | 700 | Pt | < 1.00 | < 1.00 | 10 |
| Cd | < 0.2 | < 0.2 | 2 | Rh | < 1.00 | < 1.00 | 10 |
| Co | < 0.5 | < 0.5 | 5 | Ru | < 1.00 | < 1.00 | 10 |
| Cr | < 110 | < 110 | 1100 | Sb | < 9 | < 9 | 90 |
| Cu | < 30 | < 30 | 300 | Se | < 8 | < 8 | 80 |
| Hg | < 0.3 | < 0.3 | 3 | Sn | < 60 | < 60 | 600 |
| Ir | < 1 | < 1 | 10 | Ti | < 0.8 | < 0.8 | 8 |
| Li | < 25 | < 25 | 250 | V | < 1 | < 1 | 10 |
| Mo | < 150 | < 150 | 1500 | Al | < 6 | < 20 | n.a |
| Ni | < 2 | < 2 | 20 | W | < 20 | < 20 | n.a |

Table 3: Elemental extractables profile of OXYCAPT.

## CONCLUSION

In conclusion, these latest results have contributed to the ongoing studies verifying OXYCAPT's superior properties for biologics and gene/cell therapies. In addition to the advantages of COP, such as a strong water vapour barrier, high break resistance, very low extractables and low protein adsorption, OXYCAPT also provides a strong oxygen and UV light barrier. MGC believes that OXYCAPT offers a multitude of benefits to the rapidly growing field of biologics and gene and cell therapies.

"These latest results have contributed to the ongoing studies verifying OXYCAPT's superior properties for biologics and gene/cell therapies."

## ABOUT THE COMPANY

Mitsubishi Gas Chemical is a major chemical products manufacturer, operating across a wide range of fields, from basic chemicals to fine chemicals and functional materials. In 2012, MGC established a new division as a centre for continually creating new businesses. In the field of drug delivery, the company has developed the OXYCAPT plastic vial and syringe as an alternative to glass containers.

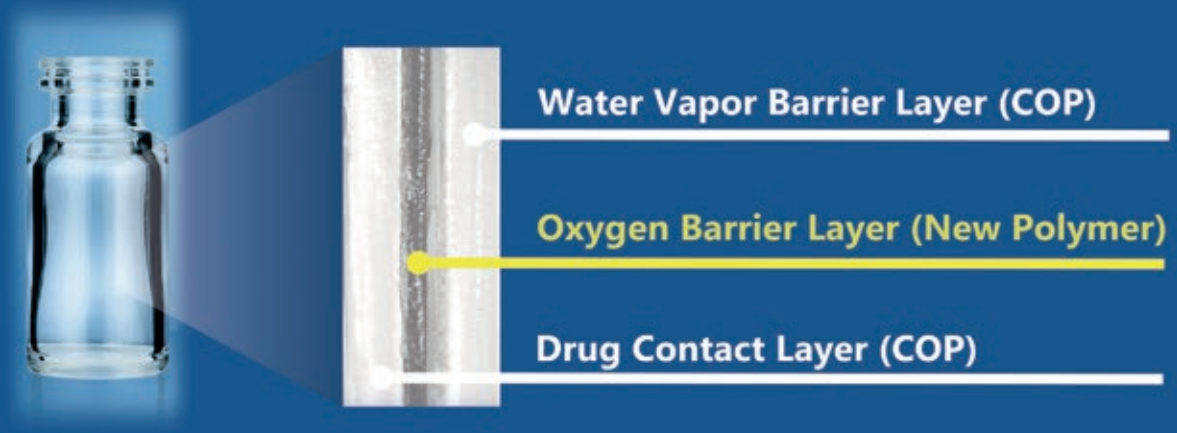
## ABOUT THE AUTHORS

**Hiroki Hasegawa**, MD, is a researcher in MGC's Advanced Business Development Division. He earned a Diploma in Science in 2013 and a Master of Science degree in 2015 from Osaka University (Japan). He has been working for MGC since April 2015, in charge of macromolecular science, especially in composition development of thermosetting resin. In 2018, he joined the development team for OXYCAPT.

**Tomohiro Suzuki** graduated from Waseda University (Japan) in 1997 and joined MGC in 1998. He belonged to the Oxygen Absorbers Division until 2011, after which he was transferred to the Advanced Business Development Division in 2012 to be a member of the OXYCAPT development team. Since then, he has been in charge of marketing for the OXYCAPT vial and syringe. His current position is Associate General Manager.

# OXYCAPT™ Multilayer Plastic Vial

## Multilayer Structure




- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Gamma-sterilized Vial
- For Biologics & Regenerative Medicine
- Customizable

2, 6, 10, 20mL Vial

Nest & Tub for Vial

MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical Company, Inc.
https://www.mgc.co.jp/eng/products/abd/oxycapt.html
Mitsubishi Gas Chemical America, Inc.
http://www.mgc-a.com
Mitsubishi Gas Chemical Europe GmbH
https://www.mgc-europe.de

# INTERVIEW

In this exclusive interview with ONdrugDelivery, Douglas Bryans, PhD, President and Chief Executive Officer of Bryllan, and John Merhige, Chief Commercial Officer at Credence MedSystems, engage in a lively and wide-ranging discussion about the changing needs of drug developers around novel dual-chamber and ready-to-use drug delivery devices, capacity and the delivery of complete solutions from CDMOs and device developers, anchored around the recently announced partnership between Credence MedSystems and Bryllan to provide these critical services.

## DOUG BRYANS, BRYLLAN

Doug Bryans, PhD, is Bryllan's President and Chief Executive Officer, responsible for the operating strategy and overall performance of the company. He is a pharmaceutical industry executive with 25 years of progressive responsibility in contract manufacturing with Catalent Pharma Solutions. Dr Bryans has held senior positions in Operations and Quality with significant experience in establishing compliant contract operations and supporting customers with their product development and growth. Dr Bryans founded Bryllan in 2010 in recognition of the need for a fill-finish contract manufacturing and packaging provider that can support innovators in complex drug development.

## JOHN MERHIGE, CREDENCE MEDSYSTEMS

John Merhige is Chief Commercial Officer at Credence MedSystems, leading the Company's commercial activities and external collaborations. Previously, he was Vice-President of Market Development at Sanofi. He came to Sanofi upon its acquisition of Pluromed, which Mr Merhige joined in its early stages and where he was a member of the executive management team leading the company's sales and marketing efforts. Prior to Pluromed, he founded Prelude Devices to target early-stage medical device technologies for development and commercialisation.

**Q To begin with, could you give us a brief overview of Bryllan and Credence MedSystems, and introduce us to the partnership between the two companies?**

DB Certainly, Bryllan is a fill-finish contract manufacturer, and we have been in business about 10 years. Our primary focus is the fill-finish of complex drug-device combination products, and we have both small-scale clinical capacity and commercial-scale capacity. Our focus is working with innovators and developers to meet the needs of new drug development opportunities and supporting capacity at clinical and commercial scale, for future drug developments.

JM Credence MedSystems is an inventor, developer and supplier of injection devices. We work very hard to see where the market needs are, oftentimes focusing on broad-based market needs and sometimes on bespoke needs for specific customers. We find solutions and commercialise them. We've just passed our 10-year anniversary and our focus throughout has been very much on injectable drug delivery.

With respect to our partnership, it's a collaboration that is fundamentally based on two things – an understanding of where the market is going for ready-to-use and ready-to-mix drug products, and a shared philosophy on providing pharma what it needs in order to satisfy those trends. There's no exclusivity attached to the collaboration. Rather, we simply focus together on bringing pharma companies what they need from a drug delivery device perspective and what they need from a CDMO (contract design and manufacturing organisation) fill-finish perspective. Offering both together is becoming increasingly important, as we will discuss in more detail.

**Q You mentioned ready-to-use and ready-to-mix drug products. What are the drivers behind the development of these types of drug and device products?**

JM There is a need to simplify the delivery of complex drugs that require mixing at the time of use. Alongside that, the delivery of medications is currently being increasingly transferred out of formal healthcare settings. Oftentimes, that's self-administration, or administration by a loved one, but the important point is that these are non-professionals, and sometimes they're compromised patients with physical and cognitive limitations. So, the user population is more naive, but the medication formulations aren't getting more simple, they're getting more complex, right?

It can be extremely difficult, or even impossible, to get liquid stable solutions. Even if it is possible, it can take years of

> "There is a need to simplify the delivery of complex drugs that require mixing at the time of use."

formulation work. This means that the drug needs to be reconstituted or resuspended at the time of use just prior to injection. And that's just the start; sometimes you're looking to combine two liquids that need to be kept separate during storage because you want to avoid co-formulation or because there's some type of reactivity between the liquids.

You can see how the drug delivery challenges are growing but the user population is more naive. It's all of our responsibility to further simplify the delivery of these complex drug products.

**DB** I agree on that. Additionally, some of the other business cases that are being developed are associated with a way to reduce cost at the hospital level by eliminating the compounding process and creating a drug-device combination that is ready-to-use or ready-to-mix, which also eliminates a number of errors and potential risks involved in the process of compounding in the pharmacies.

It also frees up nurse and healthcare provider time to spend on care rather than preparation. Policy drivers in different countries are supporting changes to the way in which certain diseases are treated, which are also tending towards better delivery of medication.

I think that the lack of fill-finish capacity is also inhibiting the speed at which some of this activity can be done. That is a key focus of the partnership between Bryllan and Credence. The more capacity available, the faster some of these changes in philosophy at the drug development stage will take place.

**JM** Doug is 100% right. This is not just an at-home phenomenon, it is also important in formal healthcare settings. Consider a scenario where you've got a conventional vial presentation where the user needs to take syringes and needles, and go back and forth between a diluent vial and a lyophilised cake vial, for example. Upgrade that to a dual chamber, ready-to-mix or ready-to-use scenario and you are eliminating potential for dosing error, contamination and exposure to highly potent drug products. Beyond that, you're reducing risk of needlestick injury, you're speeding up time of preparation, you're eliminating overfill requirements, all of which have a direct or indirect impact on cost of ownership and safety to whomever is doing the preparation.

"The more capacity available, the faster some of these changes in philosophy at the drug development stage will take place."

**DB** Something else that's come up recently across several regions, including numerous countries in Europe, is related to drug sustainability and the evolution of potential green approaches to handling drug development. One of the business cases was the cost of disposal of all the consumables involved in using traditional liquid drugs versus having a ready-to-use product where you eliminate multiple syringes, needles and other materials that not only have to be purchased, but also have to be disposed of. There's a significant cost of disposal and long-term treatment of those types of materials which, ultimately, have to be incinerated or put into landfill. I saw one business case recently that said ready-to-use is justified on that basis alone, even without taking into consideration the other substantial benefits that we've discussed so far.

**JM** And there's also the impact on the supply chain. The conventional approach includes very complex kits requiring multiple vials, syringes, needles, swabs and secondary packaging. With dual chamber and other ready-to-use systems, all of that gets simplified dramatically.

**Q** **I'd like to expand a bit on the point you raised about shifting policies influencing the direction of drug and delivery device development. Can you tell our readers more about how payers and reimbursement models are having an impact on the industry at present?**

**DB** This is a key factor in the business cases that are driving companies across different markets to move towards finding ready-to-use, ready-to-mix product solutions.

Obviously, in social-funded medicine, cost drivers are becoming more critical as patient populations get older overall; the tax base is always under pressure, and it will require wholesale operating changes to make significant cost savings. Moving significant pipelines of products to ready-to-use or ready-to-mix is one strategy that would offer a significant cost reduction – it's formulation time, it's compounding time, it's all of the items that we've mentioned that have to be purchased and disposed of, all of which could be eliminated to a significant degree if a large number of products were available in a ready-to-use, ready-to-mix format.

In insurance-based systems, policy changes are starting to allow for reimbursements of more at-home healthcare. Reimbursements of new product developments are driving innovation on where drug delivery can take place, facilitating the move from hospital to home and informal settings, which John spoke about earlier. Those are having a significant impact on the decision-making around which products should be developed and where those products should be delivered.

**JM** Building on what Doug said, covid-19, alongside all of its tragedies, opened up some opportunities within the healthcare industry. You had a period where the capacity in the healthcare setting was minimised, the number of sick patients was increasing and something had to be done. So, at that time, the Centers for Medicare and Medicaid Services funded 'acute hospital care at home', more commonly known as Hospital-At-Home here in the US, which has just been extended through 2024. And logic would say that, once it's in place, it's going to stay in place because you're increasing your capacity for acute care, right?

I'm not talking about chronic self-injections, here. This is acute care, and you're increasing your capacity by making the world your 'hospital' setting, you're dramatically lowering your costs by being outside of that formal healthcare setting. For many patients, although certainly not for all, it's a much better situation. A healthcare provider comes to them as needed to care for them, monitor them and administer their medications – it's game changing.

However, you also have to realise that, in some cases, these are probably less experienced healthcare professionals, and they don't have the structure of a hospital around them. So, all of those considerations around simplifying delivery are really relevant here. Furthermore, the industry's push to change IV (intravenous) therapies to SC (subcutaneous) therapies is a big part of this as well.

"It's not just understanding that a particular dosage form costs X, but understanding the cost of the supply chain to deliver that in a healthcare setting."

**DB** Just one other point on the business cases. It's understanding the total cost of delivering a medication that's important. It's not just understanding that a particular dosage form costs X, but understanding the cost of the supply chain to deliver that in a healthcare setting. Unfortunately, this isn't always understood by the models and financial structures we currently have in place. For example, in the US, the GPOs (group purchasing organisations) buy the medications, but the GPOs don't understand the cost of delivering them when it comes to compounding, and the time on ward and the nurse's time on top of that. On the other hand, the C-suite understands that, but only sees a cost of goods item when it comes to the GPOs. Those connections have to be made to really understand the total cost of a medication.

**Q Can you give our readers your more detailed thoughts on the current state of global fill-finish services and capacity?**

**DB** Broadly, global fill-finish capacity is legacy and reflects the developments of the last 50 years. Most products are still filled into glass vials during development and still filled into glass vials at commercial scale, and the capacity reflects that. Obviously, over the last 20 years, we've seen a move towards things like prefilled syringes, more IV bags, but fill-finish capacity is limited to a few big players. And most of those products are simple, terminally sterilised. There's not a lot of capacity for aseptic bags and or for complex biologics or toxic products that, typically, have to be aseptically filled.

For the most part, CDMOs have been slow or are slow to respond to some of the development demands coming from the pharmaceutical industry. Also, a lot of those pharma developers do not have their own fill-finish capacity, they are virtual companies with no in-house capacity, or limited capabilities, that are looking to outsource all of that work. So, the speed at which the move to ready-to-use and ready-to-mix can go is being limited by the movement of the supply chain; both for multi-chamber components and the fill-finish capacity to take the product from clinical scale through to commercial scale.

There is a "chicken and egg" element to this. Industry feedback is telling us that, if the capacity was in place, there would be a mindset shift in formulation product development within pharma companies, and things would move in this direction much faster. This is a crucial point, and the partnership between Bryllan and Credence really represents an effort to start to move the industry in that way. We feel very confident that building a capacity model from small scale to large scale will be a key enabler for moving a number of products in this direction globally.

**JM** You've got a chasm, right? On one side of it is significant and growing demand for dual chamber delivery, or ready-to-use and ready-to-mix products more broadly (Figure 1). Then on the other, we're saying fill-finish and capacity is a massively important aspect. The challenge is to bridge that chasm – it's by bringing device technology and production capacity together that you get to a solution, which is a full offering to pharma. They want to move forward and want to believe that there is a very clear path from preclinical to clinical to commercial.

Between a device manufacturer and a fill-finish CDMO, we've got all the elements in place, it's a checked box. So, the next step is creating a very clear, very executable vision for implementing the commercial scale manufacturing. And the closer these two sides come to each other, it's almost like two magnets – once they get close enough together, they start pulling towards each other. And that's happening, it's not done yet, but it's happening.

**DB** A few years ago, there was the odd company looking at dual chamber or ready-to-use, ready-to-mix, but that wasn't in itself an incentive for someone like Bryllan or Credence to move at the speed we're currently moving. But, today, the business cases are coming from the global pharmaceutical and biotech industry, which is developing new chemical entities right into new delivery systems.

The drivers for cost reduction are global, and, combined, there's a real emphasis to move capacity in this direction; enough that it makes sense for Bryllan to invest more in innovative fill-finish capacity than the last 50 years have incentivised, looking to support the development and platform fill-finish needs, along with providing a landing ground, for Credence as it develops innovative technologies for syringe delivery.

Looking at other driving factors, there are two major things that have happened at the same time, one of which is the growth of personalised medicine, which has reduced the production of mass medication.

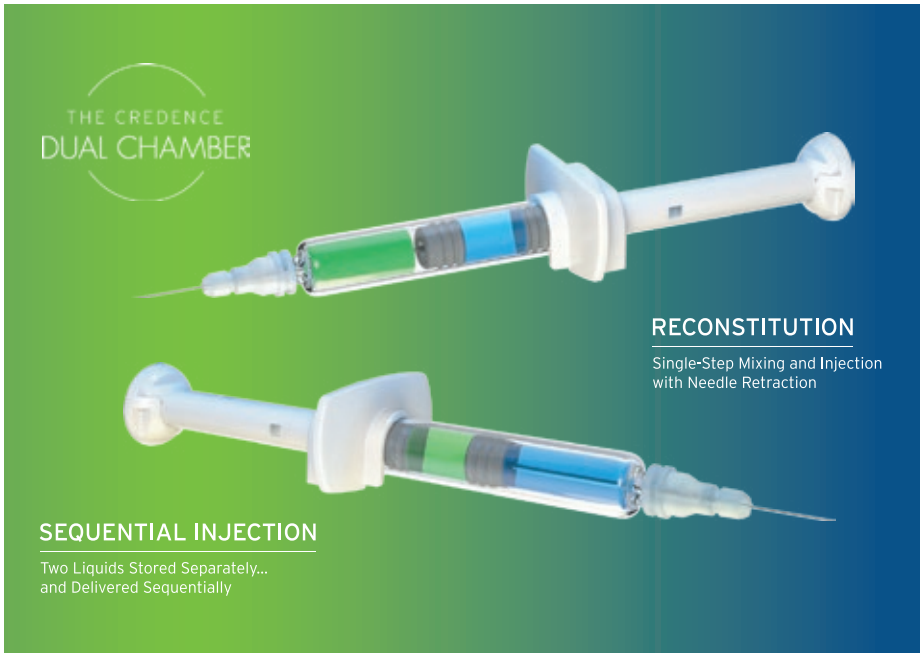



Figure 1: Credence MedSystems' Dual Chamber syringe.

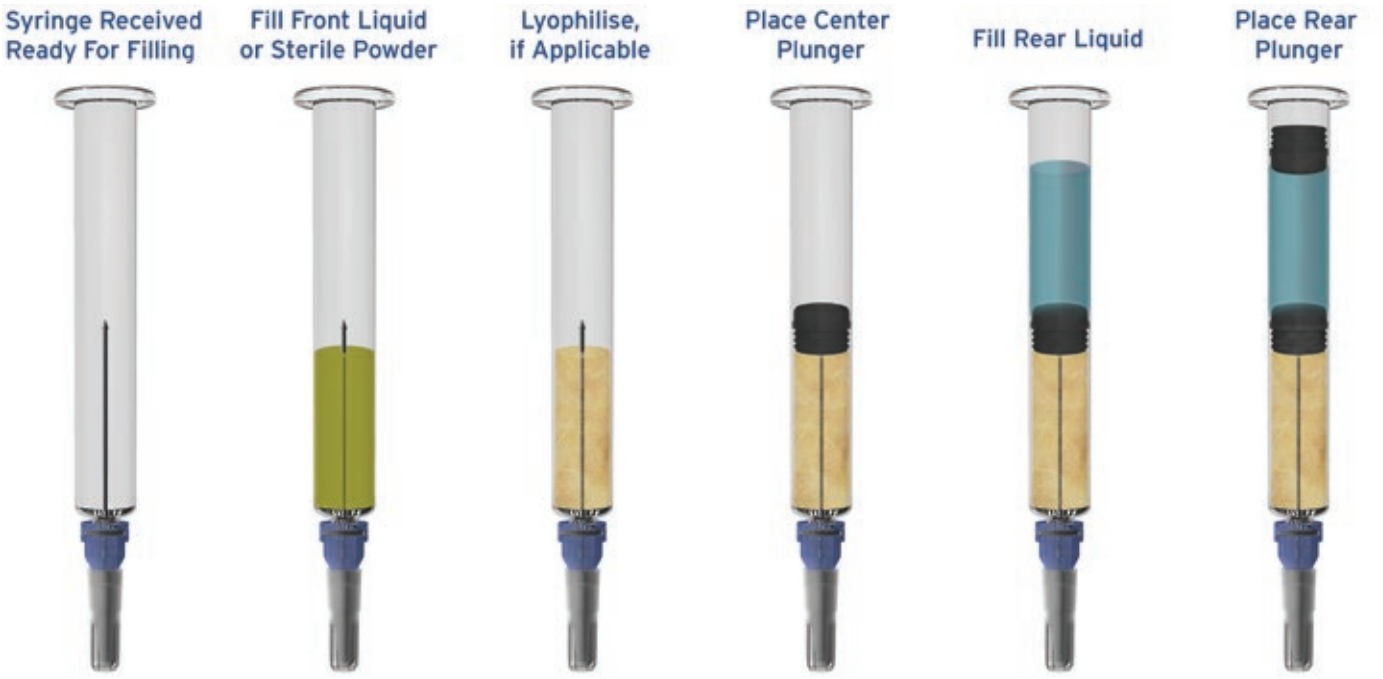



Figure 2: The fill-finish process for a prefilled dual chamber syringe.

Following this, batch size changes have changed the development and scale of capacity. Large filling lines are no longer economical if batch sizes have come down by 50% and more.

The other major change is that you now have multiple forms to deliver medication – vials, bags, mixing systems, wearable devices, dual chamber, ready-to-mix syringes, ready-to-mix bags, ready-to-mix vials and more. However, they are all growing to such a degree that it not only requires innovation on the development of the device, but also on the innovation and implementation of the capacity to produce at commercial scale.

**Q What would you say is the right capacity to support future drug device innovation and facilitate the commercial supply chain at the appropriate level?**

DB The covid-19 pandemic really highlighted the lack of fill-finish capacity in the US. The response to that is to look to onshore more of the supply chain, including fill-finish capacity; there is a clear need to onshore specific types of capacity for preparedness for the future, including pandemic concerns. But that cannot be the only type of capacity built domestically in the US. We also need to focus on the capacity required to build the supply chains for ready-to-use, ready to mix and dual chamber products (Figure 2), including the scope for innovation and new technologies for creating sterile powder.

> "Developers are now interested in looking at ways to bring new technology to create high-speed filling of bulk sterile powders."

There have been numerous techniques available for several years, many of them niche ones that haven't really been progressed, but developers are now interested in looking at ways to bring new technology to create high-speed filling of bulk sterile powders. Of course, powder filling has been done before, but typically not directly into a vial, a syringe or a bag, and those are the demands that are now being placed on CDMOs if they are going to support customer developments and commercial demands. And so Bryllan is focused on supporting numerous partners to bring those technologies onshore to provide that complete supply chain.

JM It's a very logical approach. So, today, for a lyophilised drug product, whether it's in a vial or a prefilled syringe, the lyophilisation process is the long pole in the tent, the bottleneck. It's measured in hours, or even days – a two-to-three-day cycle time, for instance, isn't uncommon. You've got these massive capital expenditures that are sitting there for two to three days to produce a batch. If you go into a company that does lyophilisation of vials, it almost looks like a solar panel farm, right? They're just lined up because you're trying to get as many units in them as possible because it takes so long to go through.

What Doug's talking about here is probably the most economic and capacity-efficient approach to commercialising what we refer to as a lyo-liquid dual chamber syringe or bag. The way this works is that the lyophilisation happens offline, and then the processes that need to be sterile, such as powder filling, happen in-line and your overall process becomes way more efficient. Now there's development work to be done, and the industry has been looking at this for a long time, but I believe it's the most efficient way to implement commercial-scale dry liquid fill.

We're doing the same thing on the device side. Right now, we're launching what we call our Flexible Clinical Manufacturing Line, which will have modest volumes across a broad array of single chamber and dual chamber products and be able to produce products for human use. And that's to feed all these programmes that are in clinical and earlier developmental stages. The next step is investment in the commercial-scale line, which will take our capacity from half a million units per year capacity to 50 million units per year.

So, it's the same strategy that Doug's talking about being implemented on the fill-finish side is also being implemented on the device manufacturing side.

**Q To wrap up, can you offer our readers your thoughts on what it takes to offer pharma a complete solution, from device development to clinical-scale production to commercial-scale production?**

JM It comes back to the first thing we said, which is that we need to meet pharma where they are and provide what they need to satisfy the macro drivers in healthcare. Some pharma have a sufficient resource and capability set such that what they're really looking for is a device company to supply them with the device and a fill-finish company to do the fill-finish and maybe some formulation work. That's the classic model of a CDMO providing a service and a device company supplying a drug-device combination.

But there's this whole other world that includes companies from large pharma to innovative biotech start-ups that can't or don't want to do that work. Whether because of capacity constraints, personnel bandwidth constraints or resource expertise, they want a full regulatory submission package as the deliverable. They see this as a powerful and efficient method of differentiating their product lines, be it for specialty generics or innovative new molecules. They want the whole package delivered to them, right up to regulatory submission.

That's where we, with Bryllan and with others, come in to fill that need. We can work together with pharma to identify where the drug product needs are, where the gaps in their portfolio are, then we can identify the appropriate development pathway, the appropriate milestones, the appropriate funding mechanisms, which can be a mix of upfront and milestone driven. And we can deliver a full product package for pharma to submit to regulators.

This approach really seems to be resonating with a variety of different pharma segments. One in particular is the traditional generic suppliers that are trying to move to more value-add and more of a specialty generic offering where the device or the formulation brings differentiation.

DB From the CDMO point of view, the way to add to the current model is proactive investment in capacity rather than reactive investment once the customer is on board. We need to move on from the attitude of "Let's wait for the customer to sign on, then we'll start to do something". If we're going to make a stepwise change, there has to be a different risk tolerance to investment in capacity at the CDMO level.

And there needs to be potential for customers to invest in capacity specific to a need. For example, at Bryllan, we have one customer who is investing in a fill-finish bag line to do a triple chamber bag because they want to take control of their own commercial volume and commercial destiny. Going forwards, I see these models becoming more of a discussion point and there being more willingness on both sides to help to drive product development and future commercial capacities forward.

JM This entire discussion is around collaboration within the supply chain to provide pharma manufacturers a suite of products and services that are needed to help them address new requirements evolving from emerging trends in healthcare. Drug technologies are more complex and are often being delivered by less-experienced users, so the need exists to simplify the delivery of these drugs, while improving the safety of doing so. Successful commercialisation of dual chamber and ready-to-mix/ready-to-use solutions requires more than just a great device and more than just great filling capability. Pharma manufacturers need delivery device companies and CDMO companies working together to provide the full system.

## ABOUT THE COMPANIES

**Credence MedSystems** is an innovator in drug delivery devices. Credence's philosophy of 'Innovation Without Change' results in products that impress and protect end-users while preserving pharma's existing processes, sourcing strategies and preferred primary package components. The company's Companion® family of syringe systems includes proprietary needle-retraction technology, reuse prevention and other critical safety and usability features in staked and luer needle formats. Credence's Dual Chamber platform offers simplified and safe delivery of complex drug products that require reconstitution or sequential injection at the time of delivery. The Credence Connect™ auto-sensing injection system incorporates automatic real-time monitoring of critical injection data into a reusable ergonomic finger grip. Additional products, such as metered dose devices, multi-length staked needles and other novel devices, address the needs of specific therapeutic markets.

**Bryllan** is a CDMO focused on supporting clinical and commercial supply of complex drug and device products. With a high containment state-of the-art facility that offers considerable flexibility in capabilities, Bryllan can safely fill potent and cytotoxic compounds, hormones, antibodies, complex biologics, live viruses and vaccines in a wide range of sterile containers. Bryllan's focus on aseptic powder and liquid filling capacity in multi-chambered components including syringes, IV bags and cartridges offers drug developers options to develop ready-to-use and ready-to-mix product formats.

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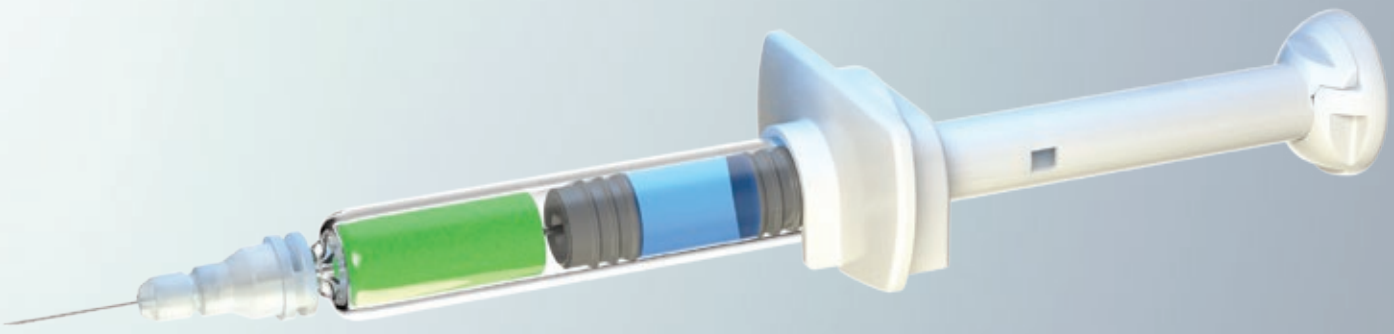
CREDENCE MEDSYSTEMS

INNOVATION WITHOUT CHANGE HAS ARRIVED



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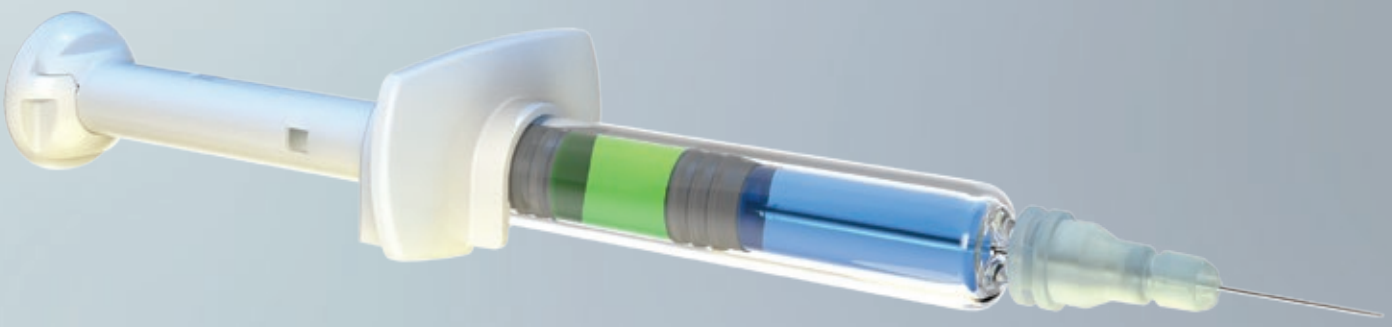

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This product has not yet been evaluated by FDA

PCI Pharma Services

## ADVANCED DRUG DELIVERY SOLUTIONS

Seeking advanced drug delivery for targeted and controlled release of novel molecules, PCI's integrated drug manufacturing and packaging solutions support biopharma companies in optimising dosing and providing convenient, easy-to-use, patient-centric therapies to patients.

## STERILE FILL-FINISH AND LYOPHILISATION

PCI's global manufacturing capabilities in complex sterile formulations and lyophilisation cover a broad range of next-generation injectable technologies, including nanoparticles, mRNA, monoclonal antibodies, proteins, oligonucleotides and other biologics across multiple delivery formats, from vials and prefilled syringes to cartridges for autoinjectors (Figure 1). PCI provides integrated large- and small-molecule solutions for clinical and commercial projects and, with over 20 years in the sterile fill-finish and lyophilisation manufacturing space, the company is dedicated to its partners' success in bringing life-changing therapies to patients.

> "PCI has the scalability to handle the dynamic volumes of biopharmaceutical therapies, whether large or small, from niche personalised medicines to large-volume treatments."

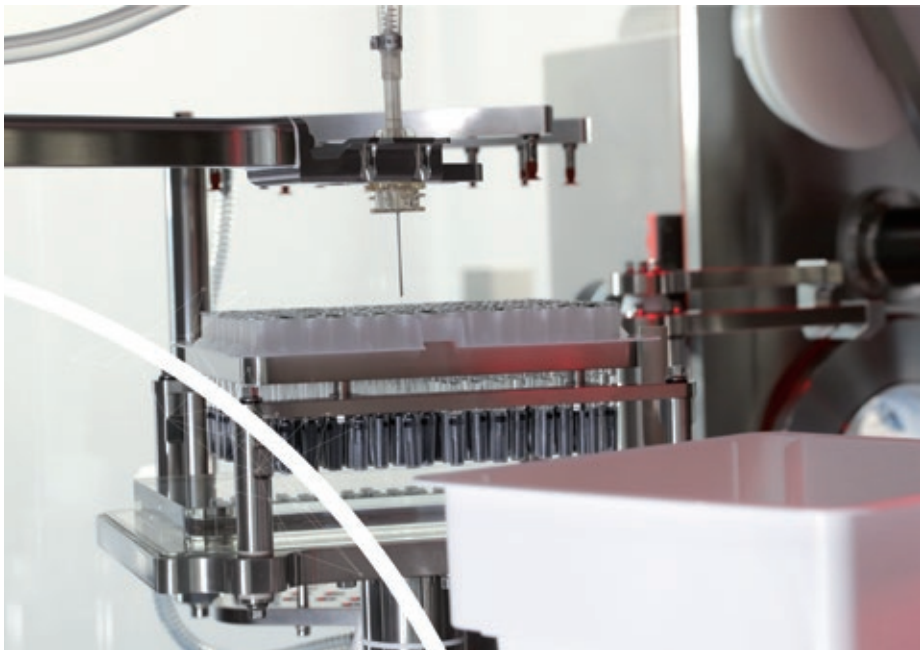

Figure 1: Aseptic syringe filling using advanced robotic isolator technology.

## DRUG-DEVICE COMBINATION PRODUCTS

Driven by innovation and patient centricity, PCI's design and development expertise, combined with its device assembly and advanced packaging capabilities, offers flexible solutions for a diverse portfolio of conventional and specialty injectable drug delivery devices (Figure 2). PCI has the scalability to handle the dynamic volumes of biopharmaceutical therapies, whether large or small, from niche personalised medicines to large-volume treatments.

Tailored to its partners' unique design, development and manufacturing needs, PCI offers a complete range of capabilities, services and expertise:

- Expert design process focused on human-factors engineering and technical functionality
- Optimising designs for manufacturability, scalability and automation
- Fully end-to-end drug-device combination packaging including:
  - Prefilled syringe assembly
  - Pen injector, autoinjector and on-body injector final assembly
  - Safety syringe assembly and precision labelling
  - Integrated top-load cartoning
  - In-process testing and final release
  - Serialisation
  - Cold-chain storage.

## INJECTABLE PACKAGING SERVICES – CLINICAL THROUGH COMMERCIAL

With true customer focus and flexibility at the core of its pharmaceutical packaging service offering, PCI is able to adapt to the unique requirements of each global market, from concept to commercialisation.

pci PHARMA SERVICES

# Your injectable drug product destination. Our world.

## Advanced Drug Delivery

Driven by innovation and patient-centricity, our design and development expertise combined with our device assembly and advanced packaging capabilities offer flexible solutions for a diverse portfolio of conventional and specialty injectable drug delivery devices.

**END-TO-END DRUG DEVICE COMBINATION PRODUCT SOLUTIONS:**

- Sterile fill-finish of syringes and cartridges for auto-injectors
- Final assembly and labeling of:
  - prefilled syringes
  - auto-injectors
  - pens
  - on-body injectors
- Integrated top-load cartoning
- Serialization
- Cold chain storage

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Your bridge between life-changing therapies and patients

Figure 2: Assembly and labelling of autoinjectors.

PCI is the partner of choice in providing scalable packaging services, supporting niche orphan drugs through to large-scale biopharmaceuticals with tailored injectable packaging solutions including:

- Labelling of vials, ampoules, pens, prefilled syringes, autoinjectors and on-body injectors
- Tyvek blistering for parenterals
- Drug-device combination product assembly
- Cartoning
- Kitting and protective packaging
- Overwrapping and pouching
- Cold chain packaging and labelling (2–8°C, -20°C, -40°C, -80°C, -196°C).

## SPEEDSOLUTIONS™

Harnessing decades of drug product development and commercialisation experience, PCI's integrated speed solutions simplify supply chains from the earliest stages of development through to approval, launch and beyond. Speed solutions, such as packaging design and artwork services, provide innovative, value-added services for its clients. PCI's dedicated team of in-house design specialists deliver insightful packaging design and practical knowledge to deliver differentiated and cost-effective packaging solutions. Using three-dimensional modelling, PCI facilitates rapid prototype design to support patient and physician focus groups that provide vital insight into patient usability and acceptability, as well as supporting regulatory filings, expediting responses andenabling true speed to market.

> "PCI facilitates rapid prototype design to support patient and physician focus groups that provide vital insight into patient usability and acceptability."

## FUTURE INVESTMENTS

Meeting the growing needs of its clients for their life-changing biologic drug products, PCI continues to invest in both its manufacturing and packaging capacities and capabilities. Over the next 12 to 18 months, PCI has committed to invest over US$250 million (£202 million) to expand its global sterile fill-finish and lyophilisation manufacturing capabilities together with its clinical and commercial advanced drug delivery packaging service offering for injectables.

These investments reflect the outlook and the market demand PCI envisages for injectable drug products. As a leading global CDMO, PCI not only wants to meet growing demand for scalable biologic manufacturing and advanced drug delivery packaging but, through innovative value-add solutions, the company aims to exceed customer expectations, delivering flexibility and excellence in all that it does to accelerate the development and commercialisation of life-changing therapies.

## ABOUT THE COMPANY

PCI is a leading global CDMO, providing integrated end-to-end drug development, manufacturing and packaging solutions to increase product speed to market and opportunities for commercial success. PCI brings the proven experience that comes with more than 90 successful product launches each year and over five decades in the delivery of supply-chain healthcare services. With 30 sites across Australia, Canada, North America, the UK and Europe and over 5,250 dedicated employees, the company's mission is to bring life-changing therapies to patients. Leading technology and continued investment enable PCI to deliver development to commercialisation solutions throughout the product lifecycle, collaborating with its clients to improve the lives of patients globally.

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TERUMO
MEDICAL CARE SOLUTIONS

# TERUMO GLOBAL PARENTERAL CDMO – INTEGRATED INNOVATION

In this article, Michele Guasti, Global Product Manager at the Pharmaceutical Solutions Division of Terumo Medical Care Solutions, discusses the advantages that Terumo's parenteral contract development and manufacturing organisation brings to customers due to its position as a single service provider from formulation to final product and its intimate understanding of Terumo's range of prefillable polymer syringes.

Working with Terumo's parenteral contract development and manufacturing organisation (CDMO) brings customers a uniquely integrated service offering. Today's Terumo combines its high-quality polymer prefillable syringe manufacturing capabilities together with its complete CDMO service offering, which includes formulation development, fill-finish services, device assembly and packaging, all in one trusted partner. For Terumo's customers, integrated innovation means end-to-end services that deliver injectable products of the highest quality, compliance and with reduced time to market.

## THE TERUMO SYRINGE EXPERIENCE

Terumo started producing its first disposable plastic syringes in 1963 and has continued to invest in the latest syringe technologies ever since. Glass is historically known for its chemical inertness and therefore widely used as the primary material for prefillable syringes. Terumo recognised the limitations of glass syringes and developed new, innovative prefillable polymer syringes with higher resistance to breakage and dimensional accuracy for the pharmaceutical market.[1]

Terumo has continued to innovate by bringing together its industry-leading polymer syringes with advanced formulation and sterile fill-finish services as an integrated CDMO. For over two decades, Terumo has been recognised for the quality and service standards it provides to many of Japan's leading biopharmaceutical companies for prefilled syringe (PFS) CDMO development and manufacturing.

> "Having recently expanded its CDMO offering to biopharmaceutical companies around the world, Terumo has positioned itself to meet global industry requirements successfully."

## THE TERUMO CDMO DIFFERENCE

Having recently expanded its CDMO offering to biopharmaceutical companies around the world, Terumo has positioned itself to meet global industry requirements successfully. Terumo conforms to international quality and regulatory standards in its three modern and efficient sterile manufacturing and development sites, all located in Japan. Combining the global standard in polymer PFS supply with exceptional sterile formulation development services through a uniquely co-ordinated approach provides significant advantages to Terumo's CDMO customers.

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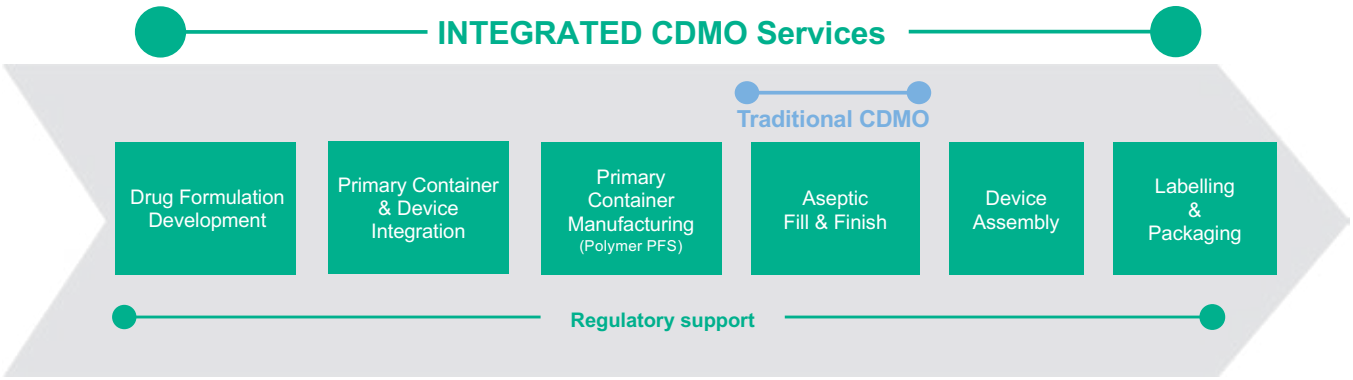


Figure 1: Terumo's integrated CDMO services.

By working as a single supplier with an unmatched understanding of the capabilities of its own syringes, Terumo is able to select the best device for each individual project. It also allows Terumo's CDMO teams to co-ordinate the formulation and device development steps and to arrive at an optimal formulation quickly, considering all the various challenges presented by potential interactions between the drug and the device. Terumo's highly efficient sterile filling operations use modern, flexible and highly automated sterile filling lines suitable for both clinical and commercial manufacturing volumes.

The result is that Terumo's integrated innovation approach can significantly de-risk a project, enabling accelerated timelines. Terumo's CDMO services span the full range of services required to take a customer's molecule from drug formulation to fully packaged commercial product, all with a single partner (Figure 1).

## TERUMO'S SERVICE CAPABILITIES PROFILE

### Drug Formulation Development

Terumo has been developing and producing sterile liquid formulations for a range of medical applications since the 1980s. For over 20 years, Terumo's skilled scientists have applied their sterile injectable formulation development knowledge to create fully optimised and scalable PFS products on a contract basis. Terumo applies a multidisciplinary approach involving a team of pharmaceutical scientists who apply their specialised knowledge in drug stability, delivery systems, pharmacokinetics and primary container drug interactions. The company's PFS development capabilities are fully supported with specialised analytical capabilities that can be used to study chemical composition, molecule characteristics, excipient selection and reactivity.

> "The practicalities of scale-up, technology transfers and regulatory filings are all incorporated into development programmes by Terumo's experienced scientists from the beginning."

Terumo's biochemistry and biotechnology experts leverage their knowledge of drug-target interactions and molecular biology techniques to produce stable, functional formulations of recombinant proteins or monoclonal antibodies. The practicalities of scale-up, technology transfers and regulatory filings are all incorporated into development programmes by Terumo's experienced scientists from the beginning.

Taking an integrated approach to both the syringe selection and formulation design is critical to advancing new PFS products into manufacturing efficiently. Terumo, as a CDMO, is uniquely positioned to achieve this and pass the benefits onto its customers.

### Primary Container and Device Integration

Any PFS product development programme must consider drug–container interactions. Terumo scientists optimise formulations to avoid undesirable interactions with syringe body, plunger and lubricant materials that may impact extractable/leachable specifications, as well as overall product stability. When considering primary container and device selection for sterile injectable products, Terumo's integrated CDMO services assess a range of product parameters, including:

- **Material selection** – contact material inertness with formulation
- **Primary container design** – dosing, drug delivery and user factors for the primary container both for the syringe alone and in combination with an injection device, such as an autoinjector
- **Compatibility** – factors such as sensitivity to light, oxygen, moisture, silicone oil, glue, tungsten, sterilisation impact, specialised container materials and coatings
- **Drug stability** – primary container impact on drug formulation stability using real-time and accelerated stability studies.

### Polymer PFS Supply

Terumo has been a well-established supplier of advanced polymer PFSs to the biopharmaceutical industry for many years. Terumo's range of polymer PFSs and components are known for excellent strength and clarity, as well as tight dimensional tolerances, contributing to a lower overall cost of ownership for customers. With ready-to-fill PLAJEX™ cyclo-olefin polymer syringes designed to meet the needs of a wide variety of drug types, including those requiring low reactive containers,[2] Terumo offers the syringe options necessary for protecting even the most sensitive biotherapeutic molecule requirements.[3] Some molecules can be sensitive to standard syringe coatings and lubricants, so PLAJEX™ mitigates issues related to silicone oil, providing superior molecule protection and minimising the risk of protein aggregation.[3]

Terumo's R&D scientists have also designed needles for better injectability without compromising patient comfort for their polymer syringe lines.[4] With Terumo, needle design and syringe features, specially

designed for different product routes of administration, syringe formats and drug delivery systems, can be customised to a degree that is not easily possible when using separate suppliers for each outsourcing step.

### Aseptic Fill-Finish Capabilities

Custom formulations, paired with the ideal Terumo syringe, can be seamlessly transferred into Terumo's network of sterile manufacturing facilities, whether it is for clinical or commercial-scale production. With three sterile manufacturing locations in Japan, Terumo offers high-quality aseptic filling or sterile fill-finish with terminal sterilisation capacities to meet virtually any demand. The company's sterile filling lines are designed to minimise the risks of human interaction throughout the process by operating under full isolator protection with highly automated controls. Terumo's highly automated lines can handle everything from container moulding to aseptic filling, sealing and packaging, all while meeting the highest regulatory standards.

### Device Assembly

Some CDMO customers require their PFS product to be assembled as part of a final safety or autoinjector device. Terumo's CDMO team perform the final device assembly under controlled conditions, with the additional autoinjector or safety device provided by the customer or sourced by Terumo from a third-party provider. The final device must be designed to accommodate Terumo's PFSs but can be included in a manual or fully automated process to deliver the final combined product, ready to ship.

### Labelling and Packaging

Every product must be appropriately labelled and packaged to meet the local market's regulatory requirements. Terumo can offer comprehensive labelling and packaging services in a variety of final formats that comply with all packaging regulations in most major markets. Terumo operates highly automated packaging and precision kitting services to meet a wide range of needs. Labelling and packaging specifications can be defined in parallel with development activities, shortening the timeframe needed to bring the product to market.

"Terumo's integrated CDMO services are performed to the company's strict quality standards, producing the highest quality products for customers."

## TERUMO QUALITY

Terumo's integrated CDMO services are performed to the company's strict quality standards, providing customers with reassurance of compliance with all relevant standards. The company applies the same quality management system principles and adheres to applicable regulatory requirements across all its operations. Terumo's expertise in quality control and quality assurance gives customers the confidence that their product will meet regulatory standards and specifications wherever they are used. The company's knowledge of analytical techniques, stability testing and compliance with good manufacturing practices (GMP) all contribute to producing high-quality products.

Terumo's Japanese manufacturing sites (Figure 2) are GMP-compliant and certified by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). Both of the company's aseptic fill-finish sites have been successfully inspected by the US FDA and the EMA has visited one site for a commercial product inspection. This track record of success with leading international regulatory bodies demonstrates Terumo's continuing commitment to achieving the highest quality standards for its PFS CDMO customers.

## BENEFITS OF INTEGRATED INNOVATION

Terumo's integrated CDMO services offer substantial benefits to its customers, including:

- **One partner** – end-to-end service offering from formulation to final packaged product
- **Quality** – quality systems that use the latest technologies and compliant processes to build quality into every aspect of its operations

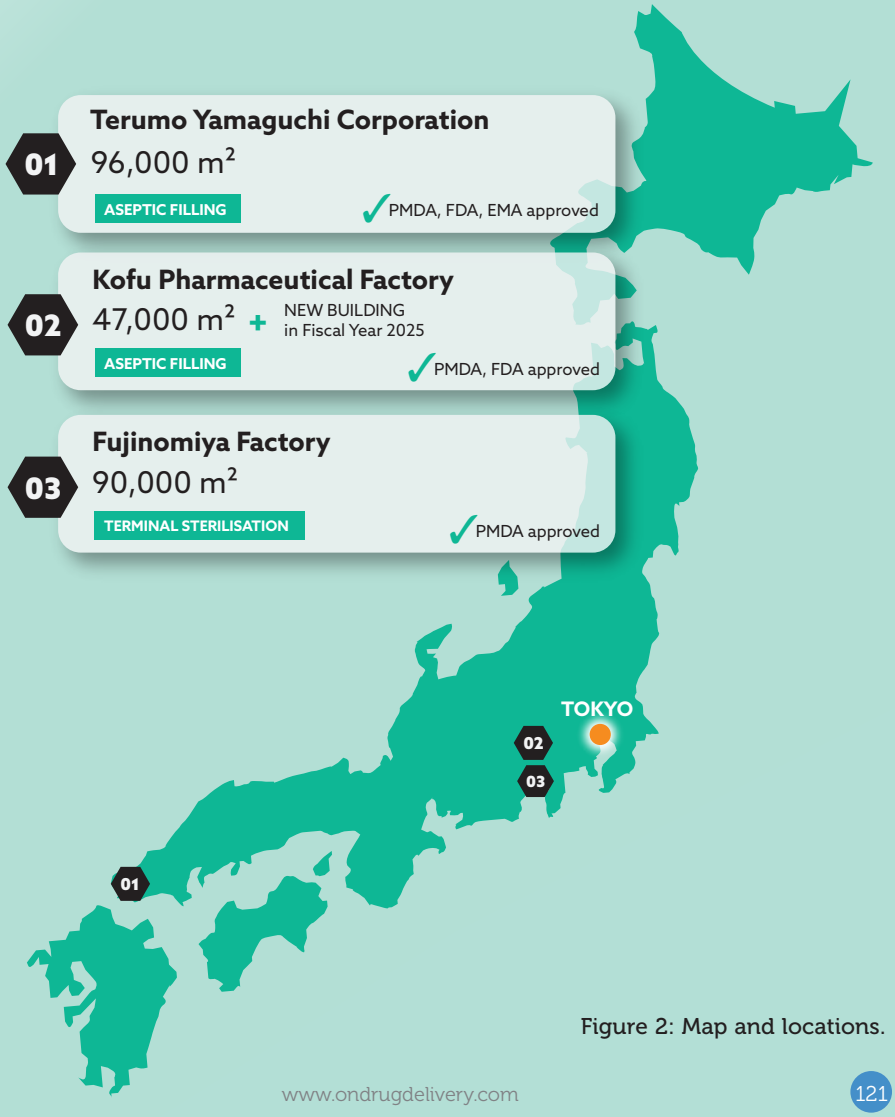


Figure 2: Map and locations.

"Considering that Terumo was founded on developing leading-edge medical products and services, it is easy to see why innovation is such a big part of the company's heritage and way of thinking."

- **Regulatory compliance** – decades of experience compliantly engineering and manufacturing combination drug products and devices
- **Reduced cost of ownership** – lower investment cost to develop new molecules when working with a single supplier
- **Time to market** – a single supplier accelerates supplier qualification, validation and communication
- **Supply chain simplification** – one single source for device technology and drug product development and manufacturing services, from small clinical batches to commercial-scale production
- **Consulting and engineering support** – support provided through development plans, regulatory applications and high-value-added products.

Terumo's integrated approach to offering complete, single-source CDMO services for PFSs is innovative. Considering that Terumo was founded on developing leading-edge medical products and services, it is easy to see why innovation is such a big part of the company's heritage and way of thinking. Terumo has always sought to create solutions to the challenges its customers face. Decades of expertise were applied to develop Terumo's industry-leading polymer-based syringes that have since become the global industry standard.

Terumo's innovative proprietary silicone oil-free containers, in combination with i-coating™ technology (chemically bonded coating) present on the stoppers, can mitigate issues related to silicone oil, providing superior molecule protection.[3] All of these technological innovations came from Terumo's scientists and engineers. Now, the same dedication to innovation through science is being applied to the company's end-to-end CDMO services, and it is the customers and patients who benefit most.

## ABOUT THE COMPANY

As Part of Terumo Medical Care Solutions, the Pharmaceutical Solutions Division develops patient-oriented parenteral delivery solutions for therapeutic performance and safety. Trusted globally for quality and precision, Terumo offers pharmaceutical and medical device manufacturers around the world comprehensive product design and development services. The company has decades of experience collaborating with pharmaceutical companies from the earliest phases of drug development to product commercialisation to optimise critical aspects of parenteral drug delivery. Innovation and creativity are central to Terumo's value proposition. Its expert teams lead the industry in developing and manufacturing advanced, high-performing infusion and injection technologies, including CDMO services for all parenteral applications.

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## ABOUT THE AUTHOR


**Michele Guasti** is Global Product Manager at the Pharmaceutical Solutions Division of Terumo Medical Care Solutions. He graduated from the University of Brescia (Italy) and holds a Master's degree in Mechanical Engineering. Mr Guasti has more than nine years of experience in primary packaging within the pharmaceutical industry. In the last five years, he has acquired expertise in fill-finish processes for injectable drugs and associated technologies. Mr Guasti has extensive experience in establishing strong partnerships and collaborations between companies and supporting pharma customers in finding solutions to their daily challenges. Previously, he worked in strategic product management at Stevanato Group.

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# AUTOMATING ASSEMBLY TO EXPEDITE TIME-TO-MARKET

In this interview, Dave Seaward, PhD, Projects Director at 3P innovation, discusses how the organisation takes a holistic approach to solving the technical challenges encountered by its clients and looks for opportunities to enhance the final product, enable efficient processing and support commercially viable manufacturing.


## DR DAVE SEAWARD, 3P INNOVATION


Dave Seaward, PhD, is a chartered engineer and 3P innovation founding director, Dr Seaward's first degree is in electrical and mechanical engineering with a PhD in control theory (applying servo motors to automation). Dr Seaward's 40-year career has focused on developing custom automation for numerous industries, including the pharmaceutical and medtech sectors. Dr Seaward is named inventor on over 20 patents, including Unilever's pyramid teabag patent, which is included in the UK Patent Office book "Inventing the 20th Century". Many of his projects have included powder or liquid dispensing, and he has recently worked on numerous dry powder inhalers, drug-eluting and injectable drug delivery projects.

**Q What are some of the key manufacturing issues faced by the pharmaceutical industry today?**

A One of the key issues in the pharmaceutical industry is scalable assembly. Automating the manufacture of a medical device, such as an injector pen or inhaler, involves handling and assembling multiple plastic components, springs, needles and, ultimately, a primary drug container (usually glass) that's full of the drug that's destined for a human being.

> "As every automation engineer knows, late-stage machinery changes can be very costly and also lead to significant delays."

When designing and developing such devices, immediately investing in a high-speed piece of automated technology is often unwise. Aside from the fact that new chemical entities often fail during clinical studies, there is also a risk that the device will require changes to ensure that it performs as required. As such, you might well end up with a complex production machine that can't actually handle the final components. As every automation engineer knows, late-stage machinery changes can be very costly, and can also lead to significant delays.

**Q What are the issues faced by small companies developing novel devices?**

A Smaller companies trying to develop novel injection devices frequently face the issue of running out of cash before they generate any revenue from their finished products. That's one of many hurdles we need to help our clients overcome. How do you get representative samples of your device without significant investment in full-scale machinery?

In these situations, people typically attempt to construct a prototype by hand; they put engineers in a cleanroom and get them to tack stuff together. There are two problems with this approach – firstly human beings have a habit of making mistakes, and secondly, they're also very good at manipulating parts so they go together when, in reality, they would fail in an automated machine. Owing to the nature of the product, any failure in the use of an injector pen is serious; development projects can be derailed by a single failure. Ideally, there should be no debate about whether the failure is attributable to an inherent design flaw, human error during assembly or part tolerances.

**Q What is the solution to human error?**

A With a machine, you eliminate the human factor. Most devices are put together using a "stack" design. As the name implies, you start with the bottom piece and stack one part on top of another until the top part completes the device assembly. Many of the parts are plastic and will clip together. In automated assembly, you simply apply a linear push force and, if the device is designed correctly, the two parts seamlessly come together.

**Q Without automation, what happens during development?**

A During this stage, parts are usually assembled by hand. Initially, they might be 3D-printed or are often made from single-cavity moulds without masterbatch (the colourant). They will resemble final parts, but single-cavity parts and masterbatch can create subtle differences compared with multicavity commercial ones. The development parts might clip together successfully when production parts won't. Even worse, if two plastic parts don't quite fit together, or if the clips aren't properly aligned, a person can manipulate the parts until they do assemble. It's human nature, and it's a time bomb waiting to derail the project.

These challenges aren't unique to medical devices. Across multiple industries, we've seen the same common engineering solutions work successfully for our clients. These solutions have become a methodology

enshrined within 3P's DNA – it's all about process understanding and how you go about obtaining that understanding. Manual assembly is avoided and replaced with simple jigs and fixtures that are "manually assisted".

Operators load the parts to be assembled into tooling that mimics what you'd find on a production machine. Then, crucially, instead of clipping things together with their hands, the personnel involved are only allowed to pull a handle or move a slide. As such, we're mimicking a production system, if the plastic components break or don't clip together when the push force is applied, that's what would happen in a commercial scale machine and you get early insight that there is a problem. We can also go a step further to gain valuable process understanding – by "mis-setting" the automation in a controlled way, we can start to understand real world tolerance limits for the parts and the automation.

**Q What happens when clients require higher output and/or greater de-risking?**

A 3P has what the company calls its semi-auto (SA) systems. The SA3, for example, is a precise, versatile and flexible platform that is designed to automate the assembly of different devices. The tooling and product location features can be easily exchanged to minimise the impact of device changes and the system is easy to adapt, making it ideal for future applications and reuse. The SA3 pallet option also facilitates changeovers – pallets can be loaded offline with components or they can be directly loaded onto pallets fixed in the system (Figure 1).

**Q Can you elaborate on the SA3 system?**

A What we've done within a compact (1 x 0.8 x 2 m) frame is develop a system whereby the operator loads parts onto a rotary table and then – to safely enable manual feeding and fully automatic assembly – they have to keep two buttons depressed. As the turntable rotates, the parts are loaded into the system and that's when the magic happens. Finished assemblies can be removed and parts loaded by the operator on one side of the turntable while, at the same time, devices are assembled within the machine. This concurrency significantly increases throughput.

Figure 1: SA3 (semi-automated gluing system).

With the components at the back, the machine automatically puts the springs, glassware and other components together with a sequence of left-to-right and up-and-down movements. It's ideal for small, engineering or clinical batch runs of autoinjectors, pens and other medical devices, such as inhalers, and the combination of rapid tooling changeover and keyboard size change means different devices can often be processed on the same machine.

The machine is also bristling with more sensors than you'd normally have in a production machine. This means you get an insight into what's actually going on during assembly – such as the forces that are generated when parts are clipped together against time – which you don't normally have, providing a process "fingerprint". This data-rich environment enables a quality by design approach to device development and, with instrumentation to provide users with real-time graphs and key process parameter trends, the SA3 makes tolerance studies a lot easier. Furthermore, the SA3's freestanding wheel-in/wheel-out design ensures that it doesn't take up precious cleanroom space when not in operation.

**Q Can you add anything else?**

A Production line equipment often incorporates complex motions, generated by either cams or servomotors, which 3P can mimic within the SA3. Preferably, the commercial-scale production machine would be one of ours, but we can simulate any host target plant and our solution is final assembly machine agnostic.

By looking at the S-curves or trapezoidal waveforms that a client's machine produces, we can analyse that motion, examine the profile and programme that same profile into the SA3; it mimics industry-standard pallet based assembly principles. In practice, as far as the product's concerned, it's going through a high-speed machine; in reality, it's being processed by a low-speed machine that's mimicking the former (Figure 2).

Figure 2: SA3 close-up.

Plus, as you'd expect from a medtech automation supplier, it's fully GMP compliant with a validation pack and control system that's suitable for a 21 CFR 11-based electronic record system. With its engineering expertise, 3P offers a custom build service to cater for specific customer requirements, should they not fit within the normal operating envelope of the system.

**Q Are there any other features you'd like to mention?**

A Another useful feature is the ability to "mis-set" the machine in a controlled manner, which allows operators to investigate real-world assembly and part tolerances, create statistical models of the device assembly and run Monte Carlo simulations. Ultimately, these machines provide small-scale representative batches and de-risk device development. Consequently, the unit can be used to develop the device for ease of assembly and to test the part's assembly features.

Understanding uncertainty and minimising risk early is key to reducing time-to-market, saving money and, if you are backed by venture capital, avoiding the "Valley of Death". This ensures that optimised product handling parameters can be developed from the outset with the knowledge that the same parameters can then be applied to the scaled-up commercial manufacturing process. One notable example of this methodology, from the fast-moving consumer goods sector, resulted in payback for 3P's client in less than two months; they eliminated a problem that had dogged their high-speed production lines for decades as a result of insights from 3P's pilot equipment.

**Q Can you explain why this approach saves 3P's clients costs and provide some examples?**

A The cost of providing devices for small-scale clinical trials can be significant because the volumes do not justify commercial equipment and production processes. Equally, manual assembly systems suffer from human error and, as discussed earlier, they can also lead to successful assembly from defective parts. The SA3 provides a cost-effective solution and can run as an autonomous unit – precisely assembling devices, time after time – thereby decreasing variability and lowering the costs associated with producing clinical batches.

"The SA3 provides a cost-effective solution and can run as an autonomous unit – precisely assembling devices, time after time."

This methodology runs deep in the 3P psyche, with many successful examples. The Lab Dosator was designed in response to a client request and our process understanding mindset. Now part of our Pharma Equipment Discover range, it fully replicates commercial dosator-based powder dispensing at a laboratory scale. Where did it come from? A client told us that they had a system with 72 dosators that was suffering from an unacceptable frequency of dosator seizure. Initially, we were asked to source a full set of dosators with a "tweak" to the design in an attempt to solve the issue.

Instead of trying to develop a solution on the commercial equipment with 72 dosators, 3P recommended construction of a small instrumented simulator with a single dosator. What we did was examine the existing system, modelled it and then produced a single-head prototype. Again, we applied more sensors than usual to assess the forces working within the unit and the tolerances that needed to be managed (Figure 3).

The insights from the data meant that we were able to optimise the dimensions and parameters with just a few iterations. We then produced a set of 72 and fitted them successfully on the production machine. As a laboratory-scale device, this dosator fits within small fume enclosures and operates with a very small powder bed. This is critical in the early stages of formulation and process development when active ingredients for testing may be scarce.

Some of the Lab Dosator's significant benefits include its inherent flexibility and ability to replicate commercial processes. It can fill medical devices, inhalers, capsules or blisters under controlled laboratory conditions, and dispenses consistent samples directly into delivery units for clinical or pharmaceutical evaluation. It is primarily used as a formulation screening tool.

**Q Could you give us an insight into 3P's fill-finish process?**

A The same methodology has been used in the fill-finish of vials and cartridges that are typically used in high-value parenteral applications or cell and gene therapies. 3P repackaged fill-finish technology from our larger tub-based isolators into the Discovery range's Fill to Volume (F2V) compact fill-finish system and associated crimper (F2C). Cell and gene products typically rely on highly skilled technical staff to pipette products within a biosafety cabinet. What if the risk

Figure 3: LAB dosator close-up.

Figure 4: F2V (liquid fill-finish platform).

of error from the technical staff could be eliminated with a miniature and sensor-rich fill-finish system that could fit within a biosafety cabinet? Sound familiar? 3P's Liquid F2V is an isolator-ready, flexible platform for both filling and finishing a wide variety of containers and devices, including syringes, cartridges, vials, bottles and customised primary drug containers.

Whereas most lab-scale systems only offer individual process stations, F2V provides a GMP-compliant, all-in-one integrated system for nitrogen purging, liquid filling, vacuum stoppering and other processes on the same machine. This increased level of automation improves productivity, product quality and patient safety, while still providing the flexibility you would expect from a low-volume benchtop system. Operators are not required to transfer containers between the critical fill and stoppering processes, thereby simplifying the process and reducing risk. Using the same principle, 3P used sensors that wouldn't normally be seen in a production system to provide operational feedback and made it benchtop scale (Figure 4).

**Q** **Are there any final thoughts you'd like to share?**

**A** If you look at an SA3 next to a Lab Dosator or an F2V/F2C, you would be hard pressed to recognise any obvious similarities – other than the 3P logo. To 3P engineers, however, they all offer clients a way to reduce technical risks through process understanding. They share a common 3P heritage of successfully developing robust automation. The take-home message here is that the concept of using sensor-rich pilot equipment that mimics commercial-scale systems – which is a fundamental part of 3P's modus operandi – has been successfully used to develop systems specifically for the inhalation space, powder dispensing and, more recently, vial and cryovial filling. Perhaps the only question remaining, therefore, is what comes next?

## ABOUT THE COMPANY

3P innovation is a UK-based, employee-owned engineering and custom automation company. The company works with pharma and medical device businesses to help develop new products, devices and production processes. 3P innovation specialises in aseptic automation and powder/liquid filling technologies. The company designs and builds scalable production solutions, supporting from lab-scale/benchtop equipment to pilot plant and full production systems. The company has two divisions: 3P pharma equipment and 3P custom automation, which specialise in standard equipment and fully customised solutions, respectively.

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# Aseptic Fill-Finish Technologies to Power Your Journey from Clinical to Commercial

DISCOVER

## **Fill-Finish** Platform and **Rotary Crimper**


Our ultra compact, our **Liquid Fill-Finish Platform** and **Rotary Crimper** are designed to be used in research and small scale manufacturing settings.

EXPLORE

## **Robotic Fill-Finish** Cell


The **Robotic Fill-Finish Cell** is a fully autonomous system, offering flexible processing of up to 600 RTU containers per hour. Ideally suited for cell and gene applications.

EVOLVE

## **Robotic Fill-Finish** Cell PRO


The **Robotic Fill-Finish Cell PRO** is a fully autonomous system, offering hands-free flexible processing of up to 3000 RTU containers per hour. Ideally suited for MABs, ADCs and other ATMPs.

3P innovation

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# INTERVIEW

Claire Raynal-Olive, Vice-President of Global Market Development, and Pierre-Yves Favennec, Vice-President of Global Operations, both at Aptar Pharma, discuss the strategy and objectives of Aptar Pharma's expansion programme of its global rubber component manufacturing, implementing advanced technology, increased capacity and local-for-local manufacturing capability.

## CLAIRE RAYNAL-OLIVE, VICE-PRESIDENT OF GLOBAL MARKET DEVELOPMENT

Claire Raynal-Olive serves as the Vice-President of Global Market Development at Aptar Pharma, leading business development and R&D for the Injectables Division, where she has been driving innovation and growth for the company for the past four years. Before joining Aptar Pharma, Ms Raynal-Olive was previously a Global Marketing Director and Strategic Innovation Leader for the Pharmaceutical Systems division at BD. She has also held various commercial and marketing roles at Sanofi for its vaccine business. Her professional journey also includes a stint in consulting and owning a retail pharmacy for close to three years. Ms Raynal-Olive holds a pharmacist diploma and a degree from the EMLyon Business School (Écully, France).

## PIERRE-YVES FAVENNEC, VICE-PRESIDENT OF GLOBAL OPERATIONS

Pierre-Yves Favennec has been serving as the Vice-President of Global Operations for Aptar Pharma's Injectables Division for the past three years. In this role, he spearheads Aptar Pharma's ambitious global expansion programme, leveraging his industrial experience to drive the company's growth globally. Prior to joining Aptar Pharma, Mr Favennec built a career in the food industry, where he took on roles such as Chief Operations Officer and Operations Director. He began his professional journey in the steel industry, focusing on maintenance and operational excellence. He holds a Bachelor's of Engineering and a Master's degree in Management from the *École nationale supérieure d'Arts et Métiers* (ENSAM, Paris, France)

**Q Can you start by giving us a brief overview of Aptar Pharma's place in the pharma and drug delivery sectors, particularly where it comes to injectable drug delivery?**

**CRO** Absolutely, Aptar Pharma is a major manufacturer of drug delivery systems and components. We provide a wide variety of products across multiple delivery routes, including nasal, respiratory, eye-care, dermal and injectables. With regard to injectables specifically, we offer a range of best-in-class components for vial, prefilled syringe, autoinjector and cartridge applications, such as our state-of-the-art PreumiumCoat® ETFE-coated elastomeric components and our comprehensive catalogue of rigid needle shield designs and formulations. We're active across a number of applications throughout the sector and support the development and commercialisation of biologics, vaccines, small molecules, anti-thrombotics and veterinary medicines.

To give you an idea of our scale, Aptar Pharma components are used in the delivery of more than 13 million injections in over 70 countries every day. So, as you can see, we're a truly global player. Coupled with our full-service offering and comprehensive range of components, Aptar Pharma's worldwide reach makes us one of the go-to partners for anyone looking to market and manufacture injectable medicines.

**Q Given Aptar Pharma's position in the market, how are you planning to build on this success and improve your offering for current and future partners?**

**CRO** Aptar Pharma is more than just a component producer, we're a full-service provider able to help our partners achieve success at every stage of the product development journey. To ensure that we can offer the best possible service to our partners, Aptar Pharma's injectables division is making excellent progress through a massive programme of investment to expand our capabilities worldwide, with several elements already delivered. For a major investment such as this, it's important to ground the programme with a clear guiding principle, based on a clear understanding of current market needs and how to address them. Therefore, we've focused this expansion on three key pillars – expanding our capacity, improving our capabilities and working more closely with our partners.

We've set ourselves ambitious goals and are already transforming expectations of what an injectables partner can be. The first part of this, the first pillar, is expanding our production capacity to meet the increasing market demand we're seeing in the injectables sector. This is critical for us, as the greater capacity will enable us to guarantee long-term supply security for our partners. At the same

Figure 1: Aptar Pharma is making excellent progress with its expansion and investment programme, including new and expanded facilities.

> "We've focused this expansion on three key pillars – expanding our capacity, improving our capabilities and increasing our proximity to our partners."

time, we're expanding our capabilities in accordance with our second pillar by investing in state-of-the-art manufacturing technology that will contribute to improved product quality and reliability.

A fundamental principle of our current expansion is to regionalise our operations so that we can serve the needs of our partners more locally, as part of the third pillar. We're constructing an additional factory at our Granville site in France, expanding our capabilities at our Congers site in New York (US) and our acquisition of Hengyu in Weihai, China, give us substantial manufacturing capability there. With factories in France, the US and China, as well as our global network of sales offices, we can be even more responsive and efficient in meeting the needs of our partners around the world (Figure 1).

**Q Which key capabilities is Aptar Pharma aiming to improve on with this expansion?**

PYF Along with increasing our manufacturing footprint, we're investing in our production methods to enhance quality and reliability. This evolution of our process includes implementing state-of-the-art robotisation in our facilities to increase the reproducibility of our processes and reduce the risk of contamination from human interaction with the product on our production lines. In conjunction with this, we're adding ISO 5 and 7 cleanrooms to minimise the risk of particulate contamination throughout the process (Figure 2). We are also expanding our automated vision control with new machines on some of our finishing lines, which will contribute to a lower incidence of defects in our products and therefore rejects on customers' filling lines. Additionally, we're moving toward more digitalisation in our factories, with the aim of improving traceability and ensuring consistent quality control.

Our investments focus on injectables components that address key market needs. This includes our PremiumCoat® products, PremiumFill® manufacturing process, ready-to-use (RTU) gamma-sterilised components and rigid needle shields for prefilled syringes and autoinjectors.

Whilst our products are the key focus of the current expansion, it is important to note that Aptar Pharma is a full-service provider that supports partners at every stage of the drug development journey, from primary packaging selection and formulation development, through clinical trials, regulatory filing through to market launch, and including patient onboarding solutions and digital therapeutics.

**Q With a key aim of Aptar Pharma's investment being to improve the company's ability to meet its partners' needs, can you elaborate on what trends you see currently shaping the injectables market?**

CRO It's of great importance to us to keep abreast of market trends so that we can anticipate the

Figure 2: Aptar Pharma is implementing ISO 5 and 7 cleanrooms in its facilities to minimise the risk of particulate contamination.

needs of our partners and offer solutions adapted to those needs. Aptar Pharma has identified three key trends that are having a major influence on today's market – first, strong market growth; second, continued growth in chronic disease and biologic treatments; and, third, rising R&D costs associated with bringing a drug to market.

On that first point, despite recent turbulence, the injectables sector is continuing to see strong market growth across all applications, especially in chronic therapies and antidiabetics. Injection is now the number one route of administration and its market value expected to increase from US$606 billion (£477 billion) in 2020 to $1,600 billion by 2027. This means that our partners require a future-proofed supply of components with embedded surge capacity to absorb fluctuations in the market. Recent years have highlighted the necessity for providers to have the capacity to respond to global events, such as the covid-19 pandemic. Aptar Pharma's investment programme will increase our production capacity by 40% to meet the long-term needs of our partners.

**Q You mentioned that one of the three key market trends is the rise in biologic treatments – how significant is this factor and how is Aptar Pharma responding to it?**

CRO There's major growth in the number of biologic treatments in development and making their way to market. Over the past few years, while there hasn't been a significant increase in the total number of drug approvals, the proportion of biologics receiving approval from regulatory authorities has increased from as low as 7% in 2000 to 50% in 2022. This incredible surge in biologics is due to their ability to meet unmet needs in the chronic disease space, which itself is growing as a result of ageing populations, as well as their applicability to immune disorders and oncology. On top of this, there's a lot of interest in biologics due to their lower incidence of side-effects compared with traditional small-molecule therapeutics, which makes the additional difficulty in manufacturing them worthwhile.

Indeed, biologics, which are mainly represented by recombinant proteins, monoclonal antibodies or even nucleic acids, are more sensitive than traditional drugs and have much more elaborate structures. In most cases, the preferred delivery route for biologics is injection and solutions like PremiumCoat® are specially designed to help our partners tackle the challenges of manufacturing these complex drugs by protecting them from extractables and leachables, ensuring their long-term preservation once packaged.

Innovation in injectable drug delivery is also allowing for another trend we're seeing in the sector, that being the focus on moving care from the hospital to the home. Modern prefilled syringes and autoinjectors are enabling patients to take control of their healthcare and administer their own medicines in their own homes, which is both more convenient and more sustainable; however, with patients administering drugs rather than healthcare professionals, it becomes all the more imperative that injection devices are convenient and user-friendly, driving the popularity of easy-to-use devices like autoinjectors. Naturally, demand for key components such as Aptar Pharma's PremiumCoat® stoppers and plungers will rise in concurrence with increased autoinjector use, so we're both expanding our capacity and upgrading our equipment to ensure reliable supply and optimum quality.

> "As a full-service provider, Aptar Pharma is ideally positioned to partner with from step one, assisting with selecting the right packaging for our partners' drug products from early on, avoiding incredibly costly delays, or even product reworks, down the line."

**Q You mentioned that the costs associated with R&D are increasing, how can Aptar Pharma assist partners who may be struggling with this?**

CRO In 2010, the average cost of new drug development was $1.8 billion, by 2015 it was $2.6 billion, and it's only getting more expensive. Biologics may be a significant factor here, as they cost more both to develop and to manufacture. The ever increasing regulatory requirements are also a factor that contribute to making new drugs more expensive to develop. The most recent example is the new EMA GMP Annex 1 revision that puts further pressure on manufacturers who now need to demonstrate comprehensive contamination control strategies that cover their whole supply chain, including primary packaging (see this issue, Page 98, for more on this subject).

With these rising costs, derisking projects and regulatory compliance have become critical concerns for drug developers, who want to reach market as early as possible. One of the ways to achieve this is to enter partnerships with expert suppliers as early as possible in the product development journey. To derisk the development of sensitive drug products, Aptar Pharma offers a range of solutions, such as PremiumCoat®, and the newly updated PremiumFill® solution, which can dramatically help customers meet the requirements of the Annex 1 revision.

As a full-service provider, Aptar Pharma is ideally positioned to partner with from step one, assisting with selecting the right packaging for our partners' drug products from early on, avoiding incredibly costly delays, or even product reworks, down the line. To add to that, we offer a wide range of services in-house to help shepherd a project through its initial stages and on to regulatory submission and market release, accelerating, lowering risk and increasing efficiency all the way through.

**Q It's clear that increasing capabilities and capacity are at the core of meeting current market needs. Can you give any further insights on Aptar Pharma's expansion programme?**

PYF We're expanding in a big way. Over the last three years, we've already implemented a significant portion of our 40% capacity increase programme. To achieve this, we've extended our Granville factory, focusing on creating extra capacity for PremiumCoat® and PremiumFill® solutions. We also expanded our site in Le Vaudreuil (France), with a focus on rigid needle shield assembly. Furthermore, our new second factory in Granville and the expansion of our Congers facilities are expected to come online in the first quarter of 2024, which will be a huge boost for us. The Congers expansion, focused

on PremiumCoat®, is bringing manufacturing to the US and providing our US-based partners with a local production centre.

We've markedly ramped up our production capacity in a relatively short time. But we haven't simply added additional factory space, we've focused on operational excellence, which has included improving our capacity for high-value products for the industry, implementing sophisticated technologies to improve the quality of our products and we've thought strategically about how to use our expansion programme to expand geographically to bring us closer to our partners.

**Q You said you've put a keen focus on both improving operational excellence and increasing production capacity, can you explain how Aptar Pharma achieves this?**

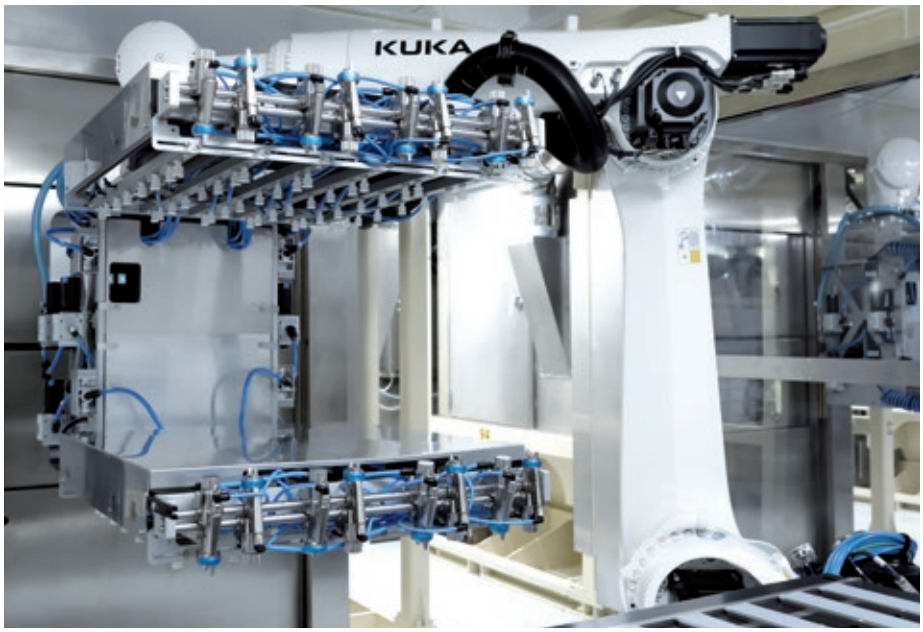


Figure 3: Aptar Pharma is using robotisation to automate its production processes.

PYF There are five key themes we've kept in mind for ensuring that we can offer best-in-class services to our partners. First and foremost, we've put a major emphasis on the safety and wellbeing of our employees – this is a fundamental component of Aptar Pharma's core values. This means that we've built risk reduction, safety and ergonomics into our new facilities by design. As a business, Aptar Pharma puts sustainability at the heart of our operations, and taking care of our teams is part of that.

The second theme we've focused on is quality. We want to deliver the highest possible quality for every component. A key aspect of this theme is implementing uninterrupted cascading cleanrooms in our facilities, minimising the risk of contamination at all stages of production. Another aspect is our implementation of full traceability across our production lines, utilising process and machine connectivity for data collection. We have also put innovative in-process vision control in place to further reduce defects.

Together, the next two themes – digitalisation and robotisation – are part of our commitment to modernisation and bringing in the latest technologies to augment our production capabilities. We've implemented robotisation to automate and semi-automate aspects of production at every stage, including mixing, moulding and finishing, reducing the need for manual labour in our manufacturing processes (Figure 3). The implementation has also given us a chance to review facility layouts and optimise them. Alongside this, digitalisation has enabled us to enhance the ways we monitor the production process and support Industry 4.0 readiness in our facilities, taking further steps towards full connectivity.

Lastly, learning the lessons of recent years, our fifth key theme is ensuring that we're fully prepared for surge demand. We understand that when an unexpected spike in demand occurs, we need to be able to guarantee reliable supply. To meet this need, we've implemented modular layouts for our moulding and finishing workshops to ensure that we can efficiently adapt our production mix to the surge demand. Furthermore, our support teams are trained to work cross-functionally and ready to respond as and when the need arises.

In summary, we've taken a strategic approach to this expansion, with clear objectives in mind. We're transforming the expectation of what an injectables partner can be, and we're eager to show what we've achieved; Aptar Pharma can provide its best-in-class injection device components with even greater quality and reliability than ever before.

***To learn more about Aptar Pharma's injectables offering, visit: www.aptar.com/pharmaceutical/delivery-routes/injectables.***

## ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, from formulation to patient, providing innovative drug delivery systems, components and active material solutions across the widest range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early-stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, it is leading the way in developing digital healthcare devices to help improve patient adherence and compliance. With a global manufacturing footprint of 15 manufacturing sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc.

Aptar pharma

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# INTERVIEW

In this interview, Jeff Henderson, Key Account Manager at Vetter, discusses the practice of outsourcing within the pharmaceutical industry. Mr Henderson considers factors that pharma and biopharma companies should consider when determining whether or not to outsource to a contract development and manufacturing organisation and many of the advantages that outsourcing can offer, especially to small- and medium-sized companies.

## JEFF HENDERSON, VETTER

Jeff Henderson, Key Account Manager at Vetter, has served in a variety of positions as an engineer, consultant and business development professional over the span of his 25-year career. He began his engineering and consulting role with Barry-Wehmiller Design Group in St. Louis (MO, US), designing, installing and validating filling and packaging lines for the food, beverage and pharma industries before earning his MBA at Pepperdine University in Malibu (CA, US). After that, Mr Henderson worked at Amgen, where he was initially responsible for managing contract manufacturing operations at various packaging and sterile fill-finish sites in the US. He later moved into a more strategic role in developing manufacturing strategies for clinical and commercial products in Amgen's pipeline. In 2007, he moved to Seattle (WA, US) to focus on downstream efforts in automated warehousing and material handling before returning to a biotech engineering role at MedImmune's pilot plant in Gaithersburg (MD, US). Following his position at MedImmune, he joined Vetter as a Key Account Manager in 2010 and has been growing a solid business footprint over the past 12 years.

Figure 1: Vetter has extensive experience operating as a tried-and-true pharmaceutical CDMO.

**Q Can you give use an overview of the role Vetter plays within the pharmaceutical industry?**

A Outsourcing in the pharmaceutical industry is anticipated to rise considerably between 2023 and 2030, according to the Pharmaceutical Outsourcing Market Insights Report 2023. Growth is projected to continue as more and more pharmaceutical and biotech companies develop strategies around the adoption of outsourcing.

Vetter is an experienced contract development and manufacturing organisation (CDMO) with a proven track record of supporting clients from the early development phases through commercialisation and lifecycle management (Figure 1). With tried-and-true experience with biologics and sensitive compounds, Vetter uses state-of-the-art technology and efficient processes and strives to put its customers a step ahead of the competition. To do this, Vetter lays a foundation of scalability, quality and sustainable value for drug products.

However, whether a customer works with a CDMO such as Vetter or not, every pharmaceutical drug developer must consider whether to outsource or insource the manufacturing of a drug product. The best strategy for one is not necessarily the best strategy for all.

**Q In your experience, what elements of a drug product's development does the biopharma industry most often outsource?**

A The most common services that drug developers choose to outsource to CDMOs vary between development and manufacturing. However, we most often see outsourcing for drug substance manufacturing, drug product manufacturing and device assembly. Because delivery devices can be very complex to assemble, it can require a deep level of technical, operational and regulatory know-how that many small biotech companies do not have. Rather than develop an entirely new knowledge base that may be costly to acquire, companies outsource to partners to leverage their robust, efficient and scalable processes, which can often integrate seamlessly into already established aseptic filling programmes.

Big pharma companies will use a total cost of ownership model to decide what makes the most financial sense to

"Using CDMOs to get products to clinic and achieve effect commercialisation can make the much-needed income to fund future drug development efforts."

outsource versus keep in house. Smaller biotech companies generally outsource based on necessity, due to a lack of required infrastructure, supply chain access or staff. Developing and manufacturing a drug product is an extremely complex process and one that requires extensive expertise, which is not common in a small or start-up drug development team outside of a specific niche.

The process of second sourcing allows smaller companies to build internal capabilities to manage risk through outsourcing. While a large pharma customer likely won't need to outsource production of its blockbuster drug, a smaller-scale company may need to take on the risk for the sake of meeting quality needs and timeline requirements.

**Q What will be some of the key trends of pharmaceutical outsourcing for the next 12 months?**

A We're seeing that big pharma is generally focused on drugs that move the needle of total revenue. Since these blockbuster drugs are often a company's primary output, they rarely have a need to outsource. However, new products are sometimes outsourced for the flexibility that contract partners can provide.

Alternatively, small biotech companies may lack in-house capability, even if it's the only drug product in development. This could be caused by a lack of staff, infrastructure or supply chain access. Using CDMOs to get products to clinic and achieve effective commercialisation can make the much-needed income to fund future drug development efforts.

**Q Considering that companies can outsource at any point in the drug development process, what are the key outsourcing strategies that you think the biopharma industry should be adapting?**

A During and after the covid-19 pandemic, it became evident that there is always a risk to the stability of manufacturing and supply chains. The result of recent bottlenecks, which are still ongoing, has been a shift towards companies across many industries going directly to partners to build more robust and reliable supply chains. However, that effort is easier said than done – it takes time, money and resources to develop a truly comprehensive and accountable supply chain. Outsourcing can be an extremely effective strategy here, whether during clinical development or at any time throughout the manufacturing process. The lack of a supply chain can impact the entire drug development process but can be mitigated with outsourcing.

Another major outsourcing strategy that biopharma companies are taking relates to new technological requirements, which is evolving at a rapid pace, particularly as the world experiences a technological transformation. To keep up with rapidly evolving technology, drug sponsors can outsource to CDMOs with state-of-the-art infrastructure, rather than acquire new specialities on their own, which are expensive, before a drug product produces any income. New modalities require outside agents to help customers produce on a fast timeline and within a set cost. As the outsourcing market grows, CDMOs face heightened scrutiny, which requires pristine reputation management. Our commitment to quality allows us to build a lasting trust with our customers that equips them to engage us with their fragile biologics.

**Q How can customers mitigate their risk when outsourcing?**

A Drug developers can take several steps to mitigate the risks associated with outsourcing. Using second or multiple sources is a reliable way for pharma or biotech companies to leverage external expertise and capacities in areas they may not currently be equipped for themselves. Having multiple supply chains enables drug owners to maintain access to the products, chemicals and materials needed to get their drug product from Phase I to commercialisation without unplanned delays.

Also, retaining a CDMO to hold capacity and maintain flexibility may serve as an insurance policy to support bringing a drug product to market despite the constant risk of external hurdles. While complex and costly, it is well worth it in the end. Work with one CDMO source and learn from the process. Take account of key findings at the end of the launch management process and implement them into all future outsourcing relationships to build on past trials and successes. Once one drug product successfully reaches the market, the income will make outsourcing easier for the next product.

**Q Are there any new technologies that are requiring greater outsourcing?**

A While it's not a requirement, we are witnessing a massive shift to digitisation in the pharma and biotech industries. As a result, we are incorporating new technologies that our customers may not have access to. For example, "HelMo" is a mobile robot that we are using to standardise and optimise routine tasks, such as thawing drug substances. Our ability to save human capacity from routine work enhances our ability to manufacture our customers' drug products in an even more efficient timeline than what they could do in-house. By outsourcing, customers leverage CDMO capabilities that are often cutting edge and outside the scope of internal expertise within a drug company.

**Q What are the main reasons an internal task should be outsourced in development and manufacturing?**

A Reasons to outsource vary greatly based on individual drug product development and manufacturing strategies. However, there are several primary reasons that we see a customer decide to outsource

"To keep up with rapidly evolving technology, drug sponsors can outsource to CDMOs with state-of-the-art infrastructure, rather than acquire new specialities on their own, which are expensive, before a drug product produces any income."

during the process. One is risk tolerance – if a drug development process fails, the cost can be detrimental to a drug company, especially small or start-up companies. Working with a tried-and-true CDMO partner can prevent risk that may be too costly to handle. Then there's internal capacity, which can relate to plant, people or expertise. If the infrastructure, staff or knowledge required to develop a drug are not available in-house, it is best to outsource to a partner who has all three capacities.

Another factor is speed to market or clinic, which is critical as a drug product does not generate profit until it reaches the market. As a result, working with a partner who can expedite the speed of development to commercialisation can be a worthwhile investment. Commensurate to this is the cost to produce a drug product, which can be immense and often outside the scope of a smaller developer. Partnering with a CDMO can be a more reasonable investment that achieves the same or better result.

Lastly, companies must consider the quality of the product that they bring to market. Drug developers must adhere to exceptionally strict regulations and quality standards. Vetter boasts in-depth knowledge of regulatory requirements that support the level of quality required to get a product to the patients who need it.

**Q For organisations that keep production and manufacturing in-house, why is this the case?**

A More often than not, organisations who keep all drug product development and manufacturing in-house do so because of a previous negative experience. They are likely faced with two major concerns – "Do we have the technology to develop our drug product?" and "Do we have enough capacity?" The lack of one or both of these factors has caused a decade-long boom in the use of CDMOs that can fill these gaps. We continue to make investments in our capabilities and production sites, which further proves the value we can bring to our customers (Figure 2). The connectivity between CDMOs and the larger industry also allows customers to keep their finger on the pulse of industry needs and expectations without expending limited internal resources.

> "We continue to make investments in our capabilities and production sites, which further proves the value we can bring to our customers."

Figure 2: Vetter's production sites make use of state-of-the-art technology and efficient processes.

To address the concern of lack of control when outsourcing, customers can establish and define quality expectations and agreements in initial contracts and through ongoing audits throughout the duration of the partnership.

Whether a drug company outsources for one major component of its drug development process – often including drug substance manufacturing, drug product manufacturing or clinical trial management, or the entire process from Phase I to commercialisation – there is value in leveraging external capacities. Incorporating the knowledge, skillsets, workforce, infrastructure and connections of a CDMO with proven success is a smart and effective business decision for large and small pharma and biotech companies looking to bring their drug product to market.

## ABOUT THE COMPANY

Vetter is a leading CDMO with production facilities in Germany, Austria and the US, as well as sales locations in the Asia-Pacific markets of Japan, China, South Korea and Singapore. Around the world, both small and large pharma and biotech companies rely on Vetter's decades of experience, high quality, modern technologies and reliability, based on the commitment of its more than 6,000 employees. Vetter provides support from drug product development, through clinical and commercial filling to a wide range of assembly and packaging services for vials, syringes and cartridges. With innovative solutions, Vetter develops prefilled drug delivery systems together with its customers to continuously improve patient safety, comfort and compliance. The company is a pioneer in the industry when it comes to sustainability, acting as a socially and ethically responsible corporate citizen. Vetter is a member of the UN Global Compact, has received multiple CDMO Leadership Awards and has been awarded several times as Best Managed Company.

VETTER

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