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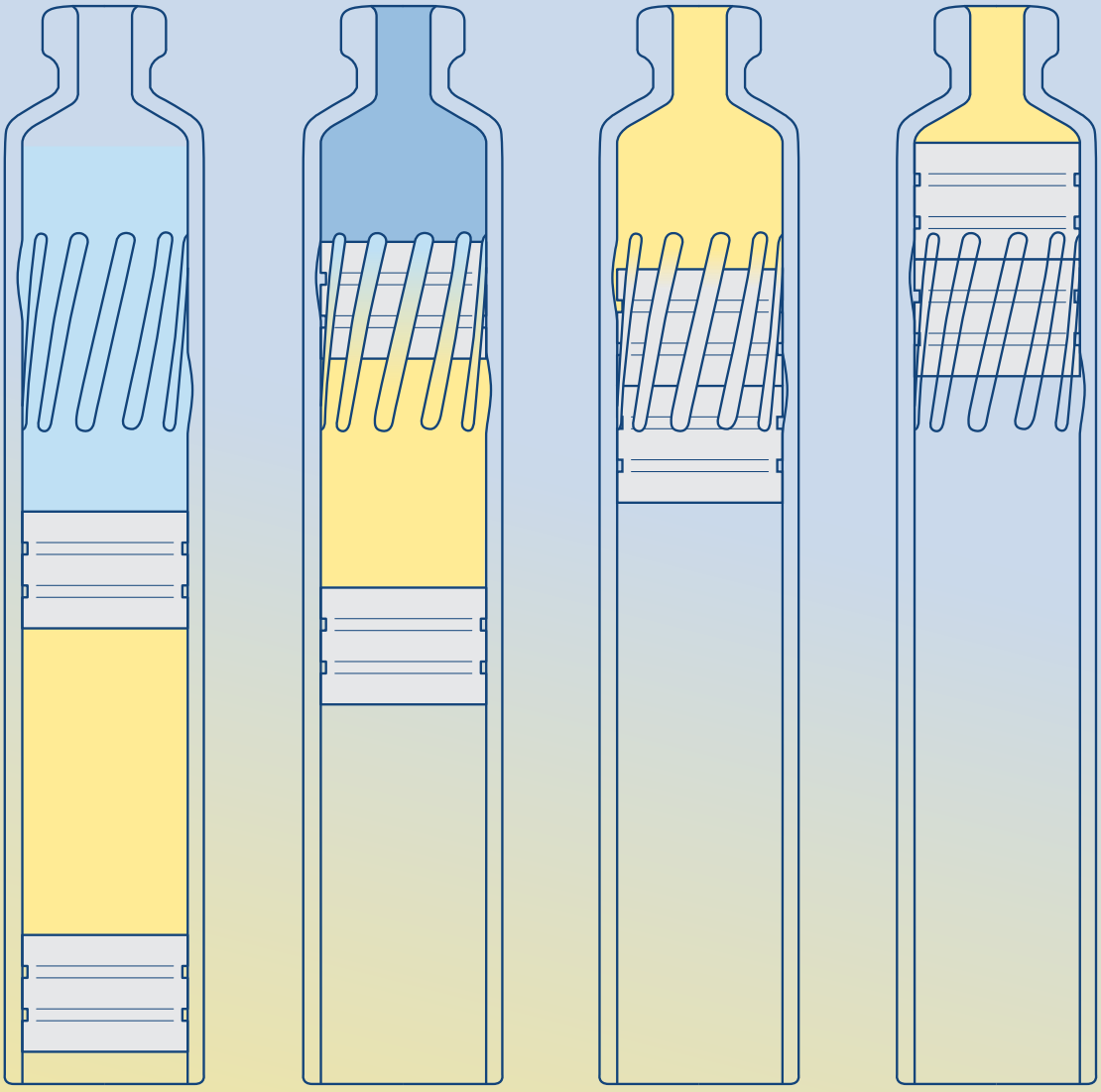
DrugDelivery

SEPTEMBER 21ST 2026

DUAL-CHAMBER DELIVERY SYSTEMS



Contents

DUAL-CHAMBER DELIVERY SYSTEMS

ONdrugDelivery Issue N° 190, September 21st, 2026

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.

Front cover image, "EZ-fill® 3 mL internal-bypass cartridge platform" courtesy of Stevanato Group (see this issue, Page 60). Reproduced with kind permission.

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- Integration into combination products through a robust system data package[9,10]

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*When compared to 12.7 mm special thin wall (STW) needle
**When compared to the BD SCF™ FluroTec® Plunger Stopper. Results are based on a sample of 100 pieces of BD Flurotec® and BD SCF™ PremiumCoat®. Variables compared were Mean (glide force reduction) and standard deviation (glide force variability)
¥ Gliding test performed at nominal design space, in BD Neopak™ Glass Prefillable Syringe 2,25mL 27G filled with WFI

1. BD Neopak™ 1mlL customer quality specification, Le Pont-de-Claix, France; Becton, Dickinson, 2017 **2.** BD Neopak™ and BD Neopak™ XSi™ 2.25 mL customer quality specifi cation, Le Pont-de-Claix, France; Becton, Dickinson, 2020 **3.** Injection time and ejection force calculation [internal study], Le Pont-de-Claix, France; Becton, Dickinson and Company, 2021 **4.** Depaz et al. Cross-Linked Silicone Coating: A Novel Prefilled Syringe Technology That Reduces Subvisible Particles and Maintains Compatibility with Biologics JOURNAL OF PHARMACEUTICAL SCIENCES 103:1384–1393, 2014 **5.** DVTR20192507_DV data BD SCF™ PremiumCoat® 1 mlL R&D data [internal study]. Le Pont-de-Claix, France; Becton, Dickinson and Company; 2023. **6.** TR20234488 Le Pont-de-Claix, France; Becton, Dickinson and Company; 2024 **7.** BD SCF™ PremiumCoat® Plunger Stopper 1mlL Customer quality specifications. Le Pont-de-Claix, France; Becton, Dickinson and Company; 2022. **8.** BD SCF™ PremiumCoat® Plunger Stopper 1-3mL Customer quality specifications. Le Pont-de-Claix, France; Becton, Dickinson and Company; 2023. **9.** Design Control Evidence BD SCF™ Premiumcoat® 1mlL with integrated biologics system data in Neopak Syringes. Le Pont-de-Claix, France; Becton, Dickinson and Company; 2021 **10.** Design Control Evidence BD SCF™ Premiumcoat® 1-3mL with integrated biologics system data in Neopak Syringes. Le Pont-de-Claix, France; Becton, Dickinson and Company; 2024

Autumn of Injection Part II:
Dual-Chamber Devices

With the autumn conference season fast approaching, our Autumn of Injection series moves on to its second topic of focus – dual-chamber injection systems, a recent addition to our annual line-up of topics. These devices are a rising star within the injection world, as the dual-chamber approach offers potential solutions to several of the most pressing challenges of the day, including how to enable reliable at-home delivery of lyophilised drugs, how to handle multi-drug combinations with poor liquid stability and how to successfully push autoinjectors beyond the perceived 3 mL limit.

Beginning the discussion, **BD**, this issue's Outstanding Sponsor, puts the spotlight on its novel valve component for converting the existing autoinjector platforms already well established in the sector into dual-chamber devices (Page 6). Designing dual-chamber systems to fit in with established practices and infrastructure is a common theme across this issue, but **Credence Medsystems**, our first Key Sponsor, is a pioneer in the field, contributing here to discuss how its Innovation Without Change® philosophy has defined the development of its dual-chamber platform (Page 14). Alongside them, **Windgap Medical** investigates how its dual-cartridge architecture offers a potential solution to delivering large-volume injections using two standard cartridges (Page 20).

Dual-chamber devices are a diverse and innovative field, with entrants into the sector taking a wide range of approaches to device design. Continuing the array of devices featured in this issue, **Kaléo** discusses how using gas power as the drive force for its Aerio™ platform enables a more compact form factor and reliability in emergency-use situations (Page 34); **Ampulis** introduces its Pristal™ reconstitution platform, explaining the advantages of its side-by-side cartridge layout (Page 40); **Capa Valve** argues for the advantages of its patented valve technology over specialist bypass-based dual-chamber systems (Page 46); **CoFlo Medical** brings a truly novel approach to the table, using dual-chamber technology to obviate the challenges of delivering highly viscous drugs by taking advantage of core-annular flow (Page 54); and **Stevanato Group** presents a new addition to its EZ-fill range – a 3 mL internal-bypass cartridge – and demonstrates its integration with **SHL Medical**'s newly launched Magnitude 3.0 autoinjector platform (Page 60).

As always, there is more to an issue of ONdrugDelivery than devices alone, and this issue promises not to disappoint. With lyophilisation and reconstitution being a central pillar of many dual-chamber offerings, **Haughton Design** dives into the technical principles behind this key subject (Page 26), while **Dr Sahab Babaee** and **Dr Matthew Hancock** present work on using modelling and simulation to investigate the complex interactions that take place within a dual-chamber device (Page 66). Joining them, **Ram Halthore** shares his thoughts on how the industry can meet the demands of increasingly complex medicines (Page 76), and **Bharat Arora** and **Hirak Bhatiya** discuss how to take a proactive approach to an increasingly stringent regulatory environment (Page 72). Rounding out the issue, **Grand River Aseptic Manufacturing** presents a Showcase on its fill-finish capabilities (Page 52), and **CPHI** shares a preview of what to expect at the CPHI Milan conference on 6–8 Oct, 2026 (Page 30). Additionally, ONdrugDelivery will be present at CPHI Milan! Please come and visit us in the Media Hub in Hall 16 (Stand 16F08).

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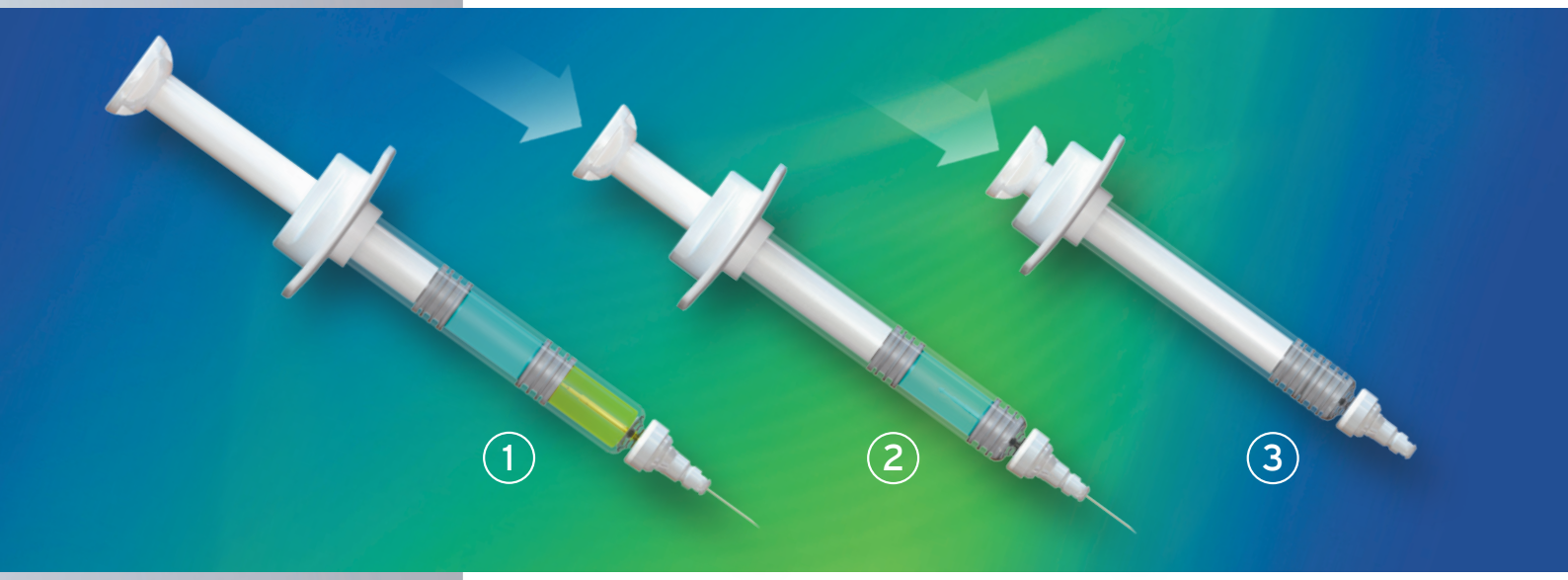

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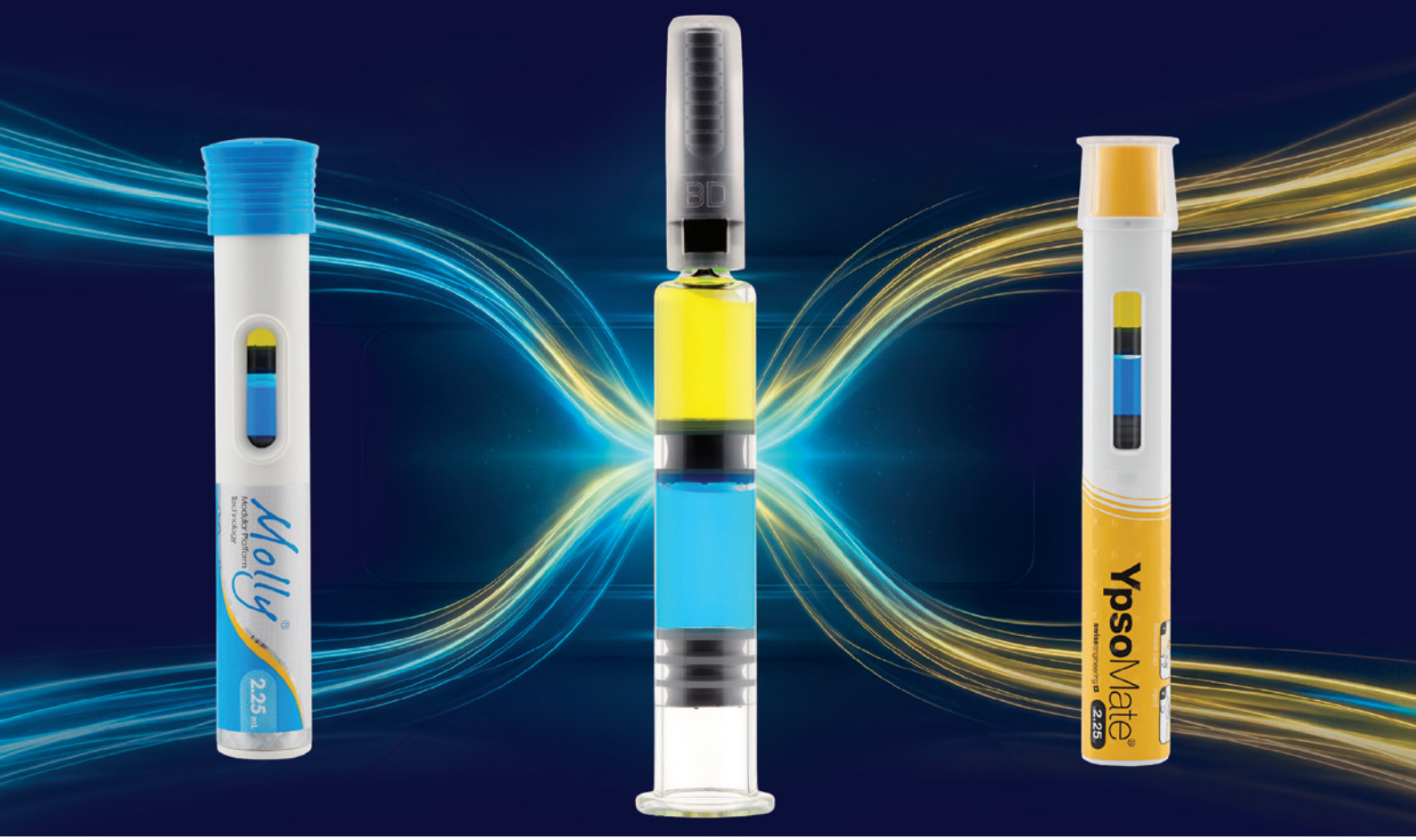

SIMPLIFYING COMBINATION THERAPIES: DUAL-INJECTION FUNCTIONALITY FOR EXISTING PLATFORM AUTOINJECTOR SYSTEMS

BD
Advancing the world of health™

Marc Flippe and **Sophie Lelias** of **BD**

discuss how dual-injection technology provides a promising approach to combination therapies and explain how, through the development of BD's novel valve component, the company has reimagined dual injection within existing and established platform systems.

As the pharmaceutical pipeline continues to evolve, combination therapies, also known as fixed-dose combinations (FDCs), are gaining traction as a strategy to enhance therapeutic efficacy, reduce treatment burden and improve patient outcomes. These benefits are especially important for complex diseases characterised by diverse pathological mechanisms, where patients may require several therapies simultaneously to achieve optimal disease management.

FDCs include two or more APIs within a single dosage form, and can include a combination of existing, approved and marketed monotherapies or a combination of marketed and novel therapies. Over the past several decades, FDCs have evolved from a niche strategy to an increasingly relevant tool within today's pharmaceutical development pipelines. Particularly, as the cost of bringing a new drug to market continues to escalate, with estimates ranging from US$314 million (£231 million) to $2.8 billion,[1] FDCs offer an interesting approach to potentially "repurpose" approved drugs with established safety profiles beyond their original therapeutic application and scope.

Unlike small molecules, where co-formulated FDCs are a well-established strategy, biologics face stability, permeability, solubility and immunogenicity challenges due to their inherent characteristics. These complex mixtures co-formulating two or more biologic drugs may introduce significant development risks, including cross-reactivity, physical and chemical instability, safety concerns

"CONSIDERING THE UNIQUE BENEFITS THAT FDCS MAY OFFER TO CHRONIC DISEASE TREATMENT, THEIR APPLICATION IN THE BIOLOGICS PIPELINE IS GAINING MOMENTUM."

and complex analytical characterisation.[2–4] This may be especially true for formulations with different pHs, excipient types and ionic strengths.[2] However, considering the unique benefits that FDCs may offer to chronic disease treatment, their application in the biologics pipeline is gaining momentum.

Recognising the challenges of co-formulation for biologics, an alternative approach may be dual injection, allowing for the co-administration of two liquid drugs while maintaining separation until use. Dual injection may avoid the risks associated with the interaction of the combined drug formulations before use while preserving the benefits of FDCs.

Although several dual-injection solutions exist, many require specialised container formats, new materials and/or significant changes to device-system architecture, limiting their compatibility with the standard container and device platforms used in the chronic disease landscape today, such as prefillable syringes and autoinjectors. Thus, a key challenge remains: how can pharmaceutical and biotech companies enable dual-injection functionality without introducing significant complexity into existing drug delivery systems and processes? To address this challenge, BD has reimagined dual injection through the development of a novel valve component designed to provide the functionality of a dual-chamber system within existing and established platform systems.

THE BD® DUAL-INJECTION VALVE AND SYRINGE SYSTEM

Within the biologic-device combination product landscape, prefilled syringes (PFSs) and autoinjectors are the most widely adopted device types, given the increasing demand for self-administration for chronic disease treatment. With the broad use of these container and device systems, pharmaceutical companies are more frequently applying a "platform approach", defining sets of components, containers and devices that can be used across multiple drug assets in their development pipelines. The potential benefits of a platform approach include using existing data, supply chain simplification, cost efficiencies, reduction of technical risks and established regulatory approval track record.

The BD® dual-injection valve (Figure 1) is a novel slitted valve component that maintains physical separation of two or more liquids within a standard single syringe until the point of delivery. It features an external shape designed to support compatibility with existing glass prefillable syringes, autoinjectors and dual-chamber fill-finish lines, allowing pharmaceutical companies to use established platform systems and manufacturing infrastructures.

Upon activation, Liquid 1 is released, followed by the release of Liquid 2, which passes through the valve (Figure 2). As the passage of the liquid is through the valve, it does not require a bypass channel or specialised container geometry, enabling multiple fill volume combinations within the same standard syringe. Uniquely,

Figure 1: BD® dual-injection valve.*

the valve component is functionally symmetrical, simplifying orientation during automated handling. Furthermore, it uses well-characterised materials and widely used packaging and sterilisation processes, thereby potentially reducing the risks typically associated with new component adoption.

Through the use of a single-valve component, dual-chamber functionality can be achieved without fundamentally redesigning existing platform systems. By reducing the scope of change required, this approach supports simplified combination product pathways, lowering development burdens compared with systems that require major changes at the container and/or device-system level, and enabling scalable integration across existing platform syringe and autoinjector systems.

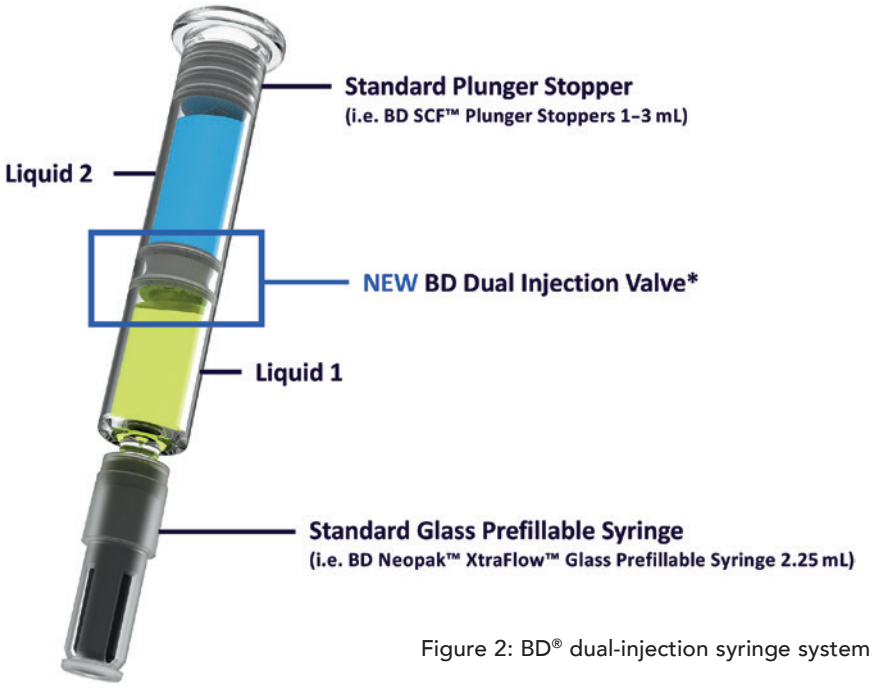

Figure 2: BD® dual-injection syringe system.*

ADDRESSING REQUIREMENTS FOR AUTOINJECTOR INTEGRATION

Enabling dual-injection functionality within existing autoinjector platforms requires satisfying a complex set of interdependent requirements across the full drug delivery system. BD approached this challenge through a system-level framework, cascading from device-level performance requirements down to component-level specifications (Figure 3). This includes autoinjector performance requirements (e.g. ISO 11608), prefillable syringe system requirements (e.g. ISO 11040-8 and ISO 11040-4), integration interfaces between syringe and device, and component-level specifications for the novel valve, as well as for the other existing components, such as the end plunger stopper.

At the core of this approach is the objective to preserve the functionality of standard PFS/autoinjector systems while introducing dual-injection capability. To achieve this, BD collaborated with leading autoinjector manufacturers, SHL Medical (Zug, Switzerland) and Ypsomed (Burgdorf, Switzerland), to de-risk integration and demonstrate the compatibility of the valve combined with the BD Neopak™ 2.25 mL Glass Prefillable Syringe platform and established platform autoinjectors such as SHL Medical's Molly® 2.25 and Ypsomed's YpsoMate® 2.25. To ensure that the valve component remains fully compatible with the mechanical output of the tested autoinjector platforms, early alignment with ecosystem partners on injection performance parameters, including break-loose and extrusion forces and overall injection force profiles, were critical.

The introduction of the valve to these systems adds an additional functional layer requiring precise control of the valve behaviour under real-world conditions. The valve must remain securely closed throughout storage, transport and handling, only opening when a defined pressure threshold is reached during injection. This ensures that the drugs remain separated until the point of delivery, preventing premature mixing or leakage, while enabling a complete dual-liquid injection. In parallel, the system must maintain dose accuracy, including controlled residual volume.

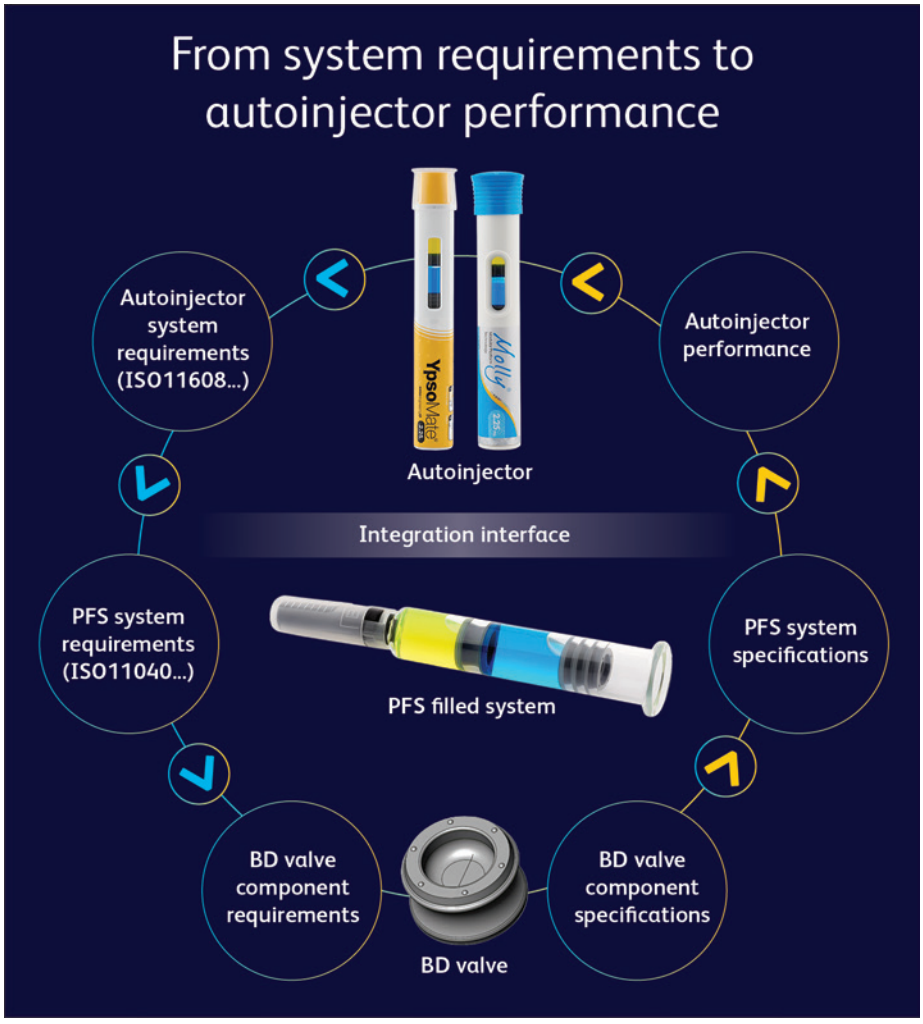

Figure 3: Interdependent requirements across PFS and autoinjector systems to allow dual-injection functionality.

These requirements extend across the entire product lifecycle, including storage, shipment and until point of injection. The system must demonstrate resilience to mechanical stresses such as drop events, maintain stability through shipping and shelf life, and ensure consistent performance at point of use. The result is a solution that behaves effectively as a standard syringe system from the perspective of autoinjector performance, while embedding additional capabilities of dual-drug delivery without requiring major architectural modifications of established platform autoinjectors.

AUTOINJECTOR COMPATIBILITY TESTING

To demonstrate compatibility of the BD® dual-injection valve with standard platform autoinjectors, BD partnered with Ypsomed and SHL Medical in separate testing programmes to evaluate system integration and functional performance. Before testing, BD employed various modelling tools developed to calculate predicted performance outputs. These modelling

"THE INTRODUCTION OF THE VALVE TO THESE SYSTEMS ADDS AN ADDITIONAL FUNCTIONAL LAYER REQUIRING PRECISE CONTROL OF THE VALVE BEHAVIOUR UNDER REAL-WORLD CONDITIONS."

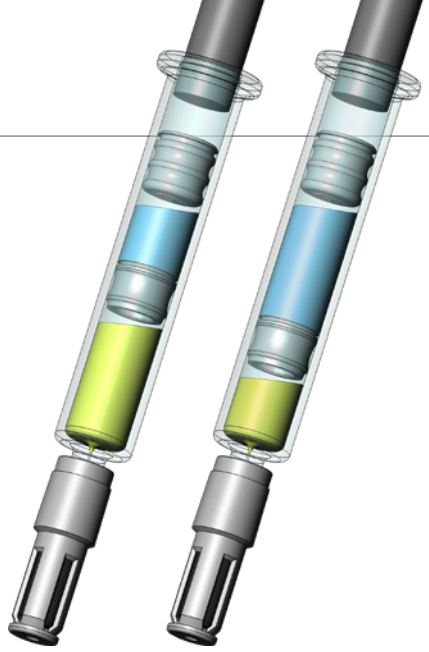

Figure 4: Varying fill volume combinations with the BD® dual-injection valve.

tools were developed to handle various autoinjector architecture features, such as spring force profile. With these tools, BD was able to verify the various parameter conditions to ensure delivery of complete dose via an autoinjector with the BD® dual-injection valve considering varying drug viscosities and fill volumes (Figure 4). Importantly, BD developed a model to assess injection time performance with the BD® dual-injection valve. This model incorporates key variables, such as syringe barrel and needle geometry, drug volume and rheological properties (including Newtonian and non-Newtonian behaviours), elastomer component properties (including ageing effects), liquid transfer dynamics (informed by computational fluid dynamics analysis), and autoinjector force profiles based on device architecture and integration principles. The model was built with direct input from BD's autoinjector partners.

Figure 5: The BD® dual-injection valve and syringe system with the SHL Medical Molly® 2.25 mL autoinjector and Ypsomed YpsoMate® 2.25 mL autoinjector.

By capturing variability in critical parameters, the model enables design space exploration and robust system optimisation.

This approach enables BD to work collaboratively with its pharmaceutical customers and autoinjector partners to guide syringe and needle selection and support successful device integration. For example, modelling results indicate that placing the higher-viscosity drug in the front chamber closest to the needle can help balance injection times between chambers and improve overall injection performance.

In addition to this modelling work, BD conducted extensive collaborative bench testing with SHL Medical and Ypsomed, beginning in the early development stages of the BD® dual-injection valve component and prototype evaluation. Integration studies demonstrated that standard autoinjector platforms could successfully accommodate the BD® dual-injection valve without modification, maintaining full device functionality (Figure 5). Key performance assessments focused on dose accuracy, injection time and compliance with ISO 11608-1 robustness requirements. Testing across a range of viscosities (1–30 cP) using the BD Neopak™ 2.25 mL Glass Prefillable syringes confirmed accurate dose delivery and consistent injection performance (Figure 6). The results also indicated that injection time results can be readily tuned through syringe and device design parameters, such as needle gauge and length and spring force.

In addition, drop testing was performed to evaluate valve integrity under simulated use conditions. Across multiple autoinjector platforms and test conditions, no liquid transfer or leakage between chambers was

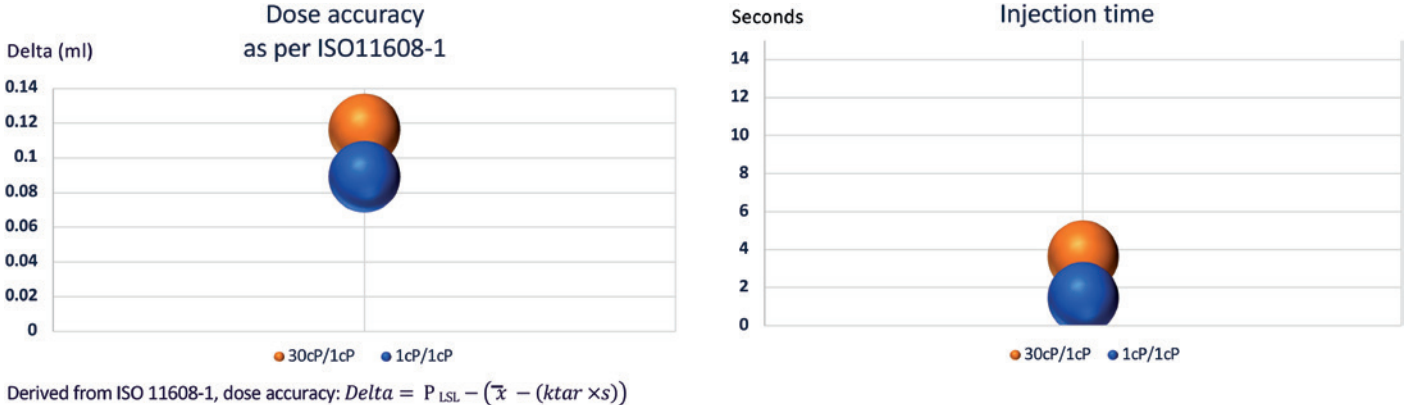

Figure 6: Summarised injection time and dose accuracy results from bench testing of the BD® dual-injection valve across different autoinjectors and varying volume and viscosity combinations. Results shown are averaged across the tests performed.

observed following drop events, meeting ISO 11608-1 free fall requirements and demonstrating the valve's ability to maintain chamber separation and support reliable delivery performance.

CONCLUSION

Interest in FDCs continues to grow across the pharmaceutical development pipeline, driven by their potential to improve therapeutic outcomes and enhance patient convenience. However, co-formulation of biologics can introduce significant formulation and development challenges, driving demand for delivery solutions that unlock these treatment possibilities while employing established drug delivery platform systems.

The BD® dual-injection valve presents an alternative approach, enabling the separate storage of two liquid drugs within a standard prefillable syringe until the point of delivery, while maintaining compatibility with established autoinjector platforms. Through a combination of system-level

"INTEREST IN FDCS CONTINUES TO GROW ACROSS THE PHARMACEUTICAL DEVELOPMENT PIPELINE, DRIVEN BY THEIR POTENTIAL TO IMPROVE THERAPEUTIC OUTCOMES AND ENHANCE PATIENT CONVENIENCE."

Marc Flippe

Marc Flippe is an R&D Engineer at BD, currently serving as the R&D lead for the BD dual-injection valve and syringe system within the BD Medical – Pharmaceutical Systems business unit. With over 27 years of experience at BD, Mr Flippe has contributed to a wide range of initiatives spanning new product development, industrialisation and the integration of product and process innovations across internal and external manufacturing environments. Mr Flippe began his career in the rubber tyre industry, later transitioning to focus on drug delivery devices. His expertise lies in navigating complex product process interactions, enabling the successful progression of concepts from early development through to commercialisation. Throughout his tenure at BD, he has played a pivotal role in advancing solutions that address evolving healthcare needs, using cross-functional collaboration and deep technical insight to drive innovation in drug delivery. He holds an Engineering degree from Grenoble INP – UGA (France).

Sophie Lelias

Sophie Lelias is an Associate Director of Business Development at BD Pharmaceutical Systems. In her role, she drives end-to-end business development across the Prefillable Solutions portfolio, from early concept through commercialisation. Prior to this, Ms Lelias led global strategic portfolio marketing for the Biologics Prefillable Syringe portfolio, including the BD Hypak™ for Biotech and BD Neopak™ Glass PFS platforms. She collaborates closely with cross-functional teams globally to deliver value-driven solutions to pharmaceutical partners. Ms Lelias has held roles across the BD Interventional – Surgery, BD Medical – Infusion Preparation and Delivery and BD Medical Pharmaceutical Systems businesses, with a strong focus on strategic innovation marketing. She holds a Bachelor's degree in Public Health from Brown University (Providence, RI, US).

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design, modelling and collaborative testing undertaken with Ypsomed and SHL Medical, this novel valve component demonstrated the ability to integrate into standard platform autoinjector ecosystems without requiring modifications to device architecture or compromising key performance attributes, such as dose accuracy and injection time.

By minimising changes to proven container and device platforms, the BD® dual-injection valve has the potential to reduce development complexity and support more efficient advancement of biologic combination products. As pharmaceutical companies continue to pursue therapies targeting multiple disease pathways, platform-compatible dual-injection technologies may help unlock new opportunities for combination drug development while enabling the use of established delivery systems already familiar to patients, healthcare professionals and regulators.

ACKNOWLEDGEMENTS

The authors would like to thank Antoine Ciboulet from BD, Christoph Egloff from SHL Medical, and Claudio Gobet from Ypsomed for their contributions to this article.

**The BD® dual-injection valve and syringe system are products in development. Some statements made are forward-looking and are subject to a variety of risks and uncertainties.*

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AHEAD OF THE CURVE: HOW INNOVATION WITHOUT CHANGE® DELIVERS AN END-TO-END DUAL-CHAMBER SOLUTION

Sian Eden and **John Merhige** of **Credence MedSystems** consider how dual-chamber solutions have moved from a niche product to a mainstream consideration for stability-challenged formulations, offering formulation teams an alternative path to get these promising therapies into the hands of the patients that need them, and highlight how Credence is uniquely positioned to deliver on the potential of dual-chamber systems.

DUAL-CHAMBER SYSTEMS HAVE ENTERED THE SPOTLIGHT

Dual-chamber syringes sit at the intersection of two key trends in the world of drug delivery. Firstly, there is an increasing number of therapies in pharmaceutical pipelines that are proving difficult to formulate in a stable liquid form. Drug development programmes are running into untenable delays, or even being abandoned entirely, as formulation teams struggle to develop a stable formulation or co-formulation. Secondly, there is the continuing demand for products with a use and safety profile that facilitates the transition of care from clinical environments to at-home delivery. Both trends put new pressures on drug delivery systems; they must meet the needs of demanding molecules by keeping drug constituents separate until the time of injection, while also supporting intuitive delivery and the continued transition towards at-home administration.

While dual-chamber systems are not a new idea, they are garnering increasing attention as a clear solution to these challenges. A current market report puts the value of the dual-chamber device market at US$6.25 billion (£4.61 billion) in 2026 and projects it to grow to $17.56 billion by 2040 at a compound annual growth rate of 7.7%.[1] This is reflected in the increased industry focus on dual-chamber systems, with the topic highlighted as a key trend to watch out for in 2026.[2]

"CHOOSING THE RIGHT PLATFORM PARTNER FOR A PROJECT IS GOING TO BE AN ESSENTIAL ASPECT OF SUCCESS OR FAILURE, SO IT IS CRITICAL TO GO WITH AN EXPERIENCED PARTNER WITH A DEEP UNDERSTANDING OF THE DUAL-CHAMBER SPACE."

The question, therefore, is why now? What has driven the transition of dual-chamber systems from a niche solution to a topic for mainstream discussion? The answer to this is multifaceted. One factor is that pharma is aggressively pursuing combination therapies, a key example being Novo Nordisk's CagriSema – a dual injection of semaglutide and cagrilintide.[3] For applications where maintaining stability in a single co-formulation presents significant challenges, sequential dual-chamber delivery of two liquids provides an alternative approach by keeping components separate until the point of administration while still providing intuitive usability that mirrors the injection of a single liquid. In addition to combination therapies, this can be particularly valuable for stacked vaccines as well as large-volume subcutaneous injections where hyaluronidase is used to increase tissue permeability prior to delivery of the therapeutic.

Another factor contributing to the increased attention is that, due to the sensitivity of many modern therapeutics – including biologics – many pharma companies require lyophilisation or spray drying as a means of storing the drug in dry form. This dry-storage approach provides a cost-effective alternative to cold-chain storage. These macro industry factors make delivering the resulting drug products significantly more complex, requiring two injections or additional preparation/administration steps, and place unnecessary risk on the user. Dual-chamber systems are a natural solution to this issue, although they come with several considerations.[4]

It should be no surprise, then, that the dual-chamber space has become increasingly competitive in recent years, with new players and devices coming in with a range of approaches. Naturally, these varying approaches come with a range of advantages and disadvantages, and prioritise different considerations. Gone are the days when a dual-chamber system only needed to prove itself against a cumbersome vial-and-syringe alternative – pharma must now navigate a complex and competitive market to find the right solution for its therapies. They must also assess the capabilities for filling dual-chamber systems, as this need has traditionally been met by only one industry service provider.

So, where to start? Much like when selecting any other drug delivery system, it is important to ask the right questions. Is the system suitable for the task at hand, be that sequential delivery of two liquids, liquid-liquid mixing or reconstituting a dry powder? What injection volumes and drug characteristics can it support? Is it ready for human use? How many novel components are involved? Is the infrastructure for filling ready and available? What are the needs of the user, and in what setting will the product ultimately be administered? Choosing the right platform partner for a project is going to be an essential aspect of success or failure, so it is critical to go with an experienced partner with a deep understanding of the dual-chamber space.

CREDENCE MEDSYSTEMS AND INNOVATION WITHOUT CHANGE®

Credence MedSystems is an established player in injectable drug delivery, having developed proven ready-to-supply platform technologies designed to solve injectable drug delivery challenges in the areas of safety, usability, delivery of unstable drug formulations and precision dosing. Its portfolio includes the Credence Companion®, Credence Dual Chamber Syringe and Credence Metered Dosing platforms. Credence has received its ISO 13485 certificate of registration and is compliant with ISO 13485:2016 and 21 CFR Part 820.

Central to the development of these technologies, and Credence's overall business model, is the company's Innovation Without Change® philosophy: introducing innovation to enable its pharma partners to deliver needed therapies to patients, while maintaining compatibility with proven primary components, established fill-finish processes and existing manufacturing infrastructure wherever possible (Figure 1). Innovation Without Change® is based on a simple principle – innovation should solve drug delivery challenges without introducing unnecessary complexity elsewhere. Credence's technologies are therefore designed around proven primary components and established manufacturing processes, helping pharmaceutical partners adopt new drug delivery capabilities while minimising implementation risk and operational disruption.

Figure 1: Credence's Innovation Without Change® philosophy maintains compatibility with proven primary components, established fill-finish processes and existing manufacturing infrastructure while addressing challenges in drug delivery.

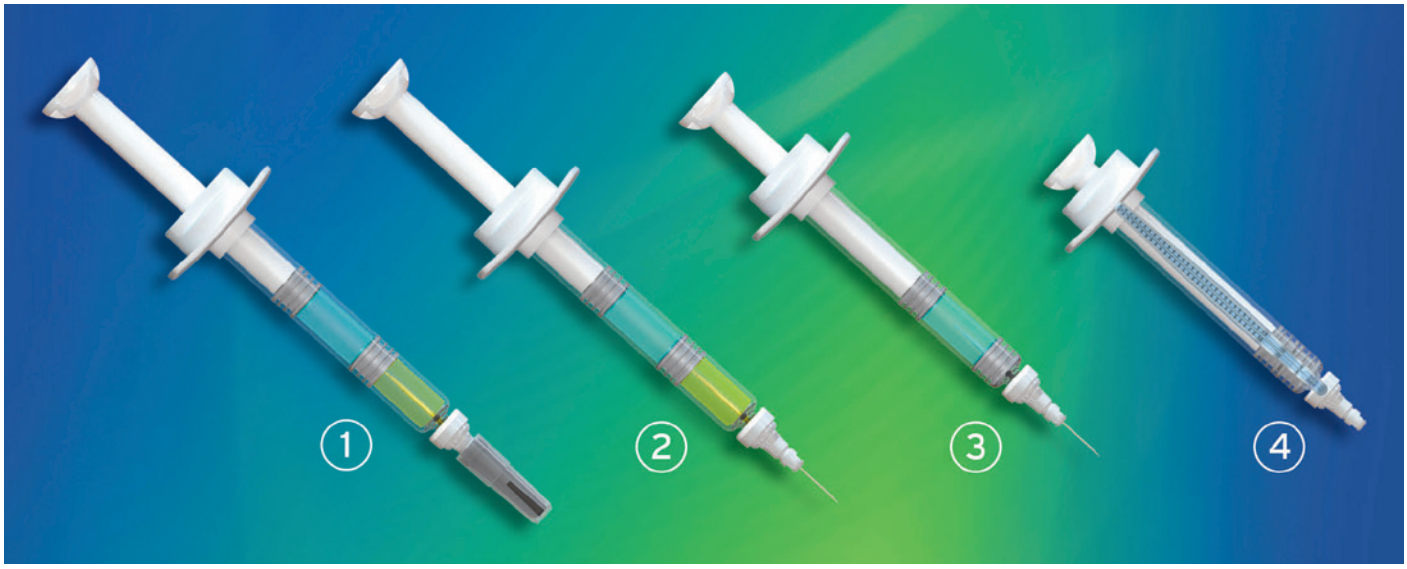

Figure 2: The Credence Sequential Dual Chamber system stores two liquids separately in the same standard PFS and allows the two liquids to be delivered with a single push of the plunger rod while also providing passive needle safety.

THE CREDENCE DUAL CHAMBER SYRINGE PLATFORM

Naturally, Innovation Without Change® is a core principle of the Credence Dual Chamber Syringe Platform. By using a standard off-the-shelf syringe barrel as a base, the Credence Dual Chamber system does not rely on a bypass built into the container barrel, instead using the combination of an innovative needle assembly with a separating stopper to facilitate dual-chamber delivery. The result is a format that is both immediately familiar and innovative at the same time. This familiarity has advantages for patients as well as industry, as the final product is presented in the form of a standard prefilled syringe (PFS), which increases usability and facilitates at-home use by patients.

Credence has led the wave of recent entrants into the sector,[5] enabling the company to offer pharma partners a deep understanding of dual-chamber device technology, filling and assembly that supports combination product development through to commercial supply. The Credence Dual Chamber Syringe Platform is an advanced delivery system enabling reconstitution or sequential injection in industry-standard PFSs, with passive integrated needle safety and clear end-of-dose cues. Designed to simplify the delivery of complex drug products, it offers straightforward administration, reduces the risk of user error and supports the transition towards at-home use.

"THE CREDENCE DUAL CHAMBER SYRINGE PLATFORM PRIORITISES USABILITY, AIMING TO EMULATE THE FUNCTION OF A STANDARD PFS AS CLOSELY AS POSSIBLE."

The Credence Dual Chamber Syringe Platform prioritises usability, aiming to emulate the function of a standard PFS as closely as possible, eliminating the need to twist the plunger or require integration within an autoinjector. Furthermore, the platform features an integrated pre-attached needle with passive safety in the form of needle retraction, which serves not only as a safety feature but also as a tactile, audible and visual cue for completion of the injection.

For the Sequential Dual Chamber system, both liquids are stored in the syringe barrel and are completely isolated from each other prior to injection (Figure 2). Performing the injection is as simple as a regular injection, with the user simply depressing the plunger in a single stroke as they would with any other syringe – the two liquids are injected in sequence, all clearly observable through the syringe barrel. Credence's design minimises dead volume and any interaction between the liquids during injection. To offer further alternatives based on pharma preference, Credence is partnering with leading collaborators to develop a two-step autoinjector that is compatible with the Sequential Dual Chamber system.

Much like the sequential system, Credence's Reconstitution Dual Chamber system stores the two drug constituents separately within the syringe barrel until use. The use sequence is designed to remain straightforward. First, the user depresses the plunger until the two stoppers meet, seamlessly transferring the liquid from the rear chamber to the front for mixing. The system allows the rear liquid to mix with spray dried or lyophilised powder as well as with another liquid in the front chamber. The mixing mechanism eliminates a common risk area in external bypass dual-chamber syringes, wherein liquid can be trapped in the rear chamber and prevent full reconstitution. After reconstitution, the user removes the needle shield and injects as they would with a standard syringe. At the end of the injection, the user feels and hears the end-of-dose cues and the needle retracts into the plunger rod to protect the user and prevent reuse.

Figure 3: The usability and safety of the Credence Dual Chamber Platform supports the transition to at-home administration of complex drug products.

This emphasis on usability across the platform offers multiple advantages. The integrated pre-attached needle eliminates user steps and risk of incorrect needle-attachment. Passive needle retraction provides needlestick protection, prevents reuse, and provides tactile, audible and visual confirmation at the end of dose. Combined with a familiar PFS format and straightforward use sequence, the system supports user confidence and at-home administration (Figure 3).

Sustainability is another important consideration in dual-chamber system design.[6] Credence understands that for sustainability measures to be implemented, they must be paired with a compelling business case – sustainable products and practices can and should be profitable. This is true in the case of the Credence Dual Chamber Platform. With the drugs all stored within the syringe itself, the complete product maintains a small, efficient form factor and keeps material requirements low. This is especially the case because the Credence Dual Chamber Platform can be used safely and effectively without an additional needle-safety exoskeleton add-on or an autoinjector. This has significant impact on material use as well as weight and footprint, which affect overall logistics costs. This becomes especially important if cold-chain storage is involved. These factors reduce the overall cost of ownership. Furthermore, Innovation Without Change® means that Credence's technology makes the most use out of existing infrastructure and components, minimising the need for bespoke infrastructure and lowering the cost of adoption.

The Credence Dual Chamber Platform is scaling to include reconstitution and sequential delivery options in 1 mL long, 2.25, 3 and 5 mL syringe barrels with 25, 27 and 29G pre-attached retracting needles. In addition, Credence supports customisation projects outside of the core ready-to-supply platform verification envelope, with examples including needle-free options and syringe barrels ranging up to 200 mL.

PROVIDING AN END-TO-END SOLUTION – ANSWERING THE FILLING QUESTION

Across the injectables sector, industrialisation is becoming an increasingly important differentiator for whether a drug development programme succeeds or fails.[7] With advances in dual-chamber syringe technologies and the need for additional dual-chamber filling options to serve the industry, a key concern is, how and where are these devices going to be filled? The more complex the system, the harder this question can be to answer.

Credence is addressing this challenge by developing the device and its fill-finish pathway in parallel. Dual-chamber syringes are supplied in a ready-to-fill format designed for implementation in established filling isolators and modules, and Credence has invested in dedicated filling equipment located with, and operated by, its CDMO collaborators. This approach is advancing GMP filling readiness while minimising disruption to established fill-finish operations (Figure 4). By establishing fill-finish partnerships

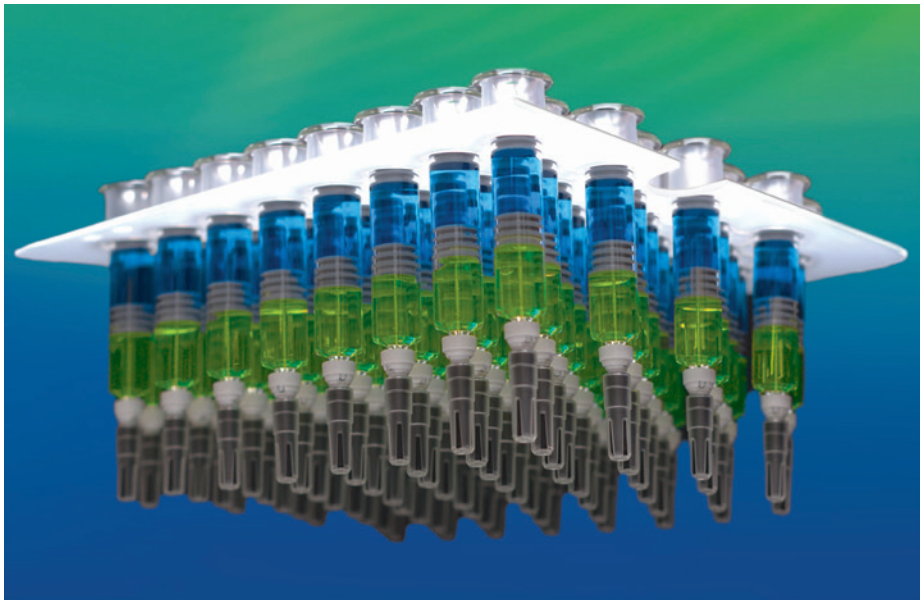

Figure 4: Credence has invested in dual-chamber fill-finish GMP readiness with its CDMO collaborators to support its pharma partners from development to commercial supply.

early in platform development, Credence supports pharma partners across device supply, filling, final assembly, labelling and packaging, providing a clear pathway from development through to commercial supply.

CONCLUSION

As pharmaceutical pipelines evolve, they are including therapies with increasingly demanding formulations, stability challenges and delivery requirements. If these challenges are not addressed, promising therapies may not reach the patients that need them. This is driving the need for advanced drug delivery solutions. Dual-chamber systems offer a new path for therapies requiring reconstitution or sequential delivery, but the growing number of available technologies means pharma must consider more than device functionality alone.

The question is no longer whether dual-chamber delivery will play an important role in the future of injectable therapies, but which approaches can provide the right balance of drug compatibility, user experience, safety, manufacturability and commercial readiness. For Credence, the answer lies in combining its advanced drug delivery capability with proven primary components, established manufacturing processes and a clear pathway to supply. It is an approach designed to solve the challenges of reconstitution and sequential delivery, without introducing unnecessary complexity elsewhere, to accelerate the delivery of therapies to patients. That is Innovation Without Change®.

"IF THESE CHALLENGES ARE NOT ADDRESSED, PROMISING THERAPIES MAY NOT REACH THE PATIENTS THAT NEED THEM."

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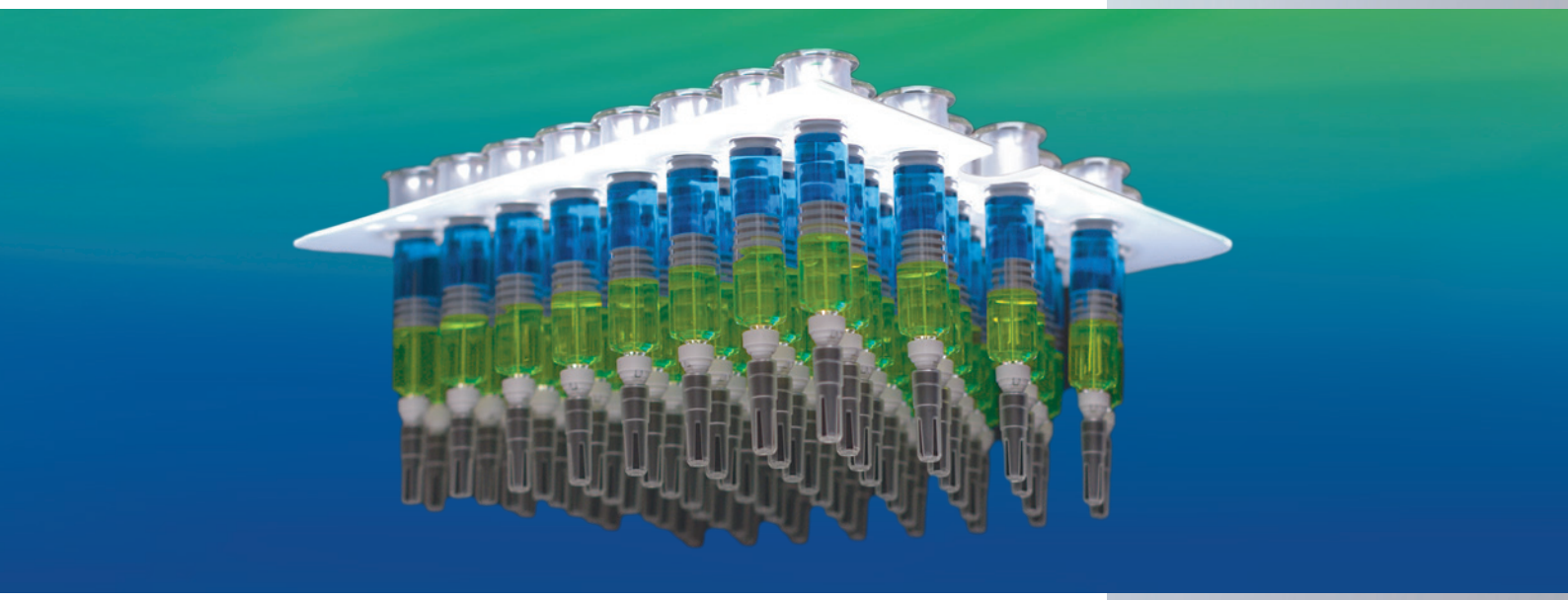
THE COMPLETE DUAL CHAMBER SOLUTION

BEYOND THE DEVICE: A COMPLETE PATHWAY TO DUAL CHAMBER COMMERCIAL SUPPLY



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DISCOVER THE DUAL CHAMBER PLATFORM DIFFERENCE TODAY

THE MISSING MIDDLE OF SC DRUG DELIVERY: HOW A DUAL-CARTRIDGE ARCHITECTURE COULD UNLOCK THE 3–10 mL OPPORTUNITY

windgapmedical

Dr Brent Buchine, **Mike Ratigan** and **Aaron Mann** of **Windgap Medical** argue that the industry's traditional 2–3 mL boundary for subcutaneous injection reflects reflects the limitations of conventional device and primary-container architectures more than the needs of any particular product or patient, considering whether two widely available cartridges, integrated into a single handheld system, could extend the simplicity and range of autoinjection.

THE BOUNDARY NOBODY ACTUALLY CHOSE

Ask where the subcutaneous (SC) injection-volume limit comes from and the answer will often sound physiological. The tissue can only accept so much. Beyond a few millilitres, injections become painful, leakage increases and local tissue effects become unacceptable. However, the literature suggests a more useful explanation: the traditional volume limit may be a hardware artefact that fused into clinical convention as much as it is a physiological boundary.

Bittner *et al* describe SC delivery as having been historically constrained to small injection volumes, often 1–2 mL. In examining how that limitation developed, they note that high-dose delivery was not feasible with the conventional 2 mL autoinjectors or syringes available at the time, when required injection volumes often exceeded 5 mL.[1]

Viewed through this lens, the container came first and the convention followed. That distinction has come to matter more as the handheld autoinjector has evolved. The industry has already

moved beyond the 1 mL devices that defined an earlier generation of self-injection and is now developing handheld platforms around substantially larger primary containers. Yet much of the thinking about what constitutes an appropriate SC injection still reflects the assumptions created by those earlier devices.

If the historical boundary was established partly by the container, rather than by the tissue, then perhaps the next increase in handheld delivery volume does not require changing the biology. It may require changing the architecture.

WHAT THE TISSUE WILL ACTUALLY ACCEPT

Clinical evidence is increasingly challenging the idea that 2–3 mL represents a fundamental physiological ceiling. Woodley *et al* evaluated 192 SC injections in 32 healthy adults using volumes as high as 10 mL in the abdomen and 5 mL in the thigh, across solution viscosities ranging from 1 to 20 cP. The injections were generally well tolerated. Favourable subject responses were at least 79.3% immediately after injection, rising to at least 96.8% at 24 hours.[2]

The conclusion should not be that every 10 mL formulation is suitable for rapid handheld administration. Formulation viscosity, needle geometry, injection site, flow rate, injection pressure and drug-specific tolerability all remain important factors.

But viewed alongside the broader evolution of large-volume SC delivery, these findings challenge a much simpler assumption: that an injection becomes unsuitable for handheld delivery merely because the volume exceeds 2 or 3 mL.[1,2] If SC tissue can accommodate substantially greater volumes, then the practical boundary begins to move upstream from physiology towards device engineering and human factors.

THE PIPELINE HAS MOVED INTO THE GAP

That distinction might have remained largely academic if pharmaceutical pipelines had stayed within the traditional autoinjector volume range. They have not. Green *et al* identified 182 large-volume SC candidates above 2 mL, representing approximately 15% of the intravenous and SC biopharmaceuticals included in their systematic review.[3]

> "THE TISSUE MAY ACCEPT 10 mL, BUT THE CONSTRAINT IS HOW LONG THE PATIENT CAN COMFORTABLY HOLD A DEVICE."

The distribution matters more than the total. The authors identified 75 anti-cancer large-volume SC products, which typically required 5–20 mL doses and were generally administered by healthcare professionals. The remaining 107 non-cancer products were more commonly positioned for self-administration, often on a monthly basis, with less than 5 mL representing the predominant volume range.[3]

These populations begin to converge precisely where conventional device categories blur. At one end are traditional handheld autoinjectors, historically built around relatively small-volume prefilled syringes; at the other end are infusion pumps and on-body delivery systems designed to remain attached to a patient while larger doses are administered over a longer period. Between them is a growing group of products requiring approximately 3–10 mL volumes.

This is the "missing middle" – the gap recognised beyond the device sector. A Bristol Myers Squibb device team recently framed the handheld large-volume autoinjector envelope as 2–10 mL and observed that the 2–5 mL handheld category has, to date, no commercially approved products.[4]

It is not that the industry lacks ways to deliver these volumes; it has several. A developer can split the dose across multiple injections, move to an on-body system or develop a larger primary container. All are valid strategies. The question is whether they represent the complete set of choices.

THE REAL HANDHELD LIMIT IS TIME

If tissue tolerance does not establish a clear 2–3 mL boundary, another constraint does begin to emerge: how long a patient can reasonably be expected to hold a handheld device against the injection site. Schneider *et al* evaluated this directly by measuring the force users applied to handheld autoinjectors during simulated injections of varying duration. Both mean and minimum holding force decreased as injection time increased. Participants successfully completed simulated injections lasting up to approximately 30 seconds, while the authors' extrapolation suggested that, for a device requiring approximately 15 N to trigger and 4 N minimum holding force, an injection duration of up to approximately 56 seconds may be feasible.[5]

That splits the problem into two – the tissue may accept 10 mL, but the constraint is how long the patient can comfortably hold a device. A conventional autoinjector cannot solve that discrepancy simply by delivering more slowly. Beyond a certain point, slowing the injection solves the fluid-delivery problem while creating a human-factors problem. On-body systems address this elegantly: remove the need to hold the device. That is a genuine advantage, and the reason the category exists, but it also suggests that volume itself may be the wrong variable on which to divide handheld and on-body delivery. Injection time may be the more meaningful boundary. A 10 mL dose requiring 20 minutes to administer is fundamentally different from a 10 mL dose that can be delivered in 30 seconds.

PATIENTS ARE MAKING A TRADE, NOT CHOOSING A DEVICE CATEGORY

Patient preference adds another dimension. A patient-preference study involving 191 participants with self-injection experience examined preferences between handheld autoinjectors and wearable large-volume injectors while varying dosing frequency and administration duration.[6]

In the base scenario, which compared a weekly three-minute handheld injection with a monthly 33-minute wearable injection, roughly two-thirds of participants preferred the handheld option. Importantly, preference shifted as administration time shortened and dosing frequency decreased.[6] The useful conclusion is not that either

device class is inherently more successful, rather that patients appear to be making a trade across injection duration, wear time, dosing frequency and convenience.

For device developers, the implication is practical. The question is not simply whether patients prefer handheld devices or on-body devices. It is how much patient burden each architecture creates for a particular treatment regimen. A handheld device capable of completing a larger-volume injection in substantially less time occupies a very different position on that trade curve to one requiring the patient to hold a device in place for several minutes.

THE CURRENT THREE-WAY CHOICE

Consider a product requiring a 6 mL SC dose. One option is to split the dose; two injections can preserve familiar containers and devices, but the additional injection burden lands directly on the patient and repeats with every administration. A second option is an on-body system; this removes the hold-time constraint and provides a compelling solution when the formulation requires longer administration. But it also introduces a wear period, an adhesive-mounted device and may add device complexity that is unnecessary for a formulation capable of much faster delivery.

Figure 1: Standard single-chamber cartridges of the type used in the dual-cartridge architecture, filled on conventional aseptic fill-finish lines using formats and component systems already established at commercial scale.

A third option is to move towards a larger primary container. However, where an appropriate device-ready container is not already available at the required commercial scale and maturity, the pharmaceutical company takes on a new primary-container development and supply-chain challenge simply to enable the device. That can mean additional container qualification, fill-finish integration, component development, capital requirements and programme risk. Standards for larger volume primary containers exist, but the commercial ecosystem around them is less established than the infrastructure supporting more widely used cartridge formats. Each of these approaches may be appropriate for certain products.

There is a fourth possibility: rather than designing one primary container to accommodate the entire dose, distribute the volume across two established containers within one automated handheld device (Figure 1).

TWO CARTRIDGES, ONE HANDHELD EXPERIENCE

The arithmetic is straightforward. Two 3 mL cartridges provide 6 mL of capacity. Two 5 mL cartridges provide 10 mL. Two 1.5 mL cartridges enable validated reconstitution, even for difficult-to-mix formulations. The more important point, however, is not simply that two containers hold more drug than one – it is that the dual-cartridge architecture allows total delivered volume to become partially decoupled from individual primary-container volume.

This is a distinct concept from a dual-chamber container. The two containers described here are standard single-chamber cartridges, filled on standard aseptic

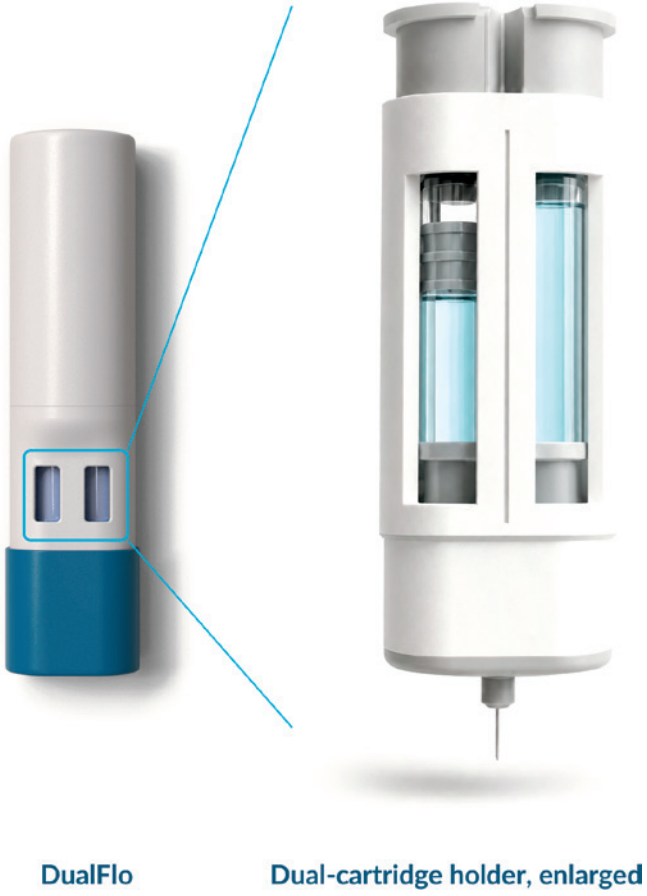

Figure 2: Windgap Medical's dual-cartridge architecture. Left: the DualFlo handheld autoinjector. Right (enlarged): the dual-cartridge holder seen through the device window, in which two standard single-chamber cartridges are integrated into a single automated handheld system, with the fluid path converging on one needle.

fill-finish lines (Figure 2). A true dual-chamber container is a single bespoke two-compartment vessel requiring a non-standard fill sequence on dedicated equipment – centre stopper placement, fill, stopper, invert and refill. In a dual-cartridge architecture, this filling complexity is eliminated from the supply chain.

A different development path emerges. Rather than continually increasing the diameter or length of a single large-volume primary container, a dual-cartridge device is built on established cartridge formats, component systems and manufacturing infrastructure that pharmaceutical companies already understand. There is a meaningful risk reduction between qualifying an established primary-container platform for a molecule and having to create a new container and filling ecosystem around it. This is one aspect of the premise behind Windgap Medical's dual-cartridge architecture. The second part is the energy source.

Once the physiological limit is no longer assumed to be 2–3 mL, the engineering problem becomes more demanding. The device must move the required combination of volume and viscosity through an acceptable needle, at the necessary pressure and within the relatively short time window that makes handheld administration practical. In this context, the power source becomes a first-order design variable.

Windgap Medical's platform uses a compact gas-cylinder energy source to drive drug delivery from two primary containers through a single handheld system (Figure 3). The objective is not simply to generate more force. The energy source, containers, flow path, needle and formulation must operate as an integrated system, with the available pressure and delivery profile matched to the volume, viscosity and target administration time of the drug product.

For the 6–10 mL range in particular, the challenge is two-fold. The dual-cartridge architecture creates the required capacity without demanding that a single primary container continuously increase in size. The gas-powered drive system provides an energy source that can be engineered around the pressure and flow requirements necessary to move that volume within a time frame appropriate for handheld delivery.

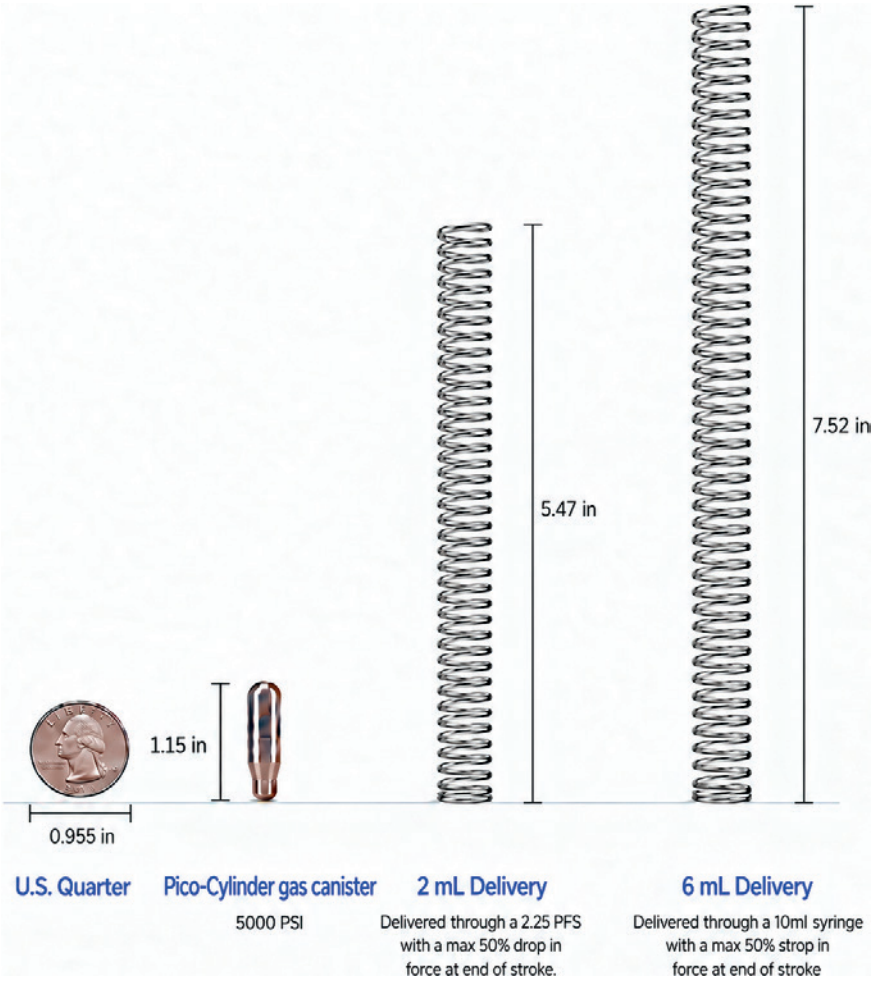

Figure 3: Energy source comparison: the compact gas Pico-Cylinder used in Windgap Medical's platform alongside a mechanical spring of equivalent stored energy. Representative scaling for illustrative purposes.

Together, those elements create a different way of approaching the "missing middle". The same dual-container architecture can also accommodate a range of drug presentations, including sequential liquid delivery or dry and suspension-based formulations that require mixing. However, the central opportunity discussed here is simpler: extending the practical volume range of handheld drug delivery.

THERE IS ALREADY PROOF

Recent clinical evidence suggests that this general design space is achievable. Kang *et al* reported a Phase I study of a third-party, prototype, spring-powered, high-volume, handheld autoinjector. This device had a different drive architecture from the gas-powered system described above, and was used to administer a 10 mL formulation containing recombinant human hyaluronidase. The mean delivery time was 27.9 seconds. Among the subjects receiving the handheld injection, 91% reported no or mild injection-site pain and 96% indicated that they would be willing to receive the injection again.[7] The use of recombinant human hyaluronidase is a necessary qualifier – these results should not be extrapolated to every formulation or molecule. However, the study does provide proof that a 10 mL dose is not inherently incompatible with the handheld autoinjector experience.

This changes the discussion – the relevant question is no longer simply "Is 10 mL too much for a handheld device?". It becomes "Can this particular combination of volume and viscosity be delivered through an appropriate needle, at the required pressure, within a patient-

acceptable injection time?". That is a substantially different engineering question, and one that opens up a larger design space than a simple volume threshold suggests.

NOT EVERY LARGE-VOLUME PRODUCT BELONGS IN A HANDHELD DEVICE

None of this should suggest that on-body systems are unnecessary. For very large doses, long administration times or formulations that benefit from slow, controlled delivery, an on-body system may clearly provide the better patient experience. In professionally administered settings, wearable systems also create workflow advantages, freeing healthcare providers from attending a long SC administration. The goal should not be to move every 3–10 mL product into a handheld device, it should be to avoid moving every 3–10 mL product out of one simply because it crossed an inherited volume threshold. This distinction matters.

A 6 mL formulation requiring twenty minutes of administration involves a very different device discussion from a 10 mL formulation that can potentially be delivered in 30 seconds. The lower-volume product may, in fact, be the less suitable handheld candidate. Volume alone cannot make that decision.

REDEFINING THE BOUNDARY

So, at what volume does a handheld autoinjector stop making sense? The evidence suggests that there is no single answer. The legacy 1–2 mL boundary emerged in an era when conventional autoinjectors and syringes were themselves limited to small-volume delivery.[1] Clinical studies have since demonstrated that SC tissue can tolerate substantially larger volumes. Human-factors research suggests that injection duration, rather than volume alone, places an important constraint on handheld use. Pipeline analyses show a meaningful population of pharmaceutical products moving directly into this emerging gap. Finally, recent clinical work has demonstrated that, under appropriate formulation conditions, even 10 mL can be delivered through a handheld autoinjector in approximately 30 seconds.

The boundary should not be defined by an inherited number. Instead of asking, "At what volume must this product move to an on-body system?", pharmaceutical developers might first consider a more precise series of questions:

- Can the required combination of volume and viscosity be delivered within a reasonable handheld injection time?
- Can established primary-container formats be used?
- Can the required pressure and flow be achieved through an acceptable needle?
- Does the available energy source provide the appropriate delivery profile?
- Can the resulting device preserve the patient experience that made auto-injection successful in the first place?

"THE "MISSING MIDDLE" MAY NOT REPRESENT THE PHYSIOLOGICAL LIMIT OF SC DELIVERY. IT MAY REPRESENT THE NEXT ARCHITECTURAL BOUNDARY FOR THE HANDHELD AUTOINJECTOR TO CROSS."

For many products, the answers may still lead to an on-body system. For others, particularly within the emerging 3–10 mL range, two established primary containers integrated into a single handheld architecture and coupled with an energy source designed around the required

pressure, flow and injection time may offer another path. The "missing middle" may not represent the physiological limit of SC delivery. It may represent the next architectural boundary for the handheld autoinjector to cross.

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Expert View

RECONSTITUTION TO CO-DELIVERY: DESIGNING MULTICHAMBER DEVICES FOR BETTER PATIENT EXPERIENCES

Jack Dunkley of Haughton Design delves into the architectural principles of multichamber systems for injectable formulations and considers how to overcome the design challenges involved.

"ONE OF THE KEY CHALLENGES IN DEVICE DEVELOPMENT TODAY IS REDUCING THE NUMBER OF USER STEPS REQUIRED FOR APIs SUPPLIED IN LYOPHILISED FORM BECAUSE OF STABILITY CONSTRAINTS."

The rise of biologics, personalised therapies and home-based treatment is changing what is expected of injectable drug delivery systems. Devices are no longer judged only on whether they can contain and deliver a dose; they must also protect sensitive formulations, simplify preparation, support confident use by patients and caregivers, and remain realistic to manufacture, assemble and validate at scale. For therapies that cannot be supplied as ready-to-inject liquids, this creates an important design challenge: how can the device take on more of the preparation burden while preserving safety, reliability and ease of use?

One of the key challenges in device development today is reducing the number of user steps required for lyophilised APIs because of stability constraints. Some of these products remain stable for only a limited period once reconstituted into a liquid for injection. Therefore they are often supplied in formats that require manual reconstitution before use, commonly involving a drug vial and a separate diluent. In practice, this preparation process may involve many individual handling steps, each of which must be completed correctly before the drug can be administered to the patient.

This has driven growing interest in simplified delivery systems that reduce user burden, ideally moving towards a two-step autoinjector format. For development teams, this is not only a usability challenge but also a systems-engineering challenge, where teams can help customers translate product requirements into practical device concepts.

As with all injectable products, the primary container closure system is the set of components that directly contains the drug product and maintains its integrity until administration. In parenteral delivery systems, this is often a syringe or a cartridge. Both formats commonly use a glass barrel with elastomeric components, although polymer barrels are also used in some applications. Syringes may be supplied with either an integrated needle or a Luer interface, whereas cartridges are typically sealed at the delivery end with a septum and require a separate or integrated mechanism for needle coupling.

The choice between a syringe and a cartridge is often closely linked to the characteristics of the API and its compatibility with the container and delivery-path materials. In some cases, prolonged contact between the formulation and needle materials during storage can contribute to issues such as corrosion, clogging or other compatibility concerns. In some designs, cartridge-based systems can help to mitigate these interactions, but they also require more complex needle-coupling strategies, such as pen needles or automatic coupling arrangements in which the needle is not in fluid contact during storage, sometimes referred to as a "dry needle" configuration. These additional interfaces can introduce further sterility and system-integration considerations, so the container decision needs to be made in the context of the wider delivery system rather than as a standalone component choice.

When reconstituting lyophilised products, the device must store the API in powder form and the diluent separately until they are combined to form an injectable liquid. A range of architectures exists for this purpose, but one of the most established is the dual-chamber primary container,

"WHEN RECONSTITUTING LYOPHILISED PRODUCTS, THE DEVICE MUST STORE THE API IN POWDER FORM AND THE DILUENT SEPARATELY UNTIL THEY ARE COMBINED TO FORM AN INJECTABLE LIQUID."

which has a similar overall form factor to a standard syringe or cartridge. In this arrangement, an additional stopper is positioned part-way along the barrel to create two chambers: the front chamber contains the powder, while the rear chamber contains the diluent and is closed in a similar way to a conventional system. During early concept development, it is important to assess how this type of architecture affects the device envelope, actuation sequence, user interaction and development risk.

To enable mixing, the barrel incorporates a bypass feature that is initially blocked by the forward stopper. When the rear stopper is pushed, the diluent – being effectively incompressible under these conditions – transmits force to the forward stopper. As there is headspace within the powder chamber, the forward stopper can move far enough to expose the bypass, allowing the diluent to flow into the front chamber and mix with the powder. Continued movement of the rear stopper then drives the liquid forward until the two stoppers come together. Figure 1 shows an illustration of the mixing process within a dual-chamber syringe.

In some configurations, continued movement of the rear stopper can then be used to expel the reconstituted drug product, meaning that reconstitution and delivery could, in principle, be combined within a single actuation sequence. This would be consistent with a two-step autoinjector user experience in which the patient simply removes the safety cap and presses the device against the skin. However, the feasibility of this process depends on whether the device can reliably complete reconstitution, fluid transfer and injection without introducing unacceptable complexity or uncertainty.

In practice, this assumes that the powder and liquid components can be mixed adequately without delay and without the need for additional agitation. However, in these small-volume systems, flow is typically laminar, which limits passive mixing efficiency and can make rapid reconstitution difficult. For this reason, many systems require an additional user step to promote mixing, such as controlled agitation, inversion or a defined waiting period before injection. Device teams should explore these usability and engineering trade-offs early, before committing to a user sequence that may be difficult to validate or difficult for patients to perform consistently.

"DUAL-CHAMBER SYSTEMS RELY ON A BYPASS FEATURE BUILT INTO THE BARREL GEOMETRY, SO CHANGES TO CHAMBER VOLUMES OR STOPPER POSITIONS MAY REQUIRE NEW PRIMARY CONTAINER COMPONENTS AND ASSOCIATED MANUFACTURING ADJUSTMENTS."

Other challenges associated with dual-chamber systems arise during filling and assembly. In dual-chamber syringe formats with a staked needle, the process can be particularly complex because the powder, stoppers and liquid must be introduced in a controlled sequence while maintaining chamber separation, sterility and freedom from cross-contamination. As a result, these systems often require specialised filling processes and may not be compatible with standard filling lines.

Customisation can also be more difficult than with conventional single-chamber syringes or cartridges. In a standard system containing a single liquid and stopper, the dose volume can often be adjusted relatively easily by changing the fill volume and stopper position. In contrast, dual-chamber systems rely on a bypass feature built into the barrel geometry, so changes to chamber volumes or stopper positions may require new primary container components and associated manufacturing adjustments. These practical constraints can lead to extended lead times and additional supply chain challenges, making manufacturability an important part of early device strategy.

Another approach is to use two standard cartridges: one containing the lyophilised product and the other containing the diluent. Such an approach can reduce reliance on custom dual-chamber primary containers, and, in some cases, the cartridges may be compatible with existing filling lines and standard components. The trade-off is that the device itself becomes significantly more complex. In this type of architecture, engineers can break the sequence down into functional requirements and identify which interfaces, motions and control steps are likely to drive technical risk.

Figure 1: Illustration of mixing within a multichamber syringe.

"BY REDUCING WORKFLOW COMPLEXITY, SUCH SYSTEMS MAY ALSO HELP TO MOVE SOME COMPLEX THERAPIES OUT OF HEALTHCARE FACILITIES AND INTO THE HOME, IMPROVING THE PATIENT EXPERIENCE WHILE REDUCING THE DEMAND ON CARE SYSTEMS."

The device must first bring the two cartridges into smooth contact so that the diluent can be transferred into the powder cartridge for reconstitution. Depending on the formulation and system design, an additional active mixing step may then be required before the device establishes the final fluid path to the delivery needle for injection. These operations are necessary to maintain separation of the constituent components before reconstitution and to ensure that the fluid follows the correct path through the device during both mixing and delivery.

Because this sequence can take longer than in a dedicated dual-chamber system, careful consideration is needed as to what triggers mixing and what triggers injection. For example, removing the cap could initiate reconstitution while pressing the device against the skin could trigger injection, or both steps could occur only once the device is pressed against the skin, potentially increasing hold time. In some cases, this may require an additional user control, such as a separate button or actuator. These choices have a direct impact on usability, perceived simplicity and the level of instruction required for safe and effective use.

These examples illustrate that devices for lyophilised reconstitution and delivery present a range of technical challenges, spanning architectures with complex primary containers and relatively simple devices through to those with simpler primary containers and more complex device mechanisms. Selecting the right solution therefore requires a holistic approach that considers technical complexity, supply chain considerations, the characteristics of the product being delivered and the intended user experience. This is where an experienced development partner can help connect the technical requirements with practical design, prototyping and risk-management activities.

If these challenges can be addressed successfully, the potential benefits to patients are substantial, including simpler user steps and the potential for more consistent reconstitution. By reducing workflow complexity, such systems may also help to move some complex therapies out of healthcare facilities and into the home, improving the patient experience while reducing the demand on care systems.

Although this article has focused on reconstituting lyophilised drug products, similar architectural principles may also offer advantages in co-delivery systems designed for dual-liquid formulations. Some therapies require two products to be administered within the same treatment event. This can be achieved using two separate autoinjectors delivered sequentially, but it may also be possible to use a single device. With some architectures, the two liquids could be combined during the actuation sequence and delivered through a single needle, while in others the device could incorporate two separate needles each connected to its own primary container. A key potential benefit of co-delivery is the reduction in handling steps for the patient or caregiver, which may be particularly valuable in time-sensitive or otherwise stressful administration scenarios.

ABOUT THE COMPANY

Haughton Design (HD) is a UK-based medical device design, development and engineering consultancy specialising in drug delivery systems, medical devices, diagnostics and healthcare technologies. Founded in 1995, the company supports pharmaceutical, medtech and advanced engineering organisations across the UK, Europe and North America, helping clients to accelerate the development of innovative, compliant and commercially successful products.

Combining creativity, engineering excellence and regulatory expertise, HD provides end-to-end services spanning innovation, product design, human factors, engineering development, prototyping, verification, industrialisation and product launch support. Working to ISO 9001 and ISO 13485 quality management systems, the company delivers flexible development solutions that integrate seamlessly with clients' own processes and regulatory requirements.

Jack Dunkley

Jack Dunkley, Engineering Director at Haughton Design, achieved CEng status in 2020 following his time at Gyrus Medical and Renishaw, where he led numerous complex mechanical projects through to production. He has a deep technical knowledge across manufacturing technologies and design for assembly which helps ensure Haughton Design's design team delivers high-quality outputs. At Haughton Design, Mr Dunkley works with clients on drug delivery projects and supports the wider design team with engineering challenges.

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CONFERENCE PREVIEW: CPHI MILAN

Milan, Italy, October 6–8, 2026

PUTTING TRANSFORMATION AND COLLABORATION AT THE HEART OF PHARMA

The global pharmaceutical community is set to gather at Fiera Milano from 6–8 October 2026 for three days of insight, innovation and partnership across the pharmaceutical value chain. CPHI Milan returns this October, bringing together pharmaceutical manufacturers, suppliers, technology providers and scientific leaders from across the global drug development and manufacturing ecosystem. The new CPHI Sustainability Summit will run alongside the main event on 6–7 October.

The event will build on the scale of CPHI Frankfurt 2025, which recorded 62,000 attendees, more than 2,900 exhibiting companies, representation from over 166 countries and contributions from more than 250 expert speakers. At the heart of pharma, CPHI Milan will unite a global community that is advancing human health through new partnerships, stronger relationships and shared solutions to industry challenges.

"THE EVENT WILL BUILD ON THE SCALE OF CPHI FRANKFURT 2025, WHICH RECORDED 62,000 ATTENDEES, MORE THAN 2,900 EXHIBITING COMPANIES, REPRESENTATION FROM OVER 166 COUNTRIES AND CONTRIBUTIONS FROM MORE THAN 250 EXPERT SPEAKERS."

Highlighting how this year's programme will support that collaboration, Tara Dougal, Event Director at Informa Markets, said: "This year's expanded conference programme will bring together the people leading key industry conversations, providing practical insights into the challenges and opportunities shaping pharma's future, while the new CPHI Sustainability Summit will create further opportunities for collaboration, knowledge sharing and meaningful discussion across the pharmaceutical value chain."

MANUFACTURING TRANSFORMATION TAKES CENTRE STAGE

The 2026 conference programme will feature more than 250 speakers across five content tracks. Dr Nina Rawal, Founder of Emerging Health Ventures, will deliver the Day One keynote, "Capitalising the Next Wave in Pharma". The keynote will discuss how the pharmaceutical industry has reached an inflection point where scientific potential is outstripping traditional economic models, unpicking how pricing reforms and shifting trade policies are creating immediate fiscal pressure, and the sector's response in moving away from temporary market fluctuations towards a period of permanent structural change.

Further sessions will explore the scientific and commercial forces reshaping pharma. Fabio Di Giacomo, Associate Director Cell Therapy Procurement at Bristol Myers Squibb, will take part in a panel on bridging innovation and commercial reality in cell and gene therapies, while Steffen Saltofte, CEO of Zentiva (Prague, Czechia) and President of Medicines for Europe (Brussels, Belgium), will consider how geopolitical, regulatory and market shifts are redefining the global industry.

Technology, quality and supply resilience will also feature prominently. Marco Luppi of Marchesini Group (Bologna, Italy) and Giulio Bolzonello of SEA Vision (Pavia, Italy) will discuss how automated line clearance can strengthen compliance, manufacturing safety and patient trust, while Mike Martin, President and CEO of ISPE, will breakdown how GLP-1 therapies are reshaping pharmaceutical manufacturing, drug delivery, and supply chain economics.

FOUR NEW ZONES REFLECT A CHANGING INDUSTRY

CPHI Milan 2026 will introduce four dedicated zones focused on areas where demand, investment and regulatory attention are increasing:

- **Artificial Intelligence (AI) and Tech:** A meeting point for technology businesses and pharmaceutical decision-makers seeking practical digital solutions, where exhibitors will showcase technologies supporting smarter manufacturing, predictive maintenance, quality management, data integrity, regulatory compliance and commercial intelligence.
- **Cold Chain and Logistics:** This zone will bring together providers of specialist packaging, transportation, warehousing, digital monitoring, automation and risk-management technologies with companies managing biologics, vaccines, advanced therapies and other temperature-sensitive products.
- **Contamination Control:** Pharmaceutical manufacturers working to meet EU GMP Annex 1 and other international requirements will be able to explore modular cleanrooms, environmental monitoring systems, air-filtration technologies, isolators and other contamination-control solutions.
- **Labelling:** This zone will connect manufacturers, CDMOs and packaging specialists with suppliers of labelling, printing and coding technologies – areas of focus will include regulatory compliance, serialisation, track and trace, anti-counterfeiting, electronic labelling and more sustainable printing solutions.

"THE KEYNOTE WILL EXPLORE HOW PHARMACEUTICAL MANUFACTURERS ARE PREPARING FOR FUTURE DEMAND THROUGH TECHNOLOGY-DRIVEN MODERNISATION, PROACTIVE CAPACITY INVESTMENT AND STRATEGIC REDESIGN OF GLOBAL SUPPLY NETWORKS."

The new zones reflect the technologies and capabilities that are becoming increasingly important across pharmaceutical development and manufacturing. Commenting on the need to advance innovation within a highly regulated environment, Ms Dougal, added: "Pharma is highly innovative, but also tightly regulated, so the challenge is to integrate AI responsibly into the systems on which the industry depends. The new AI and Tech zone will give technology providers and pharmaceutical leaders a dedicated space to explore practical applications, build confidence and form the partnerships needed to scale these technologies".

MOVING SUSTAINABILITY FROM DISCUSSION TO ACTION

New for 2026, the CPHI Sustainability Summit will provide a dedicated, discussion-focused forum for pharmaceutical professionals working to accelerate sustainable transformation across the value chain. The two-day summit is expected to convene more than 300 sustainability stakeholders and industry decision-makers for over 20 roundtables, interactive discussions and peer-to-peer working groups.

Designed to turn discussion into practical action, the programme will bring together pharmaceutical leaders and specialists from across the value chain to share knowledge and address common barriers. Through collaborative sessions, participants will be able to explore how different functions can work together to develop strategies that deliver measurable commercial and environmental progress.

RECOGNISING EXCELLENCE ON OPENING NIGHT

The first day of CPHI Milan will conclude with the CPHI Celebration and the annual CPHI Pharma Awards. The awards will celebrate the companies, teams and individuals driving meaningful progress across the pharmaceutical industry, from developing new technologies and improving manufacturing to advancing more sustainable ways of working. Alongside recognising achievements with the potential to shape pharma's future, the evening will bring finalists, exhibitors and industry leaders together to connect and build new relationships.

"THE AWARDS WILL CELEBRATE THE COMPANIES, TEAMS AND INDIVIDUALS DRIVING MEANINGFUL PROGRESS ACROSS THE PHARMACEUTICAL INDUSTRY, FROM DEVELOPING NEW TECHNOLOGIES AND IMPROVING MANUFACTURING TO ADVANCING MORE SUSTAINABLE WAYS OF WORKING."

CONNECTIONS AT THE HEART OF PHARMA

CPHI Milan will offer three days of face-to-face networking across the full pharmaceutical supply chain. Attendees will be able to use CPHI's digital platform prior to the event to research companies, explore products, arrange meetings and build personalised agendas. The platform will also help participants maintain conversations and develop potential partnerships after the exhibition closes. By bringing scientific expertise, manufacturing capabilities, emerging technologies and commercial decision-makers together under one roof, CPHI Milan aims to help the industry turn connections into collaboration, and collaboration into progress for patients.

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GAS-POWERED AUTOINJECTORS: MEETING THE CHALLENGES OF AN EVOLVING DRUG LANDSCAPE

Ram Halthore of **Kaléo** presents the company's Aerio™ autoinjector platform, discussing how gas-powered autoinjectors have the potential to tackle the challenges currently facing injectable drug delivery, including high-viscosity and large-volume formulations, increased demand for patient-centricity and stringent regulatory requirements for reliability in emergency-use applications.

The expanding biologics market is creating new and challenging demands for drug delivery that conventional spring-powered autoinjector systems are finding increasingly difficult to address. Kaléo's Aerio autoinjector platform can use compressed gas technology to provide a controlled and predictable drug delivery profile across a range of formulation viscosities and injection volumes, without negative impact on the drugs that pharmaceutical companies want for their therapies and the patients who use them.

Kaléo's journey began more than 25 years ago, when the passion of its founders and their personal experiences inspired them to develop an autoinjector with features like a never-seen needle. That product led to development of the Aerio autoinjector platform of drug delivery device technologies that are designed to support the increasing large-volume therapies, high-viscosity formulations and combination therapy requirements of the evolving pharmaceutical landscape.

WHY GAS POWER: HIGH VISCOSITIES AND HIGH FLOW RATES

As of late 2025, large-molecule biologic therapies accounted for an estimated 35–40% of the global pharmaceutical market by value, and that fraction is projected to exceed 50% by 2030.[1] As the biologics market has continued to expand, there has also been a shift in delivery trends away from large volumes

"PHARMACEUTICAL STAKEHOLDERS ARE SEEKING INJECTION SYSTEMS THAT CAN ADDRESS EVOLVING DELIVERY REQUIREMENTS WHILE SIMPLIFYING THE SELF-INJECTION PROCESS TO FACILITATE HOME USE."

of biologic drugs typically administered intravenously at hospitals, clinics and infusion centres over several hours, towards smaller-volume subcutaneous injections administered at home (or elsewhere) over the course of seconds or minutes.[2,3] These trends and emerging formulation requirements for at-home administration are placing new challenges on conventional delivery systems, including the need to deliver highly viscous formulations or large volumes quickly.

The viscosity of a formulation is dependent on multiple factors, including the drug's concentration and the formulation recipe. As the concentration of the formulation increases – for example, because the total volume for injection is reduced – viscosity also increases. In turn, the higher the viscosity of the formulation, the greater the force that is required to push the drug through the narrow needles typically used for injectable drugs.

These viscosity and large-volume challenges are further compounded by the trend towards reasonable injection times for self-administration. This requires an increased flow rate of fluid through the needle and a concomitant increase in the force required to achieve that flow. However, at higher flow rates, some high-molecular weight biologic formulations may be susceptible to shear-related effects,[4] potentially resulting in degradation, aggregation, altered solubility and reduced biological activity.

Apart from the technical challenges posed by drug formulations and their injection times, pharmaceutical companies are extending the activity duration of their products through encapsulation and other timed-release technologies.[5] This move enables less frequent dosing schedules and longer periods between injections, which may increase patient convenience and support adherence.[2]

For all these reasons, pharmaceutical stakeholders are seeking injection systems that can address evolving delivery requirements while simplifying the self-injection process to facilitate home use. To address the emerging and evolving needs of the pharmaceutical industry, Kaléo has developed the Aerio autoinjector platform, an autoinjector with compressed-gas capabilities that enables the delivery of a broad range of viscous formulations at a predictable rate, while maintaining the potential for a user-friendly form factor and ease of use.

Using the same proven pressurised gas-powered technology in the company's US FDA-approved autoinjector products, along with additional enhancements, Kaléo is developing innovative solutions for delivering larger volumes of high-viscosity formulations in a range of formats.

THE BENEFITS OF AERIO

Kaléo's gas-powered injection technology offers several important benefits in device size, delivery consistency and device robustness. One benefit is the platform's size, achieved by minimising its length. Larger-volume containers often have larger diameters and plungers with correspondingly larger surface areas that require greater force to provide consistent delivery. To achieve this, a conventional device would need to use larger, higher-force springs. By contrast, the gas-powered Aerio platform is mostly unaffected by the container diameter, because the same gas pressure applied to a larger area still results in a higher force. This attribute allows for the use of a larger diameter container in the device design and thus reduces overall length.

Gas-pressurised Aerio autoinjectors use pressurised gas technology to deliver predictable and consistent force for the drug delivery. In addition, the pressure in the gas cylinder can be modified to accommodate larger volumes and higher viscosities without an increase in gas cylinder size, which also contributes to the ability to minimise the size of the autoinjector and configure it according to specific patient or caregiver needs.

Another benefit of gas power is the highly controlled flow rates it enables. By controlling the uniform force applied to the plunger throughout the injection process, Kaléo's gas-powered Aerio autoinjector platform is designed to support a controlled and predictable delivery profile across a range of viscosities and injection volumes.

Gas power also enables the Aerio platform to help reduce overall device length via a patented non-coaxial layout that places the drive system adjacent to, rather than in line with, the primary container. This configuration means that the Aerio device is often only slightly longer than the combined length of the drug container and the needle, and has a shorter overall length than is achievable with the coaxial layout of conventional spring-powered autoinjectors. These features of the Aerio platform allow Kaléo's designers to tailor the device to meet the unique aspects of a therapy's use/carry environment, including the addition of optional custom electronic features.

Finally, the controlled and uniform application of force on the drug container in gas-powered autoinjectors may reduce mechanical stress on critical container components. As a result, this minimises the risk of container breakage, improves

"THESE FEATURES OF THE AERIO PLATFORM ALLOW KALÉO'S DESIGNERS TO TAILOR THE DEVICE TO MEET THE UNIQUE ASPECTS OF A THERAPY'S USE/CARRY ENVIRONMENT, INCLUDING THE ADDITION OF OPTIONAL CUSTOM ELECTRONIC FEATURES."

overall device robustness and increases the reliability of drug delivery during use.

THE AERIO AUTOINJECTOR PLATFORM

Kaléo's Aerio autoinjector platform combines proprietary technology and customisable device design to support a broad range of therapies, formulations and patient populations. Aerio platforms can be designed with the following capabilities and flexible features:

- Consistent drug delivery profile through gas-powered technology
- Accurate and precise administration of dose volumes ranging from 0.1–20 mL
- Potential flow velocity ranging from 1 mL/min up to 90 mL/min
- Ability to deliver high-viscosity formulations (up to 2,000 cP) through a range of needle gauges
- Ability to use standard or custom syringes or cartridges
- Rapid automatic needle injection and retraction (the patient never sees the needle)
- Injection steps that can be tailored to the target patient population and use environment
- Form factor flexibility to suit patient needs
- Needle safety features with automatic needle retraction at the end of drug delivery
- Subcutaneous or intramuscular delivery.

The platform consists of three different types of autoinjector: AerioUno (Figure 1), AerioDuo (Figure 2) and AerioMix (Figure 3).

AerioUno

- Single-container autoinjector platform
- Designed for single-drug delivery with patient-centric features, including optional electronic-assisted audio guidance and visual cues

AerioDuo

- Dual-container, dual-injection platform
- Supports two independently filled containers through storage and administration
- Supports two different formulations with different viscosities and different fill volumes in different size containers
- Upon activation, one power source delivers two separate injections simultaneously
- Cartridge or prefilled syringe
- Can be used as a large-volume drug delivery system with the same drug in both containers
- Dual-needle technology enables drug delivery across a larger surface area compared with current technologies on the market.

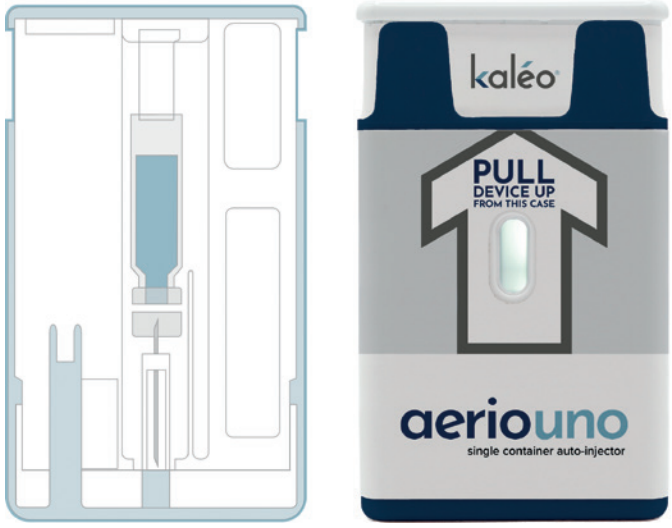

Figure 1: AerioUno single-container autoinjector.

Figure 2: AerioDuo dual-container autoinjector.

Figure 3: AerioMix dual-chamber autoinjector.

AerioMix

- Dual-chamber platform, one chamber for lyophilised or dry-powdered drug and the other chamber for a liquid, or two chambers with two different liquids
- Upon activation, automatic delivery of reconstituted or mixed product
- Supports applications requiring component separation to extend the shelf life prior to administration, including lyophilised formulations, powders and incompatible dual-liquid applications
- Can be either spring- or gas-powered.

Customisable Features

In addition to AerioUno, AerioDuo and AerioMix, Kaléo has developed proprietary connected health technology capable of the following:

- Automatic pairing with a mobile device to facilitate setup
- Motion detection to confirm appropriate carrying and adherence
- Automatic detection of activation
- Automatic temperature trend notification to warn of unsuitable temperatures
- Last known location feature to help locate the device and/or user
- Power management features to facilitate extended battery life.

Any of these features can be added to any of the Aerio autoinjectors to create a customised device built on the company's core delivery mechanism. In fact, Kaléo's AUVI-Q® is the first epinephrine autoinjector to include electronic voice prompts to guide the user through the injection process. This feature was designed to help first-time users and users in the high-stress environments where emergency-use autoinjectors are needed.[6] Kaléo has also developed an electronic trainer to support ongoing practice before first use and reinforcement of correct device use between injections.

DELIVERING RELIABILITY FOR PATIENTS AND PARTNERS

Kaléo evaluated the reliability of two approved autoinjectors after the FDA's draft guidance for emergency-use injectors was published in 2020. 99.999% reliability was verified for successful injection, meeting the requirement for emergency-use injectors as published in the draft guidance.[7]

In 2019, Kaléo was selected to develop a 10 mg naloxone autoinjector as a rapid opioid countermeasure system (ROCS) for the US Department of Defense to treat military personnel and first responders exposed to weaponised, ultra-potent synthetic opioids, using the Aerio autoinjector platform. During the development of this device, which the FDA approved in 2022, Kaléo demonstrated that its 10 mg naloxone autoinjector met the rigorous requirements of MIL-STD-810H testing.[8] Kaléo applies these same standards of reliability and ruggedness to the entire Aerio platform to facilitate consistent device performance.

Kaléo's pressurised gas technology, combined with its patented non-coaxial configuration, automatic needle injection and retraction makes the Aerio autoinjector platform well positioned to address the emerging needs for administration of high-volume, high-viscosity and complex formulations at home or in other appropriate settings where they are needed. With more than 13 million Aerio autoinjector products distributed in the market, Kaléo is a leader in gas-powered autoinjectors that helps solve some of the complex drug delivery challenges of today, making the company an experienced, capable and reliable partner for drug developers.

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Ram Halthore

Ram Halthore is Vice-President, Development at Kaléo, where he leads device and drug development activities from early design through manufacturing transfer. His responsibilities include developing the company's human factors engineering programme, leading integrated drug-device product development and overseeing the company's intellectual property portfolio development. Mr Halthore has more than 25 years of experience spanning medical devices, pharmaceuticals, biologics and combination products, including autoinjectors, prefilled syringes, inhalation devices, implants and on-body injectors. His prior experience includes leadership roles at Merck, Teva, Amgen, Johnson & Johnson and 3M.

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UNSTACKING THE DUAL-CHAMBER SYRINGE: A CARTRIDGE-BASED PATH TO RELIABLE RECONSTITUTION

Eric Sugalski and **Tom Handel**, both of **Ampulis**, introduce the company's cartridge-based reconstitution platform Pristal, and explain how it overcomes some of the usability, manufacturing and supply chain challenges that have limited stacked dual-chamber syringes.

Pristal™ is a cartridge-based reconstitution platform built on standard fill-finish infrastructure, designed to make reconstituted drug delivery faster and simpler for self-administration and for emergency and critical-care settings where speed of delivery is paramount.

Many of the most promising biologics and other sensitive therapeutics are lyophilised to preserve stability and extend shelf life. This format carries a price, however. The drug must be prepared before use, and the speed and consistency of this step matter greatly across different settings. For at-home self-administration, there is no clinician present to prevent a misstep. In emergency settings, every second counts, and any errors can delay critical care. Conventional vial-and-transfer preparation requires the user to manage multiple components and steps under the exact conditions least suited to it.

Dual-chamber syringes (DCSs) reduce that burden, storing lyophilised drug and diluent separately within a single device and combining them at the point of use.

> "MANY OF THE MOST PROMISING BIOLOGICS AND OTHER SENSITIVE THERAPEUTICS ARE LYOPHILISED TO PRESERVE STABILITY AND EXTEND SHELF LIFE."

The dominant approach to date has been a "stacked", or coaxial, chamber configuration, and despite years of availability, this configuration has struggled to solve the very problems it set out to fix.

THE LIMITATIONS OF STACKED DCS DESIGNS

In a stacked DCS, the lyophilised formulation (lyo) and diluent chambers sit coaxially, one behind the other, within a single barrel. Most stacked designs require a vented air pocket to enable diluent transfer and, depending on the orientation in which the device is held, that air pocket can cause diluent lockout. Furthermore, as the air pocket compresses and bypass features or valves engage, users can experience a variable force profile during diluent transfer: this force can spike, drop suddenly once a bypass is reached or double when two plungers must be pushed simultaneously. These situations are suboptimal for either a patient self-administering at home or a clinician needing to respond quickly in an emergency setting.

These usability compromises are compounded by formulation and manufacturing constraints. Fixed cartridge geometries limit achievable lyo-to-diluent ratios, and the specialty valves and alternative rubber formulations used to enable diluent transfer can introduce extractables and leachables (E&L) risk, particularly in tip-up filling operations.

On the fill-finish side, most stacked DCS primary containers require tip-up lyophilisation, where the liquid formulation is further from the freezing plate. This results in a low-efficiency thermal process that prolongs cycle time in the lyophilisation chamber. Meanwhile, this tip-up configuration leaves the liquid formulation resting against the plunger for a longer time, potentially worsening E&L concerns for sensitive formulations.

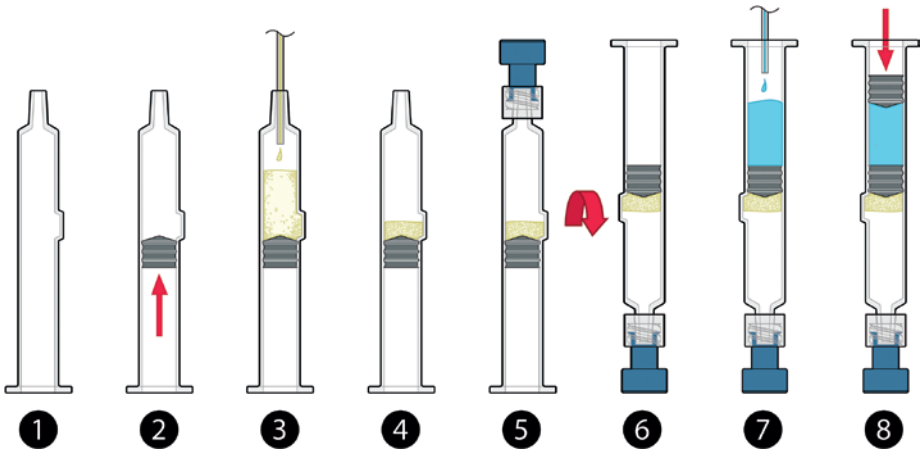

Figure 1: Aseptic fill-finish process for stacked DCS devices.

After the lyophilisation process is complete, the container is capped, often maintaining an internal vacuum. It is then flipped 180 degrees so that the tip is pointed down, and the second stage of diluent filling and stoppering occurs. Completed in an aseptic environment, this eight-step fill-finish process (Figure 1) often requires extensive automation to scale.

Multistep filling, the need to flip containers mid-process, the delicate balance of materials and tolerances required to prevent inadvertent plunger movement and the premature mixing that follows, all add cost, complexity and supply chain risk. Few contract manufacturers are equipped to run these non-standard processes, particularly at the low volumes typical of early development and clinical trials.

BYPASSING DUAL-CHAMBER LIMITATIONS: THE PRISTAL SOLUTION

Ampulis developed Pristal to sidestep these usability and manufacturing constraints that exist within the single-body, stacked-chamber architecture. Instead of housing both lyo and diluent within one device's coaxial chambers, Pristal stores each in its own standard, off-the-shelf cartridge, physically separated until administration, with no possibility of premature mixing. A safety cap conceals the plunger rod in its stored state, preventing accidental activation before use (Figure 2).

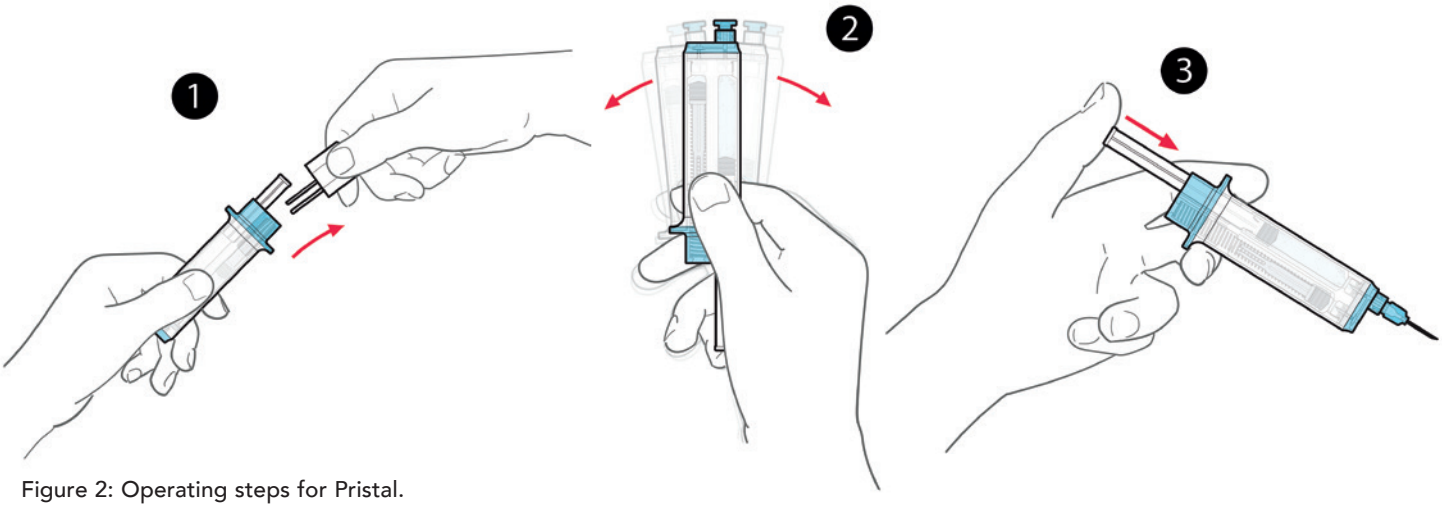

Figure 2: Operating steps for Pristal.

Operating Pristal takes three simple steps.

Step 1: Remove Cap

First, the user removes the cap. This triggers an internal spring mechanism that causes both cartridges to be pierced by internal needles. These internal needles connect the cartridges to a fluid pathway between them. After the cartridges are fully seated, the spring continues to advance, driving the diluent from its cartridge into the lyo cartridge while automatically raising the lyo plunger and plunger rod into the injection position, all without any user input.

Step 2: Agitate

Second, the user agitates the device to confirm complete reconstitution of the drug, in the same way as with vials. Agitation duration depends on the solubility of the drug. The user can view the solution through clear housings to confirm mixing completion.

Step 3: Dose

Third, the user doses the drug exactly as they would with a standard prefilled syringe: prime and inject. As reconstitution happens automatically during cap removal and agitation, the dosing step itself involves moving only a single plunger: there is no air pocket to compress, no bypass to clear and no change in force profile partway through the plunger stroke. That matters most in exactly the two settings where stacked DCS designs can struggle – home self-administration, where an automated process with consistent force leaves far less room for user error, and emergency or critical-care use, where a faster, simpler, more predictable path from cap removal to injection can meaningfully shorten time to treatment.

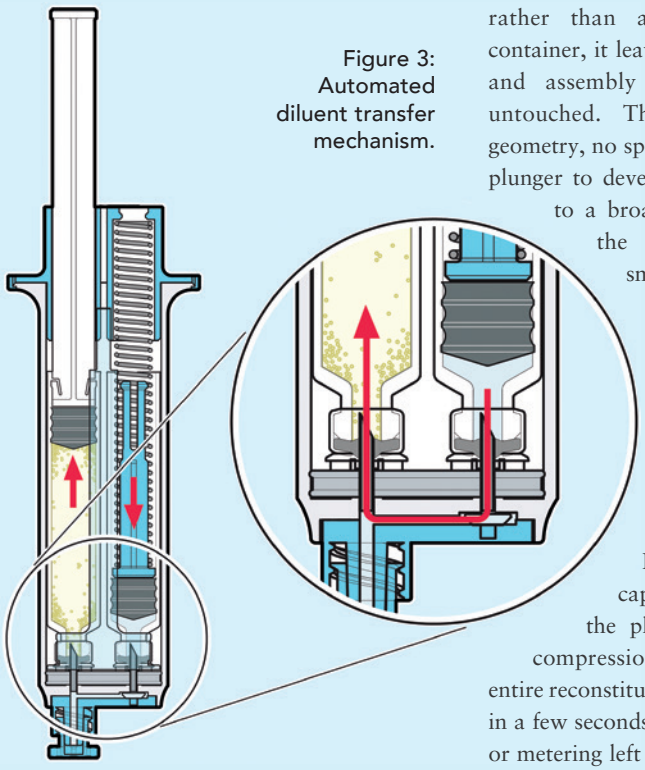

Figure 3: Automated diluent transfer mechanism.

> "AS PRISTAL IS BUILT FROM TWO INDEPENDENTLY FILLED, STANDARD CARTRIDGES, IT LEAVES FILL-FINISH, LYOPHILISATION AND ASSEMBLY INFRASTRUCTURE ESSENTIALLY UNTOUCHED."

As Pristal is built from two independently filled, standard cartridges rather than a specialty dual-chamber container, it leaves fill-finish, lyophilisation and assembly infrastructure essentially untouched. There is no new bypass geometry, no specialty valve and no custom plunger to develop, which opens the door to a broader supplier base, making the platform viable at both small clinical batch sizes and high commercial volumes, without a large capital outlay.

AUTOMATED DILUENT TRANSFER

Removing the safety cap does more than expose the plunger rod – it releases a compression spring that drives the entire reconstitution sequence to completion in a few seconds, with no timing, technique or metering left to the user (Figure 3).

As the spring decompresses, it advances the cartridge carrier until two rigid needles simultaneously pierce the septa of the lyo and diluent cartridges. This opens a sealed fluid pathway between the two cartridges. The spring continues to travel, acting on the diluent cartridge's plunger and displacing its full contents through the fluid pathway into the lyo cartridge. As diluent enters, the rising volume pushes the lyo plunger, and with it the dosing plunger rod, upwards into its injection-ready position.

The automated diluent transfer process works in any orientation and does not require the careful manual transfer process required by users operating stacked DCS devices. This automated transfer mechanism is simple enough for users to complete in home environments and fast enough for clinicians to perform in emergency situations.

FORMULATION BENEFITS

As Pristal does not constrain lyo and diluent to a single fixed-geometry container, formulation ratios are not dictated by the device. Pharma partners retain the flexibility to set the lyo-to-diluent ratio for their formulation needs, rather than reverse-engineering it to fit cartridge dimensions, a constraint that stacked DCS platforms can impose by design.

Pristal also uses standard plunger and rubber formulations already validated for E&L performance across existing prefilled syringe and cartridge platforms, produced at extremely high volumes by major component suppliers. Formulation teams are not starting E&L characterisation from scratch with a specialty rubber compound. Moreover, pharma companies gain

> "AS PRISTAL DOES NOT CONSTRAIN LYO AND DILUENT TO A SINGLE FIXED-GEOMETRY CONTAINER, FORMULATION RATIOS ARE NOT DICTATED BY THE DEVICE."

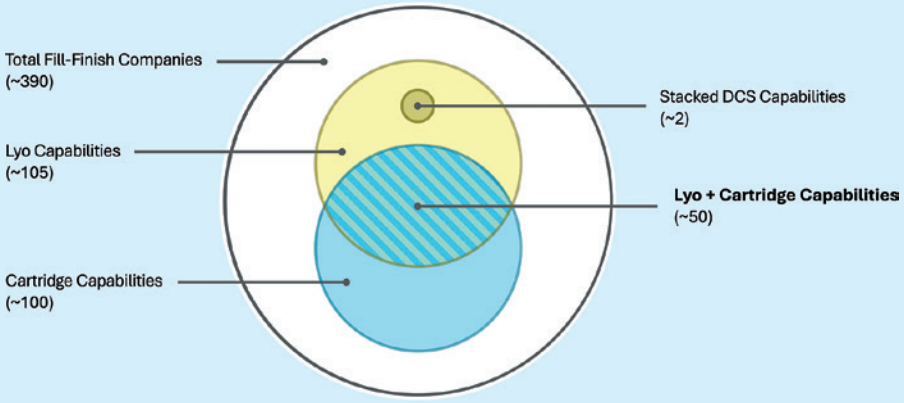

Figure 4: Fill-finish CDMOs by capability.

the economies of scale that come from sourcing components already in widespread production, rather than commissioning custom tooling for a low-volume specialty part.

FILL-FINISH BENEFITS

Pristal's two-cartridge architecture also simplifies lyophilisation and stoppering. As the lyo cartridge is a standard, single-liquid container, it can be filled and lyophilised tip-down, interfacing primarily with glass rather than resting against a rubber plunger. This tip-down orientation places the drug product proximal to the freezing plate, shortening the lyophilisation cycle relative to the tip-up processes required for stacked DCS containers.

Stoppering is similarly conventional. As there is no stored vacuum spanning multiple chambers, there is no need for the extremely tight tolerances that stacked DCS platforms rely on to mitigate unintentional plunger movement and the premature mixing it can cause. Stoppering can be performed directly within the lyophilisation chamber – a simple and conventional process that prevents moisture from entering the lyophilised drug product.

Filling is a two-cartridge process rather than a process in a single specialty container: the lyo cartridge and diluent cartridge are each filled independently, using standard, proven processes, rather than filling one cartridge with two different liquids in sequence. This eliminates the need to flip containers mid-process or perform secondary filling and secondary stoppering steps on the same device, along with the bespoke automation needed to manage the aseptic gymnastics required of current DCS devices. The result is a smoother path to reliable container closure integrity and a shorter runway from formulation to filled product.

SUPPLY CHAIN BENEFITS

Globally, there are approximately 390 pharmaceutical CDMOs capable of fill-finish at scale.[1,2] However, there are approximately 105 CDMOs with lyophilisation capabilities, and approximately 100 CDMOs with cartridge capabilities (Figure 4). The number of pharma CDMOs with both lyophilisation and cartridge capabilities is a further subset of approximately 50.

While 50 CDMOs may already seem like a small number, there are only about two companies worldwide that can perform stacked DCS fill-finish at large scale. The result of this tightly concentrated supply base is a major bottleneck: two-year backlogs to launch new programmes, high numbers of refusal to quote on sub-threshold volumes and exorbitant pricing that leaves minimal room for negotiation. Beyond the significant usability benefits of Pristal, its greatest impact may be opening new supply channels that expand the market for safe, reliable DCSs for lyophilised drugs and biologics.

Final assembly is similarly straightforward and automation-compatible – the cartridges drop into a pre-sterilised housing, and the components snap together while maintaining a sterile fluid pathway, with no additional packaging required. By using standardised components (cartridges, plungers), maintaining compliance with existing fill-finish infrastructure and simplifying the final assembly process, Pristal gives pharma partners a broader, more resilient supply chain base at every stage, from early clinical supply through commercial scale-up.

CONFIGURATION OPTIONS

Pristal is available across a range of total dose volumes (1, 3, 5 and 10 mL) to accommodate a wide range of therapeutic and dosing requirements (the device in the article's header image is the Pristal 3 mL configuration). The device accommodates staked needles for subcutaneous or intramuscular administration, a standard Luer connection for intravenous use or user-applied needle assemblies, and can be configured with an integrated safety shield to meet US OSHA requirements. The device housing also provides a large flat surface for branding, labelling and instructions-for-use content, with configurable colours to meet partner brand requirements.

A TRANSPARENT PATH TO MARKET

Ampulis built Pristal around a simple premise: the best way to solve the usability, manufacturing and supply chain challenges that have limited stacked DCS adoption is to avoid creating them in the first place by using cartridge and fill-finish infrastructure that already works at scale.

Ampulis collaborates with each partner's existing supply chain, or supports the development of a new one,

"BEYOND THE SIGNIFICANT USABILITY BENEFITS OF PRISTAL, ITS GREATEST IMPACT MAY BE OPENING NEW SUPPLY CHANNELS THAT EXPAND THE MARKET FOR SAFE, RELIABLE DCSs FOR LYOPHILISED DRUGS AND BIOLOGICS."

providing full transparency into cost structures at each volume tier and prioritising longer-term supplier risk reduction. Paired with a device that simplifies reconstitution to three simple steps, this approach makes reconstituted therapies more practical to develop, manufacture and deliver, whether in a care setting, home or the first minutes of an emergency response.

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Eric Sugalski

Eric Sugalski is Founder and CEO of Ampulis, leading product development and strategic operations. Mr Sugalski has been developing novel medical devices and combination products since 2000 and has expertise in engineering, regulatory affairs and quality management. Before founding Ampulis, Mr Sugalski was the CEO of Archimedic for 16 years, partnering with global pharmaceutical and medtech leaders to deliver breakthrough innovations.

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CAPA VALVE LAUNCHES NEW VALVE SYSTEM FOR DUAL-CHAMBER DEVICES

Dr Phil Green and **Kevin Abbott** of **Capa Valve** discuss how the company's patented valve technology provides a compelling alternative to bypass-based dual-chamber syringes, as its pressure-sensitive valve-based design enables much greater compatibility with existing fill-finish infrastructure and offers the flexibility to precisely tune the device via the geometric position of the valve within the syringe barrel.

A NEW GENERATION OF DUAL-CHAMBER DEVICES

Dual-chamber devices (DCDs) are bespoke combination drug-device products that typically contain a freeze-dried drug and its diluent in separate chambers within a single device. The two chambers are usually linked with a bypass channel formed in the barrel of the syringe or cartridge. DCDs are designed to improve the stability and convenience of biopharmaceutical products, particularly those that require reconstitution immediately before administration. By integrating both components into one system, DCDs significantly reduce the number of preparation steps, minimising the risk of handling errors and improving ease of use for both patients and healthcare professionals.

Interest in DCDs continues to grow, driven largely by the increasing demand

"CAPA VALVE'S SYSTEMS WERE DEVELOPED TO ADDRESS MANY OF THE LIMITATIONS OF THE BYPASS SYRINGE APPROACH WHILE IMPROVING BOTH MANUFACTURABILITY AND COMMERCIAL VIABILITY."

for self-administration devices and home-based healthcare. However, despite having been available for several decades, their widespread adoption has remained relatively limited. This is largely attributed to challenges associated with device design, manufacturability, formulation compatibility and overall cost.

Capa Valve's systems were developed to address many of the limitations of the bypass syringe approach while improving both manufacturability and commercial viability. Its patented technology provides a simple, robust and cost-effective solution for dual-chamber injectable products, whether for reconstitution of a lyophilised drug within a prefilled syringe or for the delivery of liquid-powder formulations for injection. The additional components are designed to integrate with standard prefilled syringes and can be scaled across a wide range of syringe sizes. To date, the Capa Valve technology has been successfully evaluated in standard 0.5 mL prefilled syringes as well as larger 60 mL infusion syringes.

Compared with conventional methods for reconstituting lyophilised drugs for injection, Capa Valve's solutions offer several important advantages. By enabling reconstitution within a closed, integrated system, it reduces the risk of contamination and preparation errors, improves patient safety and shortens the time required for preparation prior to administration. In addition, it can reduce packaging requirements, transportation and storage costs and supply-chain complexity.

The use of a valve, rather than a bypass within the syringe barrel, offers two significant advantages. Firstly, it enables a DCD to be created from an existing standard primary container, and, secondly, it allows the ratio of chamber sizes to be infinitely adjusted via precise valve placement during the fill-finish process.

THE CAPA VALVE APPROACH TO DCDs

Capa Valve's portfolio of patent-protected technology provides simple and cost-effective solutions to realise reconstitution within a prefilled syringe. The new valve variant detailed here expands Capa Valve's portfolio of valve systems. This recently developed variant enables every functional configuration required for dual-chamber syringe applications. The new design features a pressure-activated opening mechanism, with the activation threshold precisely tuneable to meet the requirements of specific clinical applications, providing a direct, cost-effective replacement for conventional dual-chamber bypass syringes. As with all Capa Valve technologies, the new valve can be seamlessly integrated into existing syringe designs, allowing primary container manufacturers to convert standard syringes into low-cost DCDs without the complexity or expense of redesigning the syringe itself.

Figure 1 shows the new valve design in the closed position separating the prefilled contents, with the solid drug contained within the front chamber and the diluent in the rear chamber. The system has been tested and works with equal efficiency with the diluent in the front chamber and the solid drug in the rear chamber, which may be a more desirable arrangement for the fill finish process and also to prevent needle occlusion in use. When the user starts to apply force to the plunger rod, the back chamber containing the diluent is pressurised and the valve opens to transfer the diluent into the front chamber (Figure 2). The activation pressure can be set by adjusting geometrical parameters of the valve parts for any specific applications, such as manually operated syringes versus syringes or cartridges for autoinjectors. Figure 3 shows the solid API in the front chamber being reconstituted within the syringe ready for immediate injection.

"THE NEW DESIGN FEATURES A PRESSURE-ACTIVATED OPENING MECHANISM, WITH THE ACTIVATION THRESHOLD PRECISELY TUNEABLE TO MEET THE REQUIREMENTS OF SPECIFIC CLINICAL APPLICATIONS, PROVIDING A DIRECT, COST-EFFECTIVE REPLACEMENT FOR CONVENTIONAL DUAL-CHAMBER BYPASS SYRINGES."

Figure 1: Valve separates solid drug and diluent.

Figure 2: Valve opening due to applied pressure.

Figure 3: Solid drug dissolves in diluent.

FILL-FINISH AND SCALABILITY

During the development of all its valve variants, Capa Valve has worked closely with companies with fill-finish expertise to ensure that its technology does not pose any significant challenges for existing processes and equipment currently being used for the fill-finish of DCDs. Close attention to detail in optimising the geometry of Capa Valve's components through extensive testing and design iterations has not only ensured robust failsafe operation of the valve but also extended to the automated processes employed to realise the technology at scale.

As an example, the original sequential valve was designed to be manipulated using the standard bowl feeders currently used for the handling and orientation of

"IN THE DEVELOPMENT OF ALL ITS VALVE VARIANTS, CAPA VALVE HAS WORKED CLOSELY WITH COMPANIES WITH FILL-FINISH EXPERTISE TO ENSURE THAT ITS TECHNOLOGY DOES NOT POSE ANY SIGNIFICANT CHALLENGES FOR THE EXISTING PROCESSES AND EQUIPMENT CURRENTLY BEING USED FOR THE FILL-FINISH OF DCDs."

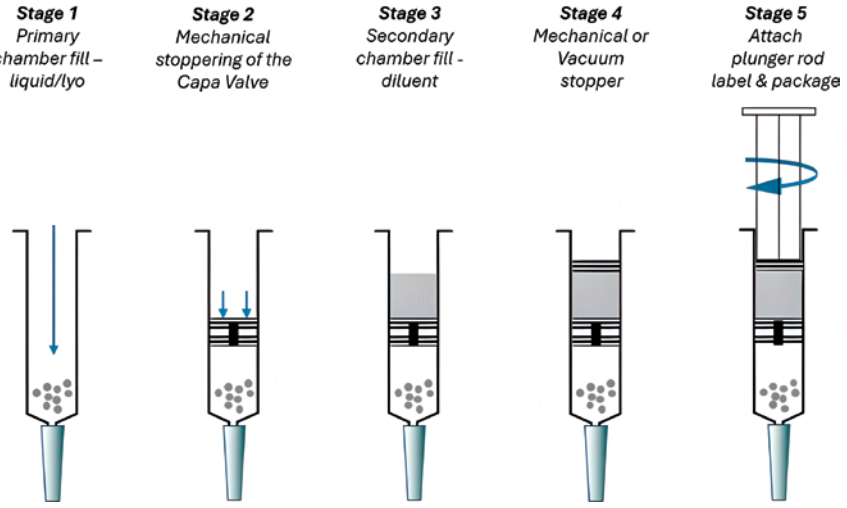

Figure 4: Fill-finish stages of the Capa Valve.

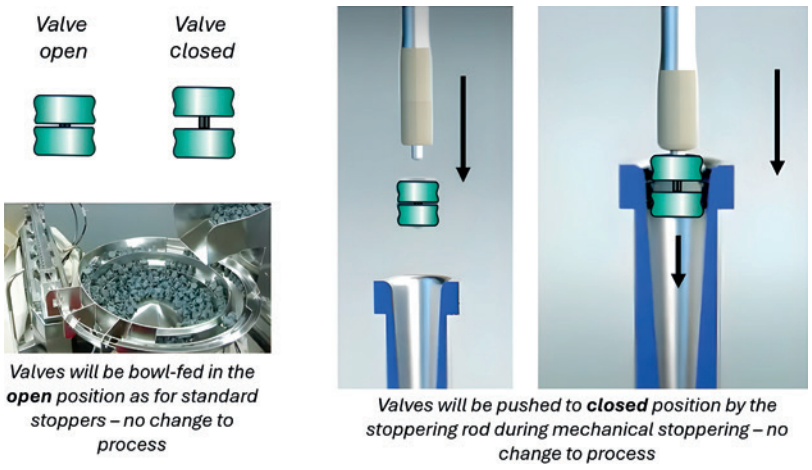

Figure 5: Automated feeding and stoppering of the Capa Valve.

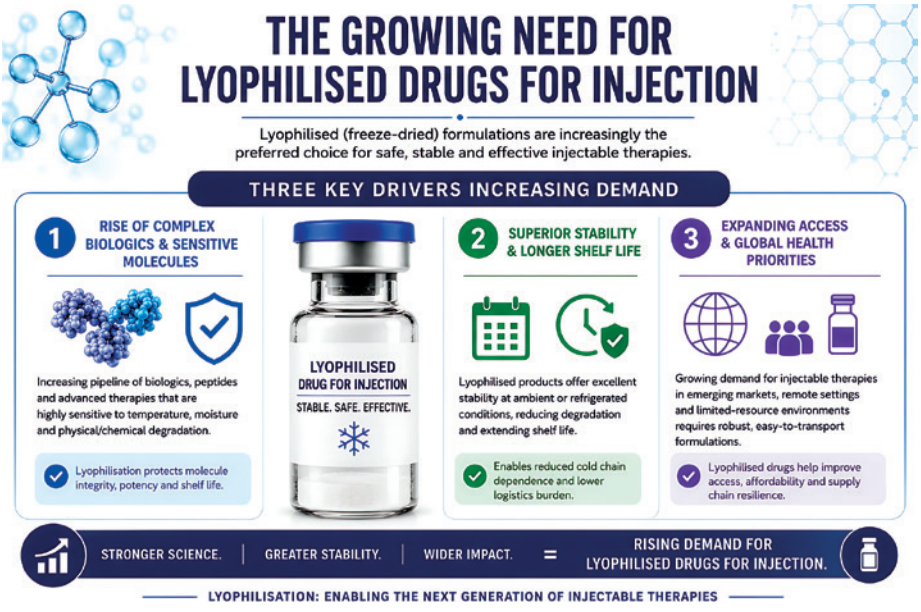

Figure 6: Market opportunity for novel lyophilised injectable device.

standard stoppers. This is achieved by bowl-feeding the valve in the open position, as, in this state, the form factor of the valve replicates that of a standard stopper. It is during the mechanical stoppering of the valve that the valve is then transitioned to the closed position.

The only modification needed for the fill-finish equipment is the size of the protrusion on the stoppering rod to ensure that the valve is always stoppered in the closed position. This same approach has been adopted with the new pressure-operated valve discussed here, again ensuring that the technology can be seamlessly introduced into existing fill-finish lines. Figure 4 provides an overview of the automated placement of the valve in the container barrel and Figure 5 illustrates the automated feeding and stoppering of the valve.

MARKET NEED AND THE CAPA VALVE VALUE PROPOSITION

The costly, time-consuming and relatively high-risk process of reconstituting lyophilised drugs or powders for injection can be addressed by a prefilled solution using Capa Valve's technology. This technology was originally developed to address the significant growth and application for DCDs in the growing market of injectable freeze-dried drugs requiring reconstitution prior to administration. There is an abundance of information and data supporting the rapid growth of lyophilised injectables (Figure 6).

Expansion of Biologics and Advanced Therapies

The rapid growth of biologics, including monoclonal antibodies, peptides, vaccines and cell and gene therapies, has increased the demand for lyophilised formulations, as many of these molecules are unstable in liquid form. Lyophilisation improves stability, extends shelf life and helps to maintain potency during storage and transport. Recent reviews also note that many first-in-class biologics were initially commercialised as lyophilised products while stable liquid formulations were still under development.[1]

Growth in Oncology and Anti-Infective Injectable Medicines

Oncology and infectious disease pipelines increasingly rely on injectable medicines that require excellent long-term stability. Many cytotoxic drugs, antibiotics and biologics are therefore formulated as lyophilised powders for reconstitution prior to administration. A recent review reported that more than 70% of antibiotics on the WHO's Essential Medicines List are supplied as lyophilised sterile powders for injection, highlighting the established and growing dependence on this dosage form.[2]

Need for Improved Supply-Chain Resilience and Reduced Cold-Chain Dependence

Healthcare systems increasingly require medicines that can tolerate storage and transport challenges. Lyophilised injectables offer a longer shelf life, reduced degradation and greater flexibility for stockpiling and distribution, particularly where cold-chain infrastructure is limited. The covid-19 pandemic exposed shortages in lyophilisation manufacturing capacity, prompting significant investment in additional freeze-drying capacity worldwide to improve resilience and support future demand.[3]

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"LYOPHILISED INJECTABLES OFFER A LONGER SHELF LIFE, REDUCED DEGRADATION AND GREATER FLEXIBILITY FOR STOCKPILING AND DISTRIBUTION, PARTICULARLY WHERE COLD-CHAIN INFRASTRUCTURE IS LIMITED."

Dr Phil Green

Phil Green, PhD, Technical Director at Capa Valve, is a mechanical engineer who works in both academia and in industry with a focus on innovative start-up companies developing patented technology. He has a passion for developing technology that both solves human issues in the simplest way and is considerate to the planet's resources and the environment. A previous innovation earned him a place as a finalist for the European Inventor of the Year (SME Category, 2019) and, through his pedagogical activities, Dr Green encourages and inspires future generations of engineers to share his passion for innovation and entrepreneurship.

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Kevin Abbott

In 2011 Kevin Abbott, Managing Director of Capa Valve, developed a piece of equipment to fill a domestic central heating system with rust inhibitor and mains water. The prototype system worked well, so Mr Abbott looked into patenting the device. His patent agent advised that, despite its simplicity, the valve was indeed novel and, if miniaturised, could be used in medical syringes to provide a dual-stage dispensing of two different liquids. Mr Abbott's original patents, granted in Europe, UK and US, form the basis of this new pressure-activated valve configuration.

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GRAND RIVER
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Company Showcase

GRAND RIVER ASEPTIC MANUFACTURING

Grand River Aseptic Manufacturing's (GRAM's) operations are focused on a strong commitment to sterile filling. GRAM prioritises patient safety by adhering to strict aseptic standards and collaborating closely with each client, using its extensive expertise to generate optimal outcomes.

GRAM's Sterile Filling Facility One opened in 2020 and features production lines approved by both the EU and the US FDA. The facility has the capacity to produce over 80 million vials as well as more than 10 million syringes and cartridges per year.

"FOR PHARMACEUTICAL COMPANIES, CHOOSING A CDMO GOES BEYOND ASSESSING CAPACITY; IT IS ABOUT FINDING A PARTNER COMMITTED TO QUALITY AND INNOVATION."

Sterile Filling Facility Two is the company's newest sterile filling facility, equipped to provide over 50 million units of syringe and cartridge filling capacity annually, starting with Line 5 (Table 1). This facility includes the infrastructure needed for future expansion to support client needs and meet market demand.

Line 1: Liquid & Lyophilised Vials	Line 2: Liquid Vials	Line 3: Prefilled Syringes & Cartridges
• Bausch+Ströbel • SKAN isolator • 4-head • IMA lyophiliser • 2R, 6R, 10R, 20R, 50R • 20 million units/yr • 6,200 lyo hr/yr • EU/FDA approved	• Bausch+Ströbel • SKAN isolator • 4-head • 2R, 6R, 10R, 20R, 25R • Up to 12,000 units/hr • 20–25 million units/yr • Identical to Line 1 • EU/FDA approved	• Bausch+Ströbel • SKAN isolator • 1/2-head • PFS: 1, 2.25, 3 mL • Cartridges: 3, 5, 10, 20 mL • 1,000–3,000 units/hr • 8–10 million units/yr • EU/FDA approved
Line 4: Liquid Vials	**Line 5: Prefilled Syringes & Cartridges**	**Available Future Space**
• Bausch+Ströbel • SKAN isolator • 8-head • 2R, 6R, 10R • External vial washer • 24,000 units/hr • 40–50 million units/yr	• Groninger • SKAN isolator • 10-head • PFS: 1, 2.25, 3 mL • Cartridges: 5, 10 mL • 24,000 units/hr • 40–50 million units/yr • Media Runs Q1 2027	Space and utilities to support three additional fill lines and client-dedicated projects 

Table 1: GRAM's fill-finish lines.

For pharmaceutical companies, choosing a CDMO goes beyond assessing capacity; it is about finding a partner committed to quality and innovation. GRAM is dedicated to delivering consistent, high-quality sterile fill-finish services that empower pharmaceutical companies in their mission to improve patient outcomes. Specialising in biologics, GRAM's five filling lines serve pharma's liquid or lyophilised vial, syringe and cartridge products.

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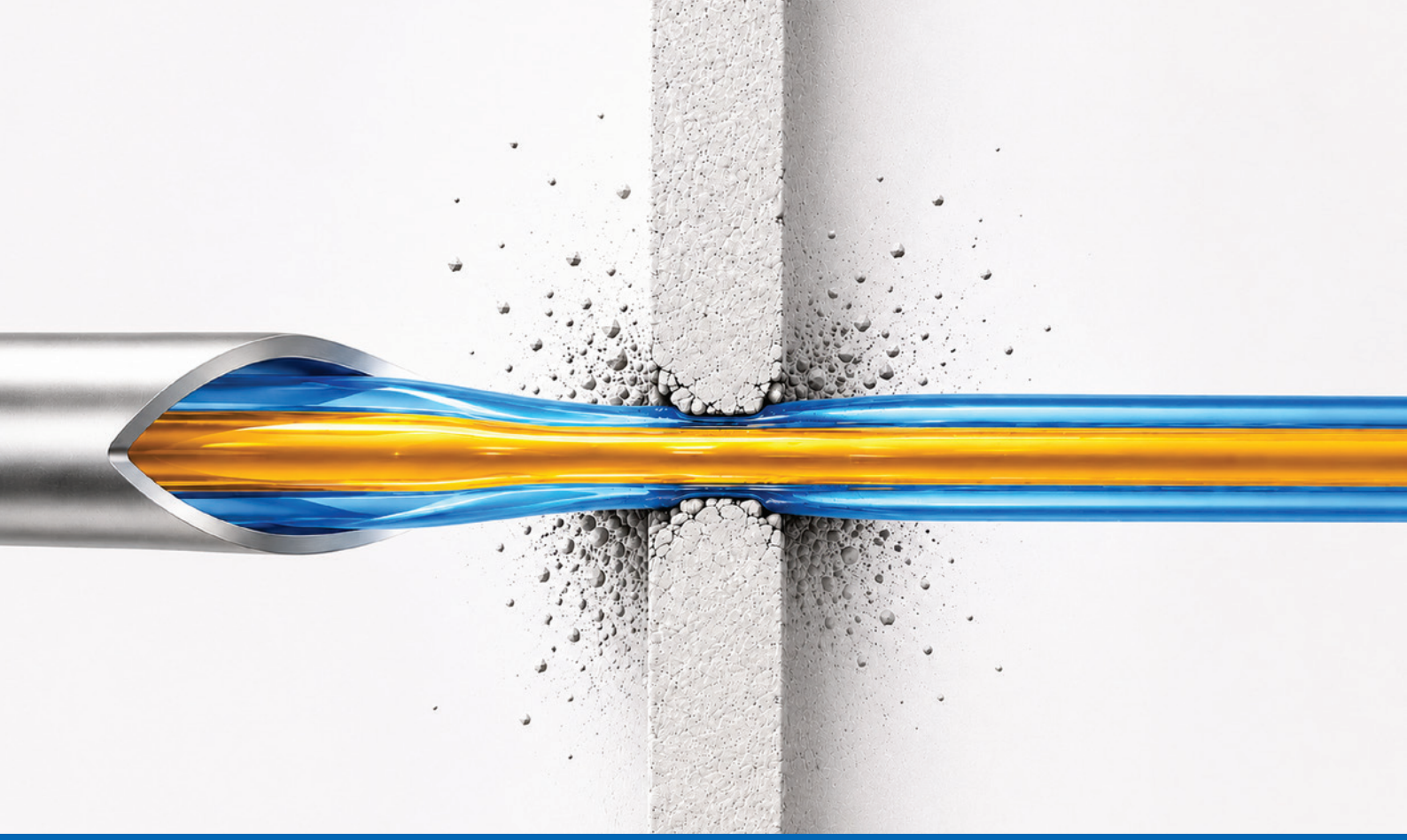
Selecting a CDMO goes beyond capacity. It's about finding a partner committed to quality and innovation.

To support commercial biologics and enhance patient-centric drug delivery systems, our newest aseptic filling platform is designed for medium- to high-volume production of prefilled syringes and cartridges. This platform ensures that pharmaceutical innovators have the precision, flexibility, and regulatory confidence they need to succeed.

Image of the new sterile filling platform taken during the FAT. Source: groninger



Early Insight

HIGH-CONCENTRATION, HIGH-VISCOSITY DELIVERY WITH CORE-ANNULAR FLOW

CoFlo Medical

Dr Simon Rufer and **Pratik Mishra** of **CoFlo Medical** introduce the company's core-annular flow platform, which promises to eliminate the long-standing viscosity bottleneck for needle-based delivery. The company's platform enables high-concentration, high-viscosity delivery for existing formulations without the need for reformulation or new compounds in a patient-friendly form.

Viscosity has historically constrained drug delivery and, consequently, upstream drug development. High-concentration therapies designed to fit within the limited subcutaneous volume highly viscous. Above 50 cP, the force required to push the viscous drug product through standard needles becomes excessive, and drug developers must turn to alternative approaches, each with their own trade-offs.[1–3]

Reformulation with viscosity-reducing excipients or as a non-aqueous microparticle suspension typically adds development, manufacturing and regulatory complexity, which can extend programme timelines and cost. Increasing the acceptable dosing volume with the use of recombinant human hyaluronidase or on-body injectors can affect the patient experience, as large volumes are often associated with longer delivery times, additional user steps and greater injection site discomfort. High-power gas or electromechanical drive mechanisms capable of overcoming high viscosity tend to increase device complexity and can expose the drug product to elevated shear during delivery.

In an attempt to avoid these viscosity-driven delivery challenges entirely, modern drug developers often implement selection criteria during drug discovery and development to screen out potential high-viscosity candidates. Unfortunately, this could force as many as 20% of early drug candidates to be abandoned,[4,5] sacrificing potentially efficacious high-viscosity compounds.

BREAKING THE INJECTABILITY BARRIER WITH CORE-ANNULAR FLOW

In injectable drug delivery, the narrow needle presents the highest fluidic resistance, making it the physical bottleneck that prevents high-viscosity drug delivery. CoFlo's technology alleviates the needle's resistance by creating a core-annular flow (CAF) within the needle. As shown in Figure 1, the viscous drug travels as the core and is shielded from the needle wall by a sheath of lower-viscosity fluid. Because the viscous drug never comes into contact with the needle wall, the injection pressure is dramatically lower than what the Hagen-Poiseuille equation would predict for the drug alone. In fact, the injection pressure with CAF depends only on the viscosity of the sheath fluid and is agnostic to the drug's viscosity.[6]

As a result, CAF makes extremely viscous formulations injectable at a very low force, as shown in Figure 2. CoFlo has demonstrated delivery of a 2 mL, 800 cP mimic solution in 20 seconds through a 27G TW needle with less than 20 N of force – a 100-fold reduction in injection force when compared with a conventional device (Figures 2 & 3). Since flow rate scales directly with applied force, CAF's force reduction leaves substantial headroom for even faster injections with only a modest increase in user-applied force. This approach opens the door to high-concentration formulations that would have otherwise been impossible to deliver. CoFlo has demonstrated a 100-fold reduction in injection force compared

"CoFlo HAS DEMONSTRATED A 100-FOLD REDUCTION IN INJECTION FORCE COMPARED WITH CONVENTIONAL DEVICES, ENABLING THE INJECTION OF mAb FORMULATIONS UP TO 400 mg/mL AND 1,000 cP."

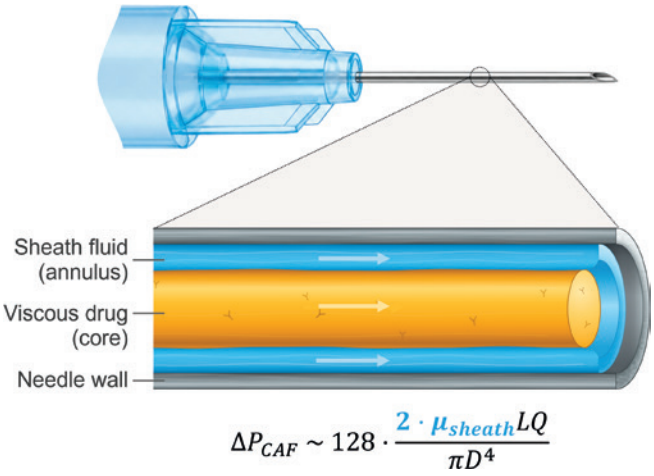


Figure 1: In CAF, the sheath fluid shields the viscous drug from the needle wall, so the injection pressure is a function of the sheath fluid's viscosity (μ_{sheath}) instead of the drug's viscosity. L is the needle length, Q is the flow rate and D is the needle diameter.

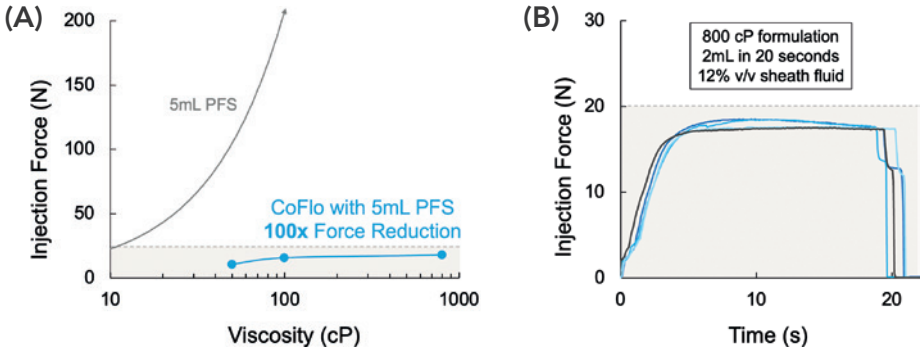


Figure 2: Injectability data for a 2 mL delivery in 20 seconds through a 27G thin-wall ½" needle. A) CoFlo's CAF reduces injection force 100-fold compared with conventional syringes, unlocking high-viscosity delivery. B) Injection force profiles at <20 N collected with a CoFlo device.

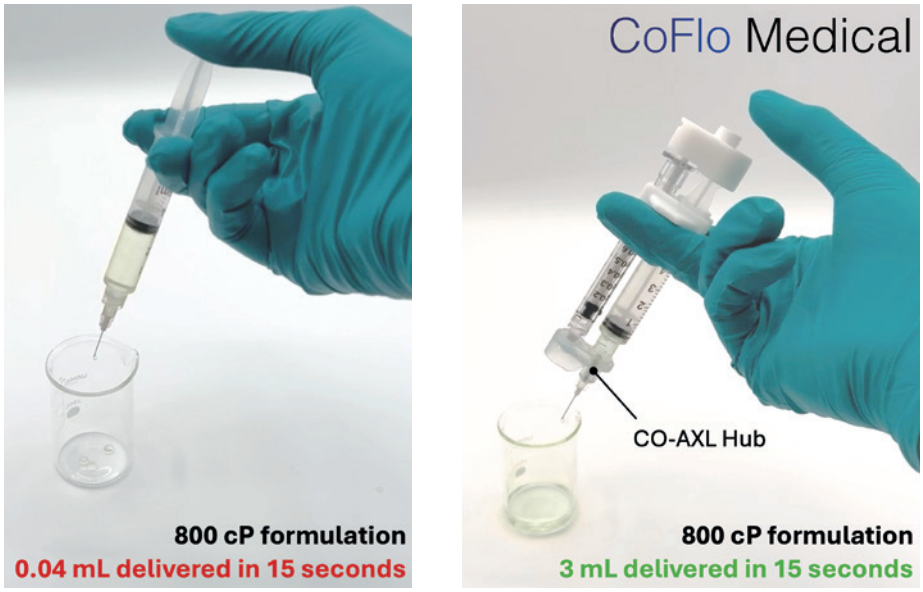


Figure 3: An 800 cP formulation is nearly impossible to inject via a standard 27G thin-wall needle. With 12% v/v saline sheathing fluid, CAF unlocks rapid injectability for the same formulation and needle. Here, the CO-AXL hub adapts disposable syringes for a vial presentation.

with conventional devices, enabling the injection of monoclonal antibody (mAb) formulations up to 400 mg/mL and 350 cP, and suspensions of up to 500 mg/mL and greater than 1,000 cP.

"THE DRUG PRODUCT ITSELF DOES NOT NEED TO BE REFORMULATED FOR THE CAF APPROACH, KEEPING HIGH-DOSE FORMULATION COMPLEXITY TO A MINIMUM."

Formulation Flexibility: No Reformulation or New Compounds

CoFlo's CAF platform is engineered to provide maximum flexibility for the sheath fluid. The sheath fluid can be a wide range of low-viscosity fluids that are at least transiently compatible with the drug. Commonly used fluids include the drug's own buffer solution, saline, a second API or even an enzyme-active formulation such as hyaluronidase. The sheath fluid can be limited to as little as 10% of the total injected volume while still delivering the force-reduction benefit of CAF. As a result, no new chemical or biological entity needs to be introduced to achieve CAF's benefits – the sheath fluid can simply be a component already present in the formulation.

The drug product itself does not need to be reformulated for the CAF approach, keeping high-dose formulation complexity to a minimum. In fact, removal of the viscosity constraint from the formulation development phase may even open the excipient design space, promoting faster development of more stable formulations. The introduction of the sheath fluid can also protect the drug product from shear-induced damage, as the sheath separates the drug from the needle wall, where shear stress is highest.

Parameter	Platform Capability
Drug viscosity	1 to >1,000 cP
Drug volume	0.05–10 mL
Sheath fluid fraction	As low as 10% of total injected volume
Injection force	Target <20 N
Primary container	Any Luer-lock syringe – glass, cyclo-olefin polymer or co-polymer, or disposable plastic
Needle	29G extra-thin-wall and larger
Injection route	Subcutaneous, intravitreal or intramuscular
Drug formulation	Biologics (antibodies, proteins, etc)
	Suspensions and gels (particles, cells, lipid nanoparticles)
	Small molecules
	Shear-sensitive compounds
Sheath fluid formulation	Drug's own buffer solution
	Saline for injection
	Second API
	Enzyme-active formulation (e.g. hyaluronidase)

Table 1: CoFlo double-barrel device platform scope.

CoFlo's UNIVERSAL CO-AXL HUB

CoFlo has developed a universal CO-AXL needle hub that adapts two syringes to create the CAF in the needle, as shown in Figure 3. One syringe is filled with the viscous drug product, and the other syringe is filled with the sheath fluid. The CO-AXL hub's design preserves primary container flexibility with ISO 80369-compliant Luer ports that are compatible with any Luer-lock prefilled syringe (PFS) or disposable syringe. Several technical innovations have led to this universal hub design that can accommodate a wide range of drug viscosities, volumes, formulations and primary containers (Table 1).

CoFlo's CO-AXL hub can enable quick-to-clinic timelines for drug products in a vial presentation using disposable plastic syringes that are connected to the universal hub, as shown in Figure 3. This opens the opportunity for quick-to-clinic timelines and physician-administered use. In an early exploratory usability evaluation, 12 first-time lay users with no prior self-injection experience or training successfully completed the full syringe filling, connection and delivery sequence on their first attempt using only the instructions for use.

Figure 4: Prefilled double-barrel delivery system for patient self-administration at home. The user steps mirror a conventional prefilled syringe.

CoFlo has integrated the CO-AXL hub into a user-friendly double-barrel CAF device that accommodates prefilled syringes (Figure 4). It is optimised for patient self-administration and its use steps mirror those of a single conventional prefilled syringe.

Demonstrated Performance De-Risks Combination Product Co-Development

Through partnerships with global pharmaceutical companies, CoFlo has demonstrated high-viscosity injectability of clinical and marketed drug formulations spanning monoclonal antibodies, small molecules and suspensions. These studies have verified injection force performance, dose accuracy, the absence of shear-induced damage or aggregation and controlled subvisible and visible particulate levels. *Ex vivo* feasibility data have also shown that CAF remains functional and stable when delivered into human subcutaneous tissue, not just in a bench fixture.

CoFlo has established a platform framework for the requirements, risks and testing needed to demonstrate device and combination product safety and efficacy. The CO-AXL hub is produced via injection moulding with standard materials and is a low-part-count component, supporting rapid manufacturing scale-up. Together, this technical and regulatory foundation de-risks the co-development pathway required to bring a combination product with the CO-AXL hub to clinical use.

SUMMARY: OPPORTUNITIES WITHOUT THE VISCOSITY CONSTRAINT

With injection force decoupled from drug viscosity, CoFlo's CAF platform opens up the potential for a new regime of streamlined injectability for formulations up to 400 mg/mL and >1,000 cP. Key opportunities for clinical and marketed drug programmes include:

- Dual-drug delivery
- Intravenous-to-subcutaneous transition for high-dose drugs (>300 mg)
- Less frequent dosing and faster delivery for existing subcutaneous and intravitreal therapies

"GIVES DRUG DEVELOPERS BACK THE FREEDOM TO OPTIMISE THERAPIES AROUND THE PATIENT AND THE MOLECULE, RATHER THAN THE LIMITS OF THE NEEDLE."

- Next-generation drug candidates developed without viscosity restrictions.

CoFlo gives drug developers back the freedom to optimise therapies around the patient, rather than the limits of the needle.

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Dr Simon Rufer

Simon Rufer, PhD, is Co-Founder and Chief Executive Officer of CoFlo Medical. During his PhD in Mechanical Engineering at the Massachusetts Institute of Technology (Cambridge, MA, US), he established the fundamental principles for stabilising core-annular flow that are at the core of CoFlo's delivery devices. His broader doctoral research spanned electrochemical separations, with an emphasis on translating fundamental transport phenomena into scalable systems. Drawing on prior engineering experience at SpaceX and NASA JPL, Dr Rufer applies a cross-disciplinary approach to invention and commercialisation. His work has resulted in more than 20 peer-reviewed publications and patents.

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LEVERAGING LARGE-VOLUME PLATFORMS FOR LIQUID-LIQUID DRUG DELIVERY

Valerio Ravazzolo of **Stevanato Group** and **Thomas James** of **SHL Medical** examine liquid-liquid drug delivery using Stevanato Group's EZ-fill® 3 mL internal-bypass cartridge platform and SHL Medical's Magnitude 3.0 autoinjector platform, demonstrating how these technologies can be integrated into a standardised container-device ecosystem, helping to reduce the cost, risk and development timelines traditionally associated with customised solutions for combination products.

WHY LIQUID-LIQUID FIXED-DOSE DRUG COMBINATIONS REMAIN UNDERSERVED

Interest in liquid-liquid fixed-dose drug combinations (FDCs) is continuing to grow, particularly for monoclonal antibody combinations.[1] However, for many biologics, co-formulation is not simple. Proteins often require different pH environments, excipient systems or ionic strengths to other co-formulants, meaning that they must remain physically separate throughout storage before being combined at the point of administration.

If incompatible formulations remain in prolonged contact, physical and chemical instability can occur, potentially leading to aggregation, viscosity changes or drug degradation. These interactions also complicate analytical characterisation, making it more difficult to attribute observed changes to an individual active substance rather than the co-formulation itself. As described by Mueller *et al*,[2] these formulation and analytical considerations represent significant barriers to the development of liquid-liquid protein co-formulations.

To overcome these challenges, developers have looked to dual-chamber delivery systems that keep incompatible formulations physically separate until the point of administration. Dual-chamber primary containers have typically been customised for individual drug products, with cartridge dimensions, bypass geometries and plungers tailored to each application. Since the primary container and delivery device must function together as an integrated system, bespoke container designs require corresponding adjustments to the device, or entirely new devices, to accommodate the container geometry and operating characteristics. Customised primary container formats can also require modifications to fill-finish and final assembly processes.

Qualification adds a further layer of complexity. Performance must be assessed at the assembled product level, as modifications to the container or device can influence injection performance, manufacturability or process robustness. Any resulting design change may therefore require verification of the complete container-device system. These additional requirements can extend development timelines and increase costs and risks, while reducing supply-chain flexibility.

A CARTRIDGE-BASED ROUTE TO STANDARDISED DUAL-CHAMBER DELIVERY

Stevanato Group's EZ-fill® 3 mL internal-bypass cartridge and SHL Medical's Magnitude 3.0 autoinjector are advanced platform technologies. Through a collaborative compatibility assessment, the companies have demonstrated how these existing platforms can be combined to support liquid-liquid drug delivery. Together, they provide a standardised container-device ecosystem that reduces the integration complexity traditionally associated with liquid-liquid FDC products.

SHL Medical's Cartridge-Based Autoinjector: Magnitude

An evolution of SHL Medical's Maggie platform, Magnitude is an advanced cartridge-based autoinjector platform supporting 3 mL and 5 mL cartridge configurations. This standard interface enables integration with Stevanato Group's EZ-fill internal-bypass cartridge platform without any modifications to the device. A conventional compression-spring-based powerpack reliably drives the dual-plunger system, while SHL Medical's Needle Isolation Technology (NIT) separates the cannula from the primary container until use, enabling independent fluid-path configuration. Decoupling cannula selection from cartridge geometry supports targeted injection times across a range of viscosities, without requiring redesign of the primary container.

Stevanato Group's Dual-Chamber RTU Cartridge

Designed using the external dimensions of standard ISO 3 mL cartridges, Stevanato Group's dual-chamber EZ-fill cartridge uses an internal bypass and standard plunger stoppers to keep two formulations separate during storage before connecting them to the same fluid path during administration (Figure 1). In the configuration tested with Magnitude 3.0, Chamber One accommodates up to approximately 1.3 mL and Chamber Two up to approximately 1.4 mL, providing a total fill volume of around 2.7 mL.

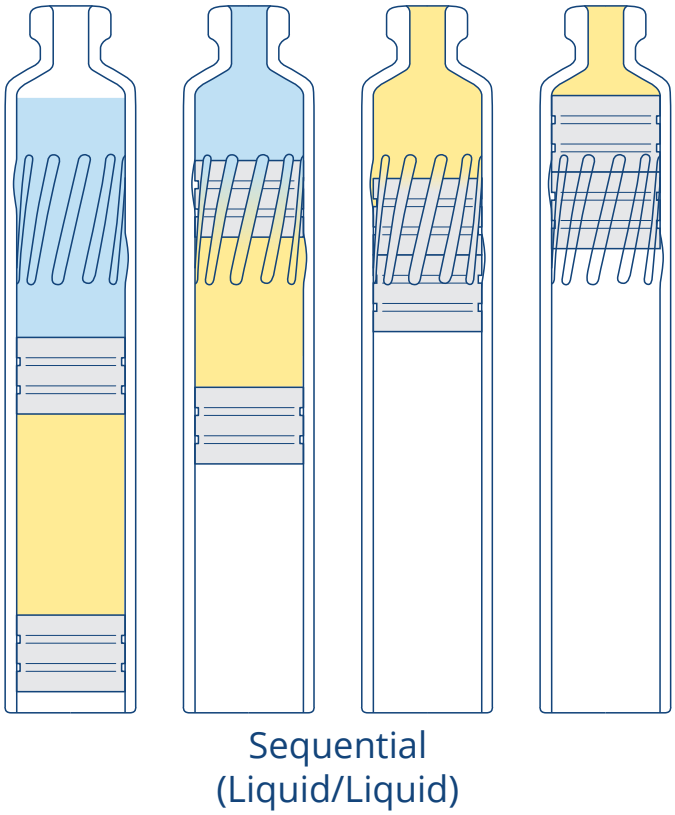

Figure 1: A dual-chamber cartridge employing an internal bypass and standard plunger stoppers.

"BY BRINGING ESTABLISHED CARTRIDGE INTERNAL-BYPASS TECHNOLOGY INTO AN RTU FORMAT, STEVANATO GROUP ENABLES PHARMACEUTICAL COMPANIES TO BENEFIT FROM ITS PROVEN EZ-FILL PLATFORM WHILE REDUCING FILL-FINISH COMPLEXITY AND STREAMLINING TIME TO MARKET."

These injection volumes can be tailored by adjusting the positions of the bypass and/or end plunger, providing additional flexibility to drug developers while maintaining the benefits of a well-known external form factor. If greater capacity is required, the concept could be scaled up using a dual-chamber EZ-fill 5 mL long cartridge in combination with Magnitude 5.0.

Internal-bypass technology has been used in bulk cartridges for decades. Its availability in ready-to-use (RTU) containers enables this well-established technology to be filled using standard fill-finish processes on combi-lines. By bringing established cartridge internal-bypass technology into an RTU format, Stevanato Group enables pharmaceutical companies to benefit from its proven EZ-fill platform while reducing fill-finish complexity and streamlining time to market.

Figure 2: (A) The standardised ecosystem combining the EZ-fill 3 mL internal-bypass RTU cartridge with (B) the Magnitude 3.0 autoinjector.

THE VALUE OF A STANDARDISED 3 mL INTERFACE

The standardised external dimensions of the ISO 3 mL cartridge provide a common interface between the cartridge and the autoinjector. The value of bringing the two platforms together is unlocked by this shared interface – the Magnitude 3.0 autoinjector can accommodate the EZ-fill cartridge without modification. These critical cartridge dimensions also support the use of standard elastomeric components and existing RTU cartridge filling and handling infrastructure, allowing manufacturing assessments to use established processing concepts.

The resulting configuration provides a more standardised starting point for container-device integration, fill-finish and final assembly, while eliminating reliance on custom geometry across the delivery ecosystem (Figure 2).

DE-RISKING DEVELOPMENT THROUGH PRE-EVALUATED COMPATIBILITY

Before a drug-specific combination product enters formal verification, feasibility assessments can be implemented to reduce development risk by demonstrating that the integrated container-device system performs its critical functions as intended. For a dual-chamber system, this includes confirming that the drive system can overcome the break-loose forces generated by the two plungers and maintain controlled delivery as the first chamber empties and the second liquid traverses the bypass.

As shown in Figure 3, at the start of injection, the drive system overcomes the break-loose forces of both plungers. The plungers then move together as the first solution is delivered. When the first plunger reaches the internal bypass, its movement stops and the second solution passes through the bypass into the fluid path, driven by the rear plunger alone. Finally, once the rear plunger reaches the first, the remaining dose is co-administered as both plungers continue together towards the cartridge shoulder.

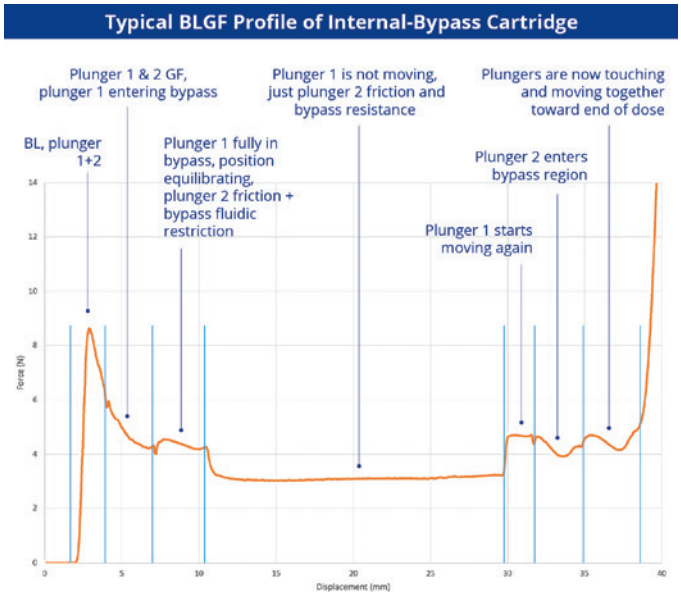

Figure 3: Force-displacement (break-loose and gliding force) profile illustrating the movement of both plungers during injection.

To assess the system's compatibility, Stevanato Group and SHL Medical tested Magnitude 3.0 with the EZ-fill® internal-bypass cartridge under standard atmospheric conditions. The assessment included a 31-point dimensional compatibility evaluation and measurements of system characteristics such as injection time, delivered volume, activation force and needle extension.

Injection time was assessed to confirm the powerpack's ability to manage the dynamic force profile of the dual-plunger system reliably and to complete delivery through the bypass across the tested container-device assemblies. Delivered dose was evaluated to assess both the nominal achievable delivered volume and the consistency of dose delivery, pointing to any variability of residual volume across samples (Figure 4).

BOX 1: FEASIBILITY STUDY AT A GLANCE

Study Basis: Feasibility assessment of 30 assembled devices under standard atmospheric conditions, with each chamber filled with a 1 cP liquid.

MEAN INJECTION TIME
6.04 seconds

Demonstrates that the assembled device reliably manages the break-loose and dynamic forces of the dual-plunger system, completing delivery without modifications to the existing powerpack or device.

DELIVERED DOSE
2.62 mL

Delivered from a total 2.7 mL fill volume, demonstrating consistently low residual volume and, importantly, low variability in delivered dose across the tested container-device configuration.

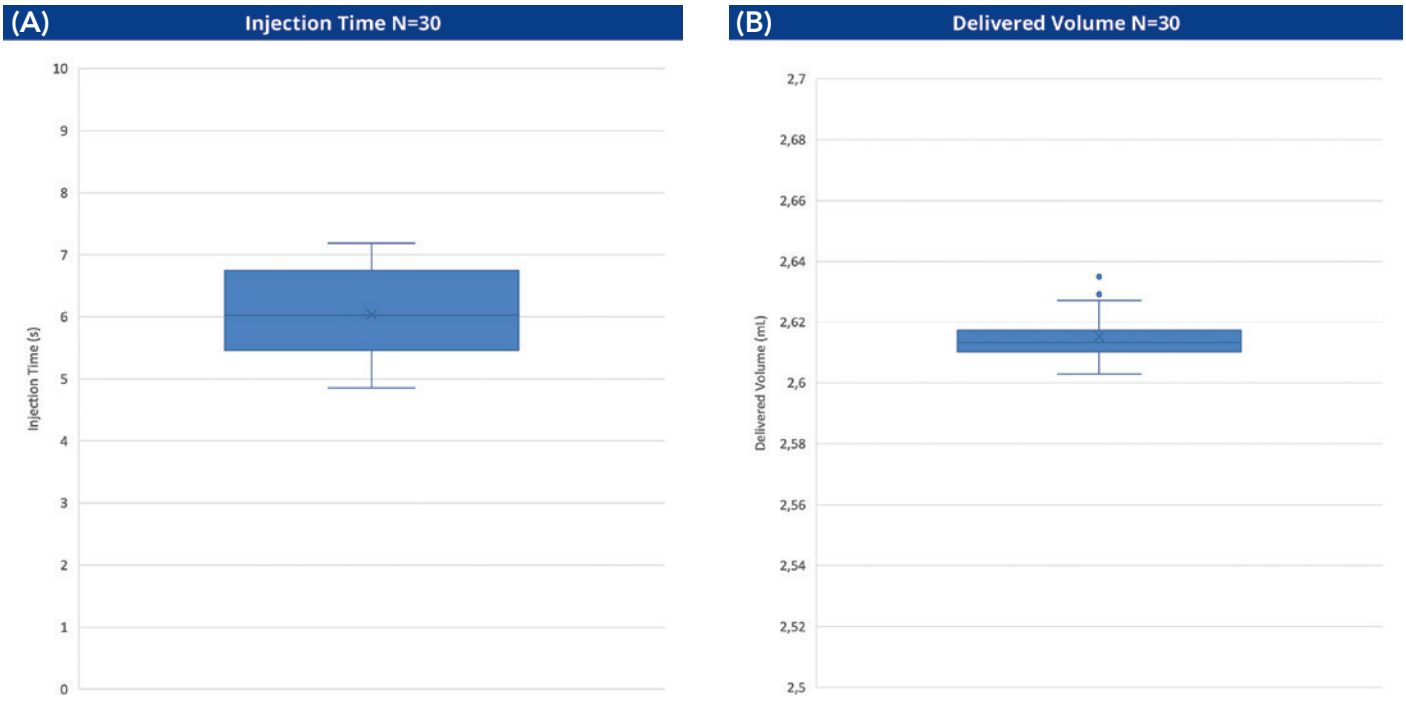

Figure 4: (A) Injection time and (B) delivered dose results for the tested container-device configuration.

The feasibility assessment revealed consistent injection time and delivered dose performance using 30 assembled devices filled with a 1 cP liquid in each chamber. Chamber One contained 1.3 mL and Chamber Two contained 1.4 mL, for a total fill volume of 2.7 mL.

The findings provided an initial feasibility baseline for the standardised container-device configuration before drug-specific development. The mean injection time of 6.04 seconds indicated that the system is capable of consistent, full-dose delivery while maintaining usability. The delivered dose results demonstrated highly repeatable performance, indicating consistent residual volumes across the tested samples.

BREAKING SILOS: A FULLY INTEGRATED ECOSYSTEM APPROACH

Successful drug delivery depends on aligning the primary container not only with the device but also the manufacturing process from the outset. Treating these as separate development challenges can allow interface requirements to emerge only after significant design decisions have already been made.

From the earliest stages of development, Stevanato Group and SHL Medical involved equipment manufacturers, elastomer suppliers and CMOs. Their input helped to assess how the dual-chamber format would move through fill-finish and final assembly under real manufacturing conditions.

The cartridge's standard external format supported this integrated approach. Its ISO 3 mL cartridge dimensions and EZ-fill® presentation aligned with established RTU fill-finish combi-lines, allowing manufacturing to begin from familiar filling and handling concepts rather than a bespoke, bulk dual-chamber cartridge process.

The dual-chamber filling process follows five defined stages (Figure 5):

- Load the empty cartridge
- Fill the first chamber
- Insert the mid-plunger
- Fill the second chamber
- Insert the rear plunger.

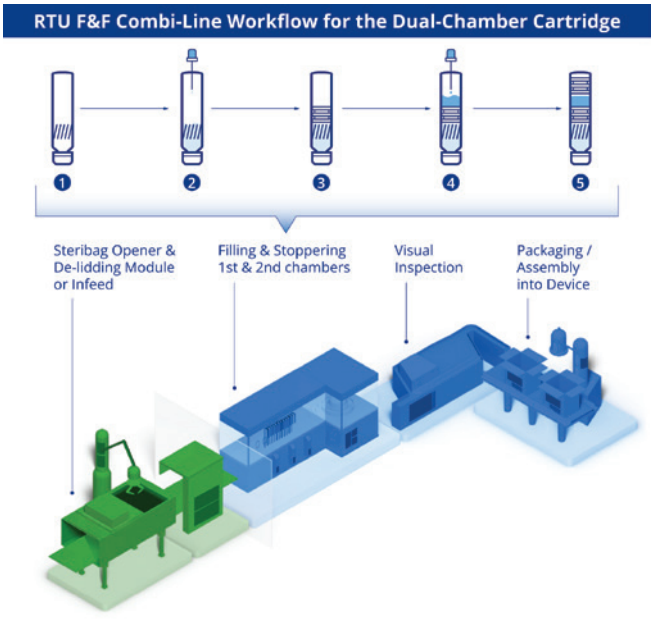

Figure 5: RTU fill-finish combi-line workflow for the dual-chamber cartridge. This shows the five filling stages followed by visual inspection and device assembly. (Implementation will still depend on the selected machine model. Some lines may require engineering adaptations for the second filling and plunger-insertion steps.)

After filling, the cartridge can proceed to visual inspection and device assembly. Its standard external dimensions support transfer between these stages because the handling systems do not require custom equipment installations. Lastly, final assembly of the cartridge into the Magnitude device leverages existing equipment which is also capable of final assembly of single-chamber ISO 3 mL cartridges with Magnitude.

ACCELERATING LIQUID-LIQUID FDC DEVELOPMENT

As demand for combination therapies grows, pharmaceutical companies need delivery systems that can maintain separation during storage without creating a bespoke development and manufacturing programme. Stevanato Group and SHL Medical are addressing this challenge by integrating two existing platform technologies into a combined configuration for liquid-liquid FDC delivery.

The standardised container-device configuration offers a practical route to self-administered liquid-liquid combination products using established RTU manufacturing concepts. Starting from a jointly assessed container-device configuration can simplify development, reduce integration risk and accelerate time to market by leveraging existing primary container, fill-finish, device and final assembly platforms.

Each programme will still require formulation-specific testing with the intended drug product and final components. However, resolving key interface considerations earlier allows development teams to focus on therapy-specific optimisation rather than custom container and device integration.

By aligning primary-container design with device compatibility, fill-finish and assembly from the outset, the standardised container-device configuration supports a more streamlined development pathway for liquid-liquid FDC self-administration. For patients, this creates the potential for combination therapies that can be administered in a single injection through a familiar autoinjector, reducing the need for separate injections and supporting the shift towards home treatments.

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Valerio Ravazzolo

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Valerio Ravazzolo, Product Manager for Cartridge Platform at Stevanato Group, has a background in mechanical engineering from the University of Padua. Mr Ravazzolo joined Stevanato Group in 2015 as part of the Quality Assurance team. In 2017, he transitioned to a Technical Account Manager role, where he worked closely with key customers, taking on greater responsibilities and eventually becoming Team Manager. Building on this experience, he took the position of Product Manager for the cartridge platform, bringing together his technical expertise and customer-oriented mindset to drive product strategy and development.

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Thomas James

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Thomas James, Customer Solutions Manager at SHL Medical, with nearly a decade of experience developing medical devices, has a particular focus on injectable drug delivery systems and combination products. At SHL Medical, he works closely with pharmaceutical and biotechnology companies to develop strategies for advancing self-administered therapies from early development through commercialisation. His experience spans new product development in autoinjectors, on-body and near-body delivery systems, emergency-use systems, infusion pumps, and dual-chamber drug delivery technologies. Mr James holds a BSc in Mechanical Engineering and is a named inventor on more than ten patents related to novel drug delivery systems.

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NEED TO SIMPLIFY LIQUID-LIQUID DRUG DELIVERY?

Courtesy of SHL Medical

By combining Stevanato Group's EZ-fill® dual-chamber cartridge platform with SHL Medical's Magnitude™ autoinjector platform, pharmaceutical companies can leverage a standardized delivery ecosystem for liquid-liquid combination therapies, reducing development complexity, risk and time to market.

Read the article in this issue.

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Expert View

ENABLING DELIVERY OF LYOPHILISED BIOLOGICS VIA SIMULATION-LED DEVELOPMENT OF DUAL-CHAMBER SYSTEMS

Dr Sahab Babaee of Sanofi and **Dr Matthew Hancock** of Veryst Engineering discuss the potential of using modelling and simulation when designing dual-chamber injection devices, which can enable device designers to investigate the complex interactions that take place within a dual-chamber system without a physical prototype and discover potential failure modes much earlier in the design process.

"IN PARTICULAR, DUAL-CHAMBER DELIVERY SYSTEMS HAVE EMERGED AS PROMISING PLATFORMS TO ENABLE INTEGRATED RECONSTITUTION AND SELF-ADMINISTRATION OF LYOPHILISED DRUG PRODUCTS WITHIN A SINGLE COMBINATION PRODUCT."

Biologics, including monoclonal antibodies, antibody-drug conjugates, peptides, proteins and vaccines, now represent a large and growing share of the pharmaceutical pipeline. There has been considerable growth in BLAs and approvals over the last several years, with a market size projected to be over US$1 trillion (£740 billion) by 2035.[1,2] Formulation stability challenges are a key factor in developing these molecules – many of them are not stable in liquid form for the shelf lives required by regulators and markets, and must be freeze-dried, or lyophilised, to preserve their structure and potency.[3,4] It is estimated that over 60% of biologics on the market today would not be possible without lyophilisation.[5] As the number of lyophilised biologic and vaccine candidates continues to grow, so too does the need for delivery systems that can reconstitute them reliably, safely and with minimal burden on the patient or caregiver.

WHY DUAL-CHAMBER DELIVERY SYSTEMS?

Historically, reconstituting a lyophilised drug for parenteral administration has consisted of several manual steps and components: withdrawing diluent, injecting it into a vial, swirling or inverting to dissolve the cake for robust reconstitution and then drawing the reconstituted solution into a syringe prior to injection. Each step is an opportunity for a dosing error, contamination or delay, along with other human factors-related use errors. Furthermore, the process assumes a level of manual dexterity, training and confidence that may vary across care settings.These challenges are particularly concerning for emergency-use products, paediatric and geriatric populations, and self-administered chronic therapies.[6]

These constraints have driven sustained industry interest in delivery devices that can automate reconstitution rather than delegating it to the user. In particular, dual-chamber delivery systems have emerged as promising platforms to enable integrated reconstitution and self-administration of lyophilised drug products within a single combination product.[7,8]

Autoinjectors with dual-chamber cartridges (AIDCs) respond directly to this unmet need. A single cartridge stores the lyophilised drug and liquid diluent in two compartments separated by a plunger stopper. Upon activation by the patient, a spring-driven mechanism moves the diluent into the drug chamber via a bypass channel, mixes and dissolves the lyophilised drug, then primes the needle and injects the ready-to-use solution, all resulting in one continuous, patient-triggered process.[7,9]

This approach offers a range of substantial advantages, including automated reconstitution and injection in a single platform, reduced user burden and training requirements, potential for at-home administration rather than in-clinic dosing, improved usability and treatment adherence, protection of sensitive drug products until the point of use and applicability across biologics, vaccines and emergency-use products alike.[6,8]

THE ENGINEERING COMPLEXITY BEHIND AIDCs

However, this simplicity for the patient is bought with considerable engineering complexity for the developer. An AIDC must execute a precise sequence of physical events, in the right order and within a tight time window, using a single drive spring or gas canister and no external power source – transfer diluent into the lyophilised drug chamber via a bypass channel, ensure that the lyophilised cake fully wets and dissolves, attach and prime the needle, and inject into tissue at an acceptable rate and within an appropriate timeframe.[9] The spring, two stoppers, bypass design, air compression, fluid motion and tissue backpressure all interact,[9,10] and AIDC-specific failure modes – missed stopper-position targets causing the stopper to fail to allow or prevent bypass flow, and incomplete reconstitution resulting in an inhomogeneous drug solution – can arise from interactions that simply do not exist in single-chamber syringes or autoinjectors.[9]

WHY CONVENTIONAL DEVELOPMENT APPROACHES ARE NOT ENOUGH

The conventional response to this complexity has been iterative prototyping: build a device, test injection time and force, redesign, retest.[11] This approach becomes disproportionately slow and expensive for AIDCs, because:

- The design space is larger and multi-dimensional, with multiple contributing parameters – including spring force, stopper friction and insertion depth, bypass channel design, chamber air volumes, cake formulation, diluent volume and tissue backpressure – all being interdependent.
- Some failure modes only reveal themselves late in development after experimental reconstitution and injection testing.
- Small dimensional tolerances in needle geometry translate into disproportionately large swings in injection force (via the fourth-power dependence of Poiseuille flow on needle radius), yet many early-stage models simulate only nominal geometry and friction conditions rather than sampling realistic manufacturing tolerances.[11]

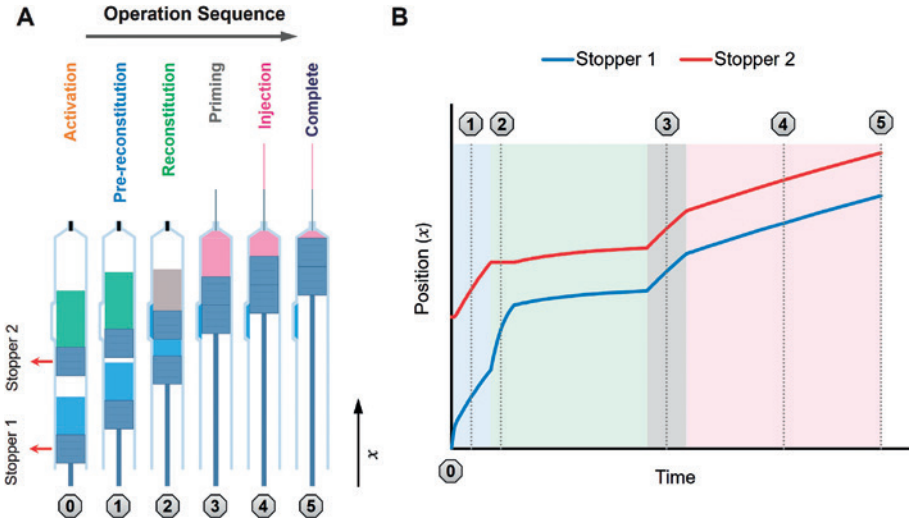

Figure 1: (A) Schematic illustration of the five-stage operational sequence of an AIDC, including: (0) activation, (1) pre-reconstitution, (2) diluent transfer into the front injection chamber via bypass channel and reconstitution of the lyophilised drug, (3) needle priming and (4) injection. (B) Model-predicted transient AIDC response, showing stopper positions throughout AIDC operation stages corresponding to the representative snapshots illustrated in A.

Simulation-led technical due diligence can change this dynamic. Physics-based and reduced-order models let developers explore spring stiffness, stopper friction, chamber air volumes, diluent volume, bypass design, cake properties and tissue backpressure ranges computationally, evaluating device and formulation configurations virtually and narrowing the design space to a small number of high-confidence candidates before committing to tooling or running full physical or clinical verification.[12,13]

This approach does not eliminate physical testing, but rather changes its role – from broad exploratory search to targeted confirmation – consistent with the risk-informed credibility principles in American Society of Mechanical Engineers Verification & Validation (V&V) 40 and the US FDA's Computational Modelling and Simulation (CM&S) credibility guidance, both of which recognise that adequately validated models can reduce the burden of physical verification for well-defined contexts of use.[13–15] The FDA's 2016 reporting guidance further standardises how a CM&S study should be documented, including governing equations, system properties, numerical methods, validation and limitations, so that a reviewer can judge whether a model's credibility matches its intended decision-support role, and a similar risk-based credibility framework has been applied to assess model risk for other device classes.[16,17]

A PHYSICS-BASED FRAMEWORK FOR PREDICTING AIDC PERFORMANCE

A modelling framework applicable to a broad class of spring-driven AIDCs for lyophilised drug and vaccine delivery makes this possible in practice. Consider a reduced-order model, developed and experimentally validated for AIDCs, that has been explicitly structured around the following stages (Figure 1A):

- Activation
- Pre-reconstitution, with drive-spring preload and initial stopper positions
- Bypass-enabled diluent transfer into the front injection chamber and lyophilised cake reconstitution
- Needle priming
- Injection.[9]

The equations of motion for the AIDC's two stoppers are coupled to the ideal gas law for the chamber air pockets and to

an experimentally derived stopper-friction-versus-glide-speed relationship, giving predictions of the stoppers' trajectories (Figure 1B), reconstitution, injection and priming time, as well as injection flow-rate time profile, peak tissue backpressure and failure modes, such as missed stopper-position targets causing the stopper to fail to allow or prevent bypass flow.[9]

This AIDC modelling framework does not require advanced simulation software to run. A snapshot of an HTML implementation is shown in Figure 2, highlighting the input variables incorporated into the model and the resulting predictions of AIDC behaviour, including the essential performance requirements across its stages of operation.

The stopper friction was found experimentally to follow a power law with glide speed rather than a classical constant or linear friction law, consistent with a lubricated stopper-barrel interface (i.e. silicone oil between a siliconised elastomer stopper and glass barrel, rather than dry solid-on-solid contact). A hybrid modelling framework built for precisely this interface captures the resulting Stribeck-type behaviour, where friction shifts between boundary, mixed and hydrodynamic lubrication regimes as glide speed changes, adding a data-driven component to describe what purely mechanistic friction laws miss.[9,18] Validation against measured injection times across a range of formulation and device configurations showed good agreement between predicted and experimental behaviour.[9]

"AS THE MODEL LINKS EVERY STAGE EXPLICITLY, IT CAN FLAG COMBINATIONS OF SPRING FORCE, DILUENT VOLUME, STOPPER FRICTION, CHAMBER AIR VOLUMES AND RECONSTITUTED DRUG SOLUTION VISCOSITY THAT WOULD OTHERWISE ONLY REVEAL A FAILURE MODE AFTER PHYSICAL TESTING."

Understanding the Interplay Between Formulation and Device Design

As the model links every stage explicitly, it can flag combinations of spring force, diluent volume, stopper friction, chamber air volumes and reconstituted drug solution viscosity that would otherwise only reveal a failure mode after physical testing.[9] As an illustrative example, increasing spring force can shorten reconstitution time by accelerating diluent delivery into the cake, but at the cost of higher injection forces or greater cavitation risk;[9,19] a gentler reconstitution profile may be kinder to the cake and formulation but push total patient-facing time (i.e. reconstitution plus injection) beyond a comfortable window. Mechanistic reconstitution models developed for formulation science, describing wetting, capillary penetration, cake disintegration and dissolution can be coupled directly to device-level bypass flow rate, turning cake microstructure and diluent delivery rate into explicit design variables alongside spring force and bypass design, rather than a lumped, black-box delay.[3,4,20–22]

Two further refinements would sharpen these predictions. First, coupling to finer-grained numerical dissolution models, such as particle- or continuum-scale simulations that move beyond classical one-dimensional dissolution formalisms.[23] Second, replacing the current constant-viscosity assumption with the shear-thinning, non-Newtonian rheology that many concentrated antibody formulations actually exhibit, where viscosity drops sharply at the higher shear rates seen in narrow-gauge needles.[24]

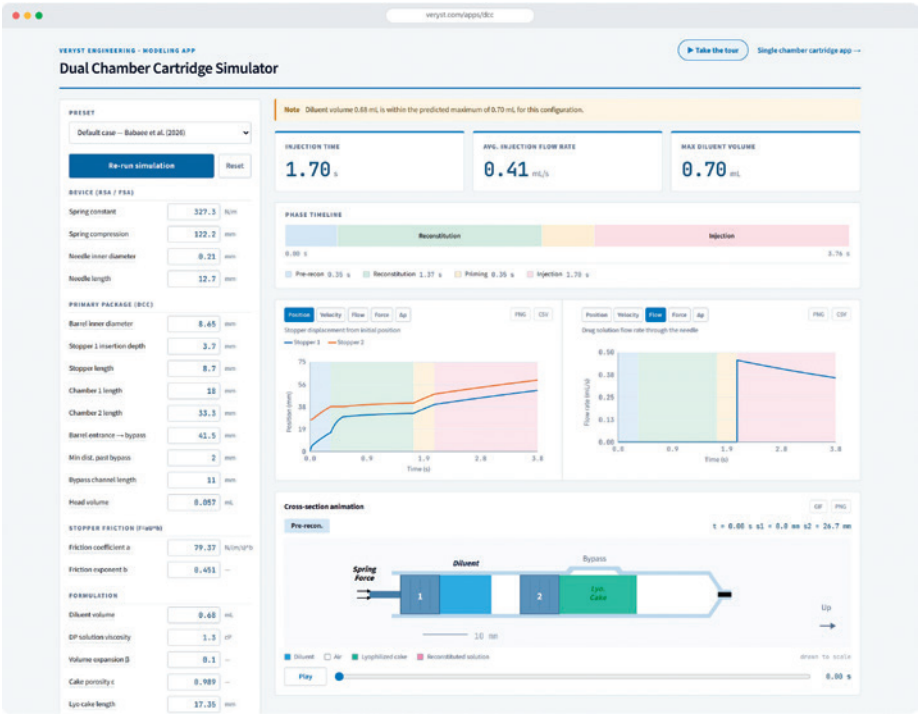

Figure 2: Snapshot of an HTML implementation of the AIDC model simulator.

DIGITAL DEVELOPMENT AND MODEL-INFORMED DEVICE DESIGN

Dual-chamber delivery systems are particularly well-suited to digital development because of their complex, multiphysics behaviour – no single test rig or bench measurement captures the full interaction between spring, stopper friction, air compression, bypass flow, reconstitution kinetics and tissue response. The industry is increasingly adopting model-informed drug device development, digital twins, virtual prototyping and simulation-based design optimisation as standard tools for precisely this class of problem, and has

begun to explore artificial intelligence (AI)-based methods for accelerating parameter identification and design search. Any such AI-assisted step would itself need to sit inside the same verification, validation and uncertainty quantification credibility framework described above before it could inform regulatory-facing decisions.[13,14]

Future Opportunities for Dual-Chamber Delivery Platforms

As the biologics and vaccines pipeline diversifies, dual-chamber delivery platforms are well placed to serve high-concentration biologics, messenger RNA (mRNA) and next-generation vaccines, long-acting injectables, emergency-use products, personalised medicines and connected or smart autoinjectors that log dose and adherence data. Each of these applications adds its own formulation and device constraints, and simulation offers a practical way to explore them before committing to a fixed platform. A further extension worth pursuing is coupling AIDC-specific models to tissue-level outcomes downstream of the needle, including depot formation, interstitial flow and absorption kinetics, as well as how patient variability in body-mass index and tissue composition shapes them, as injection conditions and device parameters can influence depot shape and, potentially, drug absorption and tolerability.[25,26]

"AS THE BIOLOGICS AND VACCINES PIPELINE DIVERSIFIES, DUAL-CHAMBER DELIVERY PLATFORMS ARE WELL PLACED TO SERVE HIGH-CONCENTRATION BIOLOGICS, MRNA AND NEXT-GENERATION VACCINES, LONG-ACTING INJECTABLES, EMERGENCY-USE PRODUCTS, PERSONALISED MEDICINES AND CONNECTED OR SMART AUTOINJECTORS THAT LOG DOSE AND ADHERENCE DATA."

CONCLUSION: FROM DEVICE SELECTION TO CLINICAL READINESS

As dual-chamber delivery systems become increasingly important for enabling self-administration of lyophilised biologics, development success will depend not only on device innovation but on the ability to understand and predict complex formulation-device interactions.[9] Simulation-led technical due diligence and model-informed development offer a practical framework to accelerate platform selection, reduce experimental burden and improve confidence in clinical and commercial success – turning dual-chamber development from a series of expensive physical iterations into a structured, model-informed path from device selection to clinical readiness.[13,14]

ABOUT THE COMPANY

Veryst Engineering is a Boston-based engineering consulting firm, providing PhD-level expertise across fluid and solid mechanics, materials science and physics. Veryst helps combination product and drug delivery device teams accelerate development, diagnose product problems and de-risk complex design challenges on an industrial timeline. For combination products specifically, the firm's work spans autoinjector performance, injection modelling, lyophilisation, drug product drying and container closure integrity. Veryst's methods are grounded in engineering and physical fundamentals and all resulting methods, models and IP are transferred directly to the client.

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PROACTIVE QUALITY AND REGULATORY ENGAGEMENT TO ACCELERATE PRODUCT DEVELOPMENT

Bharat Arora and **Hirak Bhatiya** of Vertex Pharmaceuticals discuss the quality and regulatory perspective on accelerated development pathways transitioning from an emergency measure to a mainstream route to commercialisation, going over what may be expected of pharmaceutical quality teams to manage this new paradigm.

THE INDUSTRIAL REVOLUTION IN PHARMACEUTICAL DEVELOPMENT

The pharmaceutical industry is experiencing an industrial revolution in drug development. Accelerated pathways – once exceptional accommodations for urgent medical needs – have become increasingly embedded in modern development. This represents a significant shift from the occasional use of accelerated pathways to a more consistent industrial capability.[1,2]

This shift requires a change in quality management systems (QMSs) and regulatory engagement, moving from passive compliance to a proactive, data-driven and continuous regulatory partnership. Critically, regulatory flexibility exists in the timing and sequencing of data submission, not in the rigour of the underlying requirements. Product specifications, patient safety standards and validation requirements remain essential whether approval occurs through a standard or expedited pathway. What has evolved is the sophistication of QMSs – moving from rigid sequential development to flexible, risk-based approaches that maintain stringent endpoints while strategically phasing the journey to reach them.

A PRODUCT QUALITY MANAGEMENT TRANSFORMATION

Traditional pharmaceutical QMSs, historically based on the stability of well characterised commercial processes, are undergoing substantial disruption due to the trends facilitated by accelerated pathways. In the world of accelerated pathways, QMSs should be embedded in development decision-making from inception, functioning as proactive risk assessors and lifecycle strategists. This can be achieved through template-based approaches, standardised frameworks for product families within defined boundaries, sophisticated knowledge management, systematically captured risk assessments and regulatory precedents, as well as cross-programme learning mechanisms in which each programme contributes knowledge to a broader platform.

It is imperative to clarify that this does not mean reduced product quality assurance in product development. Rather, it represents an evolution towards a more sophisticated product quality assurance framework that maintains the same stringent safety and efficacy requirements while using scientific justification and risk-based approaches to determine where and when evidence is most valuable. While fundamental quality standards would remain unchanged, the methodology for demonstrating compliance is evolving towards risk-based decision-making and comprehensive lifecycle commitments.

A science-based product quality approach, combined with regulatory compliance, prioritises risk assessment and ensures that analytical and regulatory resources are applied to the variables that most strongly affect product safety and efficacy. This model requires clear communication and justification of risk assessments, going beyond simple quality assessments to provide an evidence-based rationale for scientific uncertainties. The framework also depends on continuous

> "IN THE WORLD OF ACCELERATED PATHWAYS, QMSs SHOULD BE EMBEDDED IN DEVELOPMENT DECISION-MAKING FROM INCEPTION, FUNCTIONING AS PROACTIVE RISK ASSESSORS AND LIFECYCLE STRATEGISTS."

integration of new information from ongoing monitoring and advanced process analytics to create a living knowledge base, with the objective of establishing a development system in which knowledge generated in one programme becomes an asset for subsequent programmes.

The same principle applies to drug-device combination products and delivery systems. For products such as prefilled syringes (PFSs), autoinjectors and dual-chamber delivery systems, product quality cannot be considered independently from device performance and human interaction. Design verification, human factors, container-closure performance, delivery performance and formulation characteristics can be interdependent. Consequently, quality and regulatory engagement should begin early enough to influence the product architecture and development strategy, rather than occurring after the design has effectively been established.

RISK-BASED DECISION FRAMEWORKS

Accelerated development compresses timelines precisely because it accepts managed uncertainty through rigorous, transparent risk assessment.[3] Organisations can employ a three-tier risk categorisation to ensure appropriate focus:

- **Patient-Focused Risks (Highest Priority):** Any factor directly affecting patient safety, clinical outcomes or therapeutic experience – product impurities with toxicological potential, potency variations affecting dosing, stability failures impacting shelf life, immunogenicity triggers and delivery-system failures.
- **Regulatory and Quality Risks:** Threats to organisational credibility and data integrity – comparability gaps during process changes, insufficient process understanding, analytical method limitations, validation deficiencies and documentation gaps.
- **Operational Feasibility Risks:** Practical execution challenges – supply-chain dependencies, analytical throughput limitations, equipment availability, technical-transfer challenges and staffing constraints.

"FOR PRODUCTS SUCH AS PFSs, AUTOINJECTORS AND DUAL-CHAMBER DELIVERY SYSTEMS, PRODUCT QUALITY CANNOT BE CONSIDERED INDEPENDENTLY FROM DEVICE PERFORMANCE AND HUMAN INTERACTION."

This categorical clarity enables disciplined prioritisation – patient risks drive conservative decision-making; regulatory risks warrant appropriate mitigation strategies; and operational challenges require contingency planning rather than characterisation disproportionate to their potential impact.

For combination products and delivery systems, however, a further dimension is required: use-related risk and platform knowledge. Early quality and regulatory involvement can help determine whether or not a proposed delivery system represents a genuinely new risk or whether its critical user interactions and design characteristics are sufficiently well understood through prior product experience. This distinction can have a substantial impact on the development strategy. Rather than automatically treating every new PFS or delivery system presentation as a novel device requiring a completely new body of evidence, organisations can establish a structured comparison against relevant products in their internal knowledge base.

A US FDA review of Jubbonti (denosumab-bbdz, Sandoz, Basel, Switzerland) provides a practical illustration of this principle.[4] Jubbonti was submitted as a 60 mg/mL single-dose PFS with a needle-safety device and was evaluated as a drug-device combination product. The FDA's review specifically evaluated the applicant's use-related risk analysis (URRA) and comparative analysis against US-licensed Prolia (denosumab, Amgen, Thousand Oaks, CA, US). The FDA noted that the proposed product had the same indication, intended healthcare-provider user population, use environment, dosing, route of administration and strength as Prolia. The FDA review concluded that the URRA was comprehensive and appropriate and that the comparative analyses did not identify new, different or unique use-related risks or design differences affecting critical tasks. Consequently, a comparative human factors study was not considered necessary.

The importance of this example is not that human-factors evidence can simply be eliminated, but rather that it demonstrates the value of using prior knowledge to determine what evidence is genuinely necessary. A platform strategy provides the knowledge base against which a new product can be assessed; the product-specific assessment then determines whether the existing evidence remains applicable or whether differences introduce additional risk.

This approach is particularly important for organisations developing multiple products using similar delivery technologies. A structured database containing previous device assessments, critical tasks, use-related risks, design verification methods, acceptance criteria, human-factors findings and regulatory precedents can become an important development asset. Quality and regulatory teams can use this information to establish scientifically justified thresholds for when additional studies are necessary and when existing knowledge can be used.

"A PLATFORM STRATEGY PROVIDES THE KNOWLEDGE BASE AGAINST WHICH A NEW PRODUCT CAN BE ASSESSED; THE PRODUCT-SPECIFIC ASSESSMENT THEN DETERMINES WHETHER THE EXISTING EVIDENCE REMAINS APPLICABLE OR WHETHER DIFFERENCES INTRODUCE ADDITIONAL RISK."

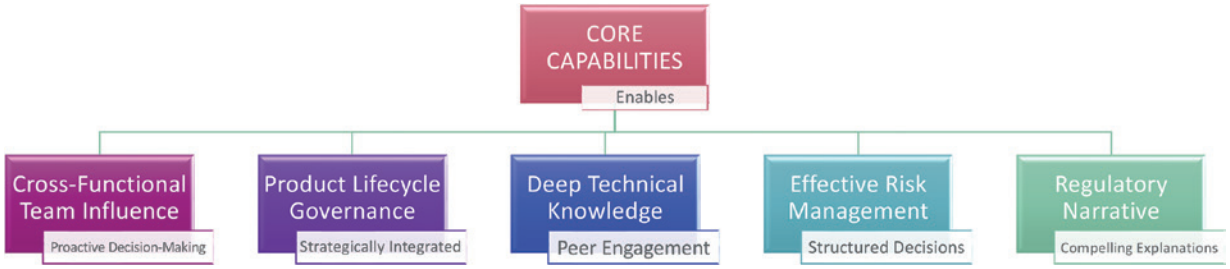

Figure 1: The five core capabilities required of quality and regulatory teams.

QUALITY AND REGULATORY COMPETENCY MODEL

Accelerated development requires five core capabilities within quality and regulatory organisations (Figure 1):

1. **Cross-Functional Stakeholder Influence:** Quality and regulatory teams should shape development decisions proactively, rather than reactively approving predetermined plans. Industrial maturity means formal integration into stage-gate decisions, cross-functional risk ownership and defined escalation protocols.
2. **Technical Fluency:** Deep scientific understanding enables knowledgeable peer engagement rather than superficial compliance checking. Organisations should establish modality-specific expertise platforms, systematic knowledge capture and continuous learning programmes.
3. **Product Lifecycle Governance:** Development, approval and commercialisation should be viewed as an integrated continuum and should extend into a platform strategy as applicable. This creates an opportunity to establish a product platform knowledge base to build upon previously characterised drug-device architecture for new programmes.
4. **Structured Risk Management:** Systematic, evidence-based approaches enable disciplined decisions under uncertainty. Industrial systems should maintain portfolio-level risk libraries, employ standard assessment templates with clear scoring criteria and use cross-programme analytics to identify patterns.
5. **Regulatory Narrative Development:** Organisations must construct scientifically compelling explanations that build regulatory confidence. Industrial organisations can use template-based narratives that incorporate regulatory precedent, maintain searchable precedent databases and implement cross-functional reviews to ensure consistent messaging.

HEALTH AGENCY ENGAGEMENT PREPARATION

A quality narrative connects risk assessment, knowledge management and lifecycle planning for a product. Effective narratives should clearly explain why certain product attributes were heavily assessed compared with other attributes and explicitly link critical material attributes and critical quality attributes to patient outcomes. In combination products, these narratives should also explain how device characteristics, critical user interactions and delivery performance affect patient safety and therapeutic outcomes.

Health authority interactions should therefore be treated as a continuous loop.[5,6] Prior to engagement with regulatory agencies, organisations should conduct a thorough review of internal databases and regulatory precedents, identify relevant similar products, anticipate questions based on knowledge gaps and build a structured briefing package. For drug delivery systems specifically, early engagement should specifically address three interconnected questions:

- What is genuinely novel?
- What existing knowledge can be used?
- What evidence will the agency expect to demonstrate that the remaining risks are adequately controlled?

This is particularly important for design verification and human factors. The objective of an early regulatory interaction should not simply be to obtain agreement on an individual study protocol. Instead, the organisation should seek alignment on the overall evidence-generation strategy, including the applicability of prior platform knowledge, the proposed use-related risk assessment, the threshold for additional human-factors work and the design-verification strategy.

The broader organisational lesson is that such analyses should not be reconstructed independently for every development programme. A mature quality and regulatory organisation should maintain a searchable database of prior products, regulatory questions, device configurations, human-factors assessments, design-verification methods and regulatory agency decisions. Such a database can then become a platform for developing evidence-based threshold analyses and regulatory narratives.

"A MATURE QUALITY AND REGULATORY ORGANISATION SHOULD MAINTAIN A SEARCHABLE DATABASE OF PRIOR PRODUCTS, REGULATORY QUESTIONS, DEVICE CONFIGURATIONS, HUMAN-FACTORS ASSESSMENTS, DESIGN-VERIFICATION METHODS AND REGULATORY AGENCY DECISIONS."

"THE SHIFT TO A COMBINED COMPLIANCE MINDSET AND SCIENCE-BASED ENGAGEMENT REPRESENTS MORE THAN A PHILOSOPHICAL EVOLUTION; IT IS AN OPERATIONAL NECESSITY."

CONCLUSION

Accelerated development pathways are no longer episodic responses to urgent medical needs; they are becoming embedded features of modern pharmaceutical innovation. As expedited approaches proliferate across global regulatory agencies, the defining challenge is not simply whether organisations can move quickly, but whether or not they can do so in a manner that is scientifically defensible, regulatorily credible, compliant and operationally sustainable.

The shift to a combined compliance mindset and science-based engagement represents more than a philosophical evolution; it is an operational necessity. Clinical milestones, chemistry, manufacturing and controls decisions, device development, human-factors assessment, and regulatory interactions are no longer sequential events – they are dynamically interdependent.

For products involving PFSs, autoinjectors, dual-chamber systems and other drug-delivery technologies, this interdependence becomes particularly important. The quality of the final product depends not only on the formulation and manufacturing process but also on the ability of the delivery system to perform as intended and to support safe and effective use.

The lesson for pharmaceutical organisations is broader than an individual product – early quality and regulatory engagement can create alignment around the development strategy itself, including design verification, human factors, use-related risk, platform applicability and the appropriate threshold for generating additional evidence. This enables development teams to use existing knowledge where scientifically justified while directing resources towards genuine uncertainties.

Ultimately, it is critical to dispel any misconception that accelerated pathways compromise quality. The distinction lies in when certain lifecycle data are generated, how knowledge is accumulated and how scientific justification is communicated in support of product quality. Accelerated pathways intensify regulatory scrutiny during development through more frequent interactions and require more sophisticated QMSs capable of managing knowledge gaps transparently while maintaining product quality. This is how accelerated development can become a repeatable organisational capability rather than a one-time achievement.

This article is meant for educational purposes. The statements expressed here are those of the writers or external reference sources and do not reflect the opinion or position of Vertex Pharmaceuticals.

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Interview:
Rethinking Drug Delivery for Increasingly Complex Therapies

In this interview, **Ram Halthore** of **Kaléo** discusses the demands of newer classes of injectable drugs and the trend towards self-administration of conventional drug delivery systems, the requirements innovative systems must meet and the importance of selecting a delivery system early in formulation development, as well as the roles that robust human factors engineering and high reliability should play in device development.

Q What new demands are large-molecule biologics, glucagon-like peptide-1s (GLP-1s) and antibody-drug conjugates (ADCs) placing on drug delivery systems compared with previous generations of drugs?

A The rapid and continued expansion of biologics, antibody-drug conjugates and peptide-based therapeutics is placing increasing demands on drug delivery systems because their formulations have higher concentrations, higher viscosities and larger delivery volumes compared with previous generations of drugs. With these formulations, the inherent challenge is generating and controlling the force needed to deliver these formulations at high flow velocities, keeping injection times short and delivering a consistent injection profile to assist with patient comfort. The required force must be achieved without negatively affecting the drug or the container – for example, by minimising shear-related effects that may contribute to protein degradation or aggregation – while maintaining reliable device performance.[1]

The evolving requirements around large-molecule therapies have become increasingly difficult for conventional drug delivery systems to meet. This has prompted drug developers to evaluate delivery platforms that are designed to provide greater flexibility in how the force is generated and how the flow velocity is controlled throughout the injection. The challenge for developers is no longer simply delivering the drug, but selecting a delivery platform capable of supporting increasingly complex formulations while maintaining the intended product quality and performance characteristics.

"THE EVOLVING REQUIREMENTS AROUND LARGE-MOLECULE THERAPIES HAVE BECOME INCREASINGLY DIFFICULT FOR CONVENTIONAL DRUG DELIVERY SYSTEMS TO MEET"

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Ram Halthore is Vice-President, Development at Kaléo, where he leads device and drug development activities from early design through manufacturing transfer. His responsibilities include developing the company's human factors engineering programme, leading integrated drug-device product development and overseeing the company's intellectual property portfolio development. Mr Halthore has more than 25 years of experience spanning medical devices, pharmaceuticals, biologics and combination products, including autoinjectors, prefilled syringes, inhalation devices, implants and on-body injectors. His previous experience includes leadership roles at Merck, Teva, Amgen, Johnson & Johnson and 3M.

Q How are more complex formats, such as combination therapies and formulations requiring component separation, lyophilised products and dual liquids, reshaping thinking around drug delivery?

A For patients and caregivers, combination therapies, dual-liquid systems and lyophilised drugs can provide important treatment benefits, but they can also make administration more complex and challenging. When a therapy involves two drugs or separation of two formulation components, the delivery system must help users prepare and administer the dose safely and reliably in an at-home administration environment.

Lyophilisation can improve drug shelf life, but it can add a significant number of steps to the preparation and administration process. Because lyophilised products must be reconstituted with a sterile diluent before injection, the process can take more time due to these added steps and can increase the probability of use errors. Dual-chamber autoinjectors can help reduce this burden by streamlining preparation and administration for patients and caregivers.

Combination therapies are becoming an increasingly common approach intended to improve therapeutic benefit to the patients. These therapies often require two drugs to be administered together. Combining two drugs into a single injection may not be possible due to incompatibility, formulation challenges or manufacturing constraints. In these situations, dual-container, dual-chamber and dual-injection systems make administration possible, as well as more practical and patient-friendly.

Dual-container systems, where both containers hold the same drug, can also be used as large-volume injectors. A dual-injector device in combination with a dual-container system enables distribution of the delivered volume across a broader surface area. Together, these formats are shifting drug delivery towards more patient-centric design. Development processes often benefit from managing formulation complexity while also helping patients and caregivers to administer their therapies safely, reliably and conveniently.

Q Historically, device selection has often come late in development, with the molecule adapted to fit an existing platform – is that approach still viable?

A That historical model of device selection is not as viable as it once was, partly because the formulations for biologics and other large-molecule therapies are more difficult to adapt or retrofit to an existing platform downstream in the development process. Development programmes can benefit from identifying the delivery architecture that is best for the molecule, and ultimately for the patient, early in the development process, rather than adapting the molecule to an existing platform later. Determining if and which autoinjector is most appropriate should be part of early development decisions – there are multiple reasons why this approach may help improve development efficiency and product optimisation.

"LYOPHILISATION CAN IMPROVE DRUG SHELF LIFE, BUT IT CAN ADD A SIGNIFICANT NUMBER OF STEPS TO THE PREPARATION AND ADMINISTRATION PROCESS"

First, no single drug delivery architecture is optimised for every therapy. Selecting one advantage often means accepting trade-offs elsewhere in formulation compatibility, stability, usability, manufacturability or lifecycle flexibility. The goal is to identify the right delivery system for the right drug, the intended patient population and the intended use environment.

Second, different delivery architectures solve different problems. Dual-chamber systems, dual-container systems, dual-injection technology and other delivery technologies should be viewed as complementary options available to the formulators rather than as competing technologies.

Finally, delivery architecture decisions made early in development influence nearly every downstream activity, from formulation strategy and human factors (HF) engineering to manufacturing, regulatory planning and lifecycle management. Device selection is therefore often most effective when integrated alongside formulation and process development rather than as a separate downstream activity.

Early collaboration helps formulators balance speed to clinic by integrating device development with drug development early in the development process. Leaving device selection until late in development can cost the formulator in terms of time lost researching available device options, potential changes in the drug's formulation or manufacturing to work with the selected device, delays in entering the clinic and, ultimately, a longer time to market.

Q What role should HF engineering play in device development and where do companies typically get it wrong?

A The trend towards at-home administration means that patients and caregivers will no longer rely on assistance from a trained healthcare professional but instead need to become self-reliant. Less frequent dosing increases the possibility that users may not recall instructions from one injection to the next. Both trends underscore the importance of a device that manages technical complexity behind the scenes with an intuitive design, clear use instructions and guidance that do not presume the user's familiarity, along with clear user feedback during correct operation to create a simple, streamlined experience for patients and caregivers.

This is where robust HF engineering comes into play. HF engineering begins with understanding the intended user, intended use and intended use environment. HF studies provide valuable insights into how patients and caregivers may interact with injectable drug delivery systems in the real world and under a variety of real-world circumstances, such as low-light settings, high-pressure or emergency situations, and limited-dexterity scenarios.

"HF STUDIES PROVIDE VALUABLE INSIGHTS INTO HOW PATIENTS AND CAREGIVERS MAY INTERACT WITH INJECTABLE DRUG DELIVERY SYSTEMS IN THE REAL WORLD AND UNDER A VARIETY OF REAL-WORLD CIRCUMSTANCES, SUCH AS LOW-LIGHT SETTINGS, HIGH-PRESSURE OR EMERGENCY SITUATIONS, AND LIMITED-DEXTERITY SCENARIOS."

In short, robust HF engineering drives usability and helps ensure that products are developed for real people, not just ideal lab conditions.

I can speak on Kaléo's approach and some important lessons we've learned along the way. One lesson we've learned is that a device should have features designed to solve real use-related challenges, not simply add functionality. Audio and visual guidance, for example, can help provide step-by-step administration guidance for first-time users and especially users in emergency situations, when urgency, fear and hesitation may make it difficult for them to think clearly or remember instructions.[2,3]

Q How does Kaléo's experience with emergency-use devices and designing for high-stress, emergency-use scenarios translate into broader development applications?

A Kaléo recognises the importance our emergency-use devices can have to the people that use them, whether they are military, police, emergency responders, parents, caregivers or patients. We are proud that our reliability studies have shown that, at the time of manufacture, 99.999% of Kaléo's autoinjectors work as intended, thus meeting the "five nines" reliability threshold established by the US FDA's draft guidance for emergency-use autoinjectors.

We bring a patient-first perspective to our work. As a company founded by patients, we understand that successful drug delivery is about more than technology; it is about helping ensure people can use a therapy when they need it most. As we've learned, that level of reliability is designed into a product long before it reaches the patient.

Designing for high-stress, emergency-use situations has taught us to anticipate the real-world factors that can challenge successful drug delivery, from variability in users and environments to the potential for human error, and to address those factors early in development. Those principles extend well beyond emergency medicine. Whether a therapy is used in an emergency, at home for a chronic condition or in another setting, patients need to be able to use it correctly.

Have we set the reliability bar exceptionally high for ourselves? Yes. But it means that Kaléo brings that same focus on reliability to all products we develop for others that we bring to our emergency-use autoinjectors. The patient-centric mindset we bring to the various stages of developing and manufacturing drug-device combination products means considering reliability, usability and the real-world needs of patients from the beginning. Ultimately, our experience designing products people can depend on in high-stress situations informs how we approach each development programme, whether on our own or for someone else.

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2026/27 Editorial Calendar

Each issue of ONdrugDelivery focuses 100% on one specific topic *within* drug delivery.

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DEC Delivering Cell & Gene Therapeutics DEADLINE: **Nov 5, 2026**	**JAN 2027** Prefilled Syringes & Injection Devices DEADLINE: **Dec 10, 2026**	**FEB** Oral Drug Delivery DEADLINE: **Jan 7, 2027**
MAR Ophthalmic Drug Delivery DEADLINE: **Feb 4, 2027**	**APR** Pulmonary & Nasal Drug Delivery DEADLINE: **Mar 4, 2027**	**APR/MAY** Sustainability in Drug Delivery DEADLINE: **Mar 18, 2027**
MAY Delivering Injectables: Devices & Formulations DEADLINE: **Apr 1, 2027**	**MAY/JUN** Dermal, Transdermal & Microneedles DEADLINE: **Apr 15, 2027**	**JUN** Industrialising Drug Delivery DEADLINE: **May 6, 2027**
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Capa Valve is a micro-company that started trading in the pharmaceutical sector in 2023, having developed and patented valve systems for installation into standard syringes to create dual chamber devices. The company has licensed its technology for sequential dispensing and continues to seek collaborations for its other patented technologies.

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CoFlo Medical is a drug delivery technology company that partners with pharmaceutical companies to enable next-generation injectable delivery. CoFlo's platform core-annular flow technology streamlines high-concentration, high-viscosity delivery and is incorporated into multiple form factors that span a broad range of formulations, molecule types, delivery modalities and patient populations.

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Kaléo is a global leader in drug delivery device technology and autoinjector innovation. Kaléo's patented Aerio™ platform, with unmatched capabilities and human factors engineering, powers its portfolio of autoinjector products, as well as products under development for third parties.

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SHL Medical designs, develops and manufactures self-injection solutions, such as autoinjectors, pen injectors and specialty delivery systems for large-volume and high-viscosity formulations. By partnering with leading pharma and biotech companies, SHL Medical will continue to develop and supply products and services to support, engage and oversee patients whose quality of life relies on innovative self-treatment therapies.

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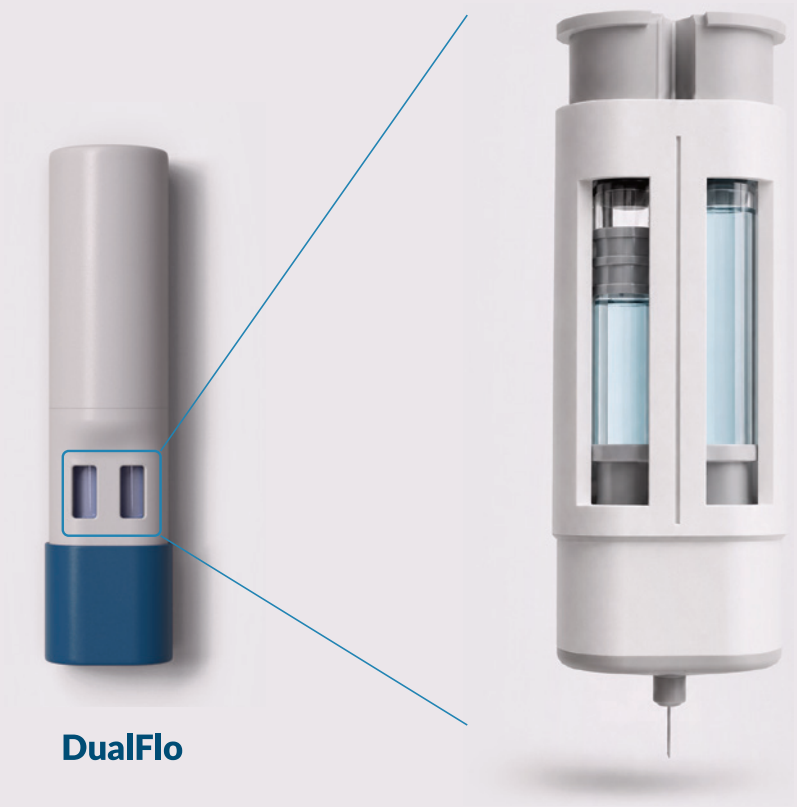

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