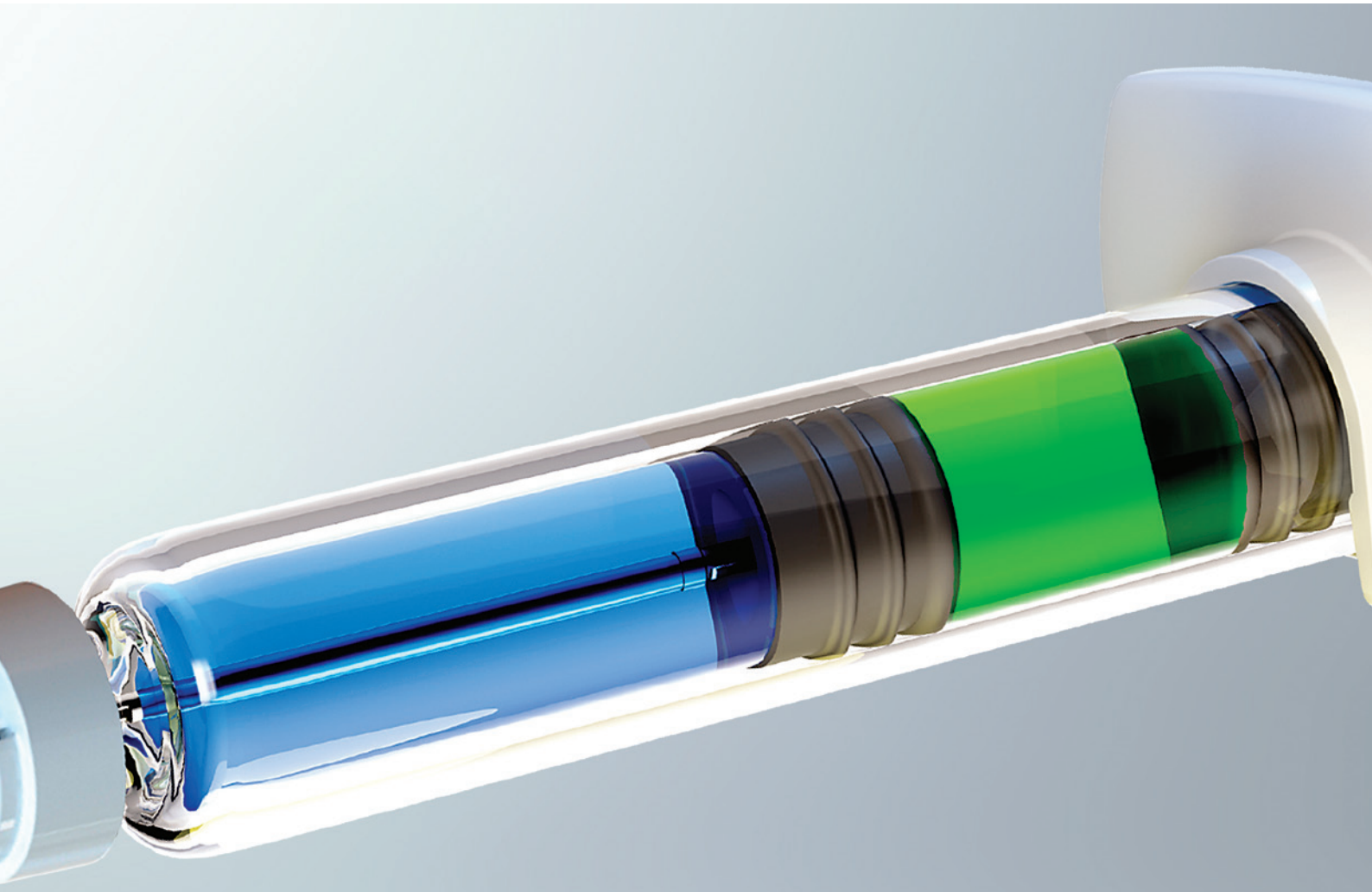
20 YEARS ON

177

DrugDelivery

SEPTEMBER 25TH 2025

DUAL-CHAMBER DELIVERY SYSTEMS



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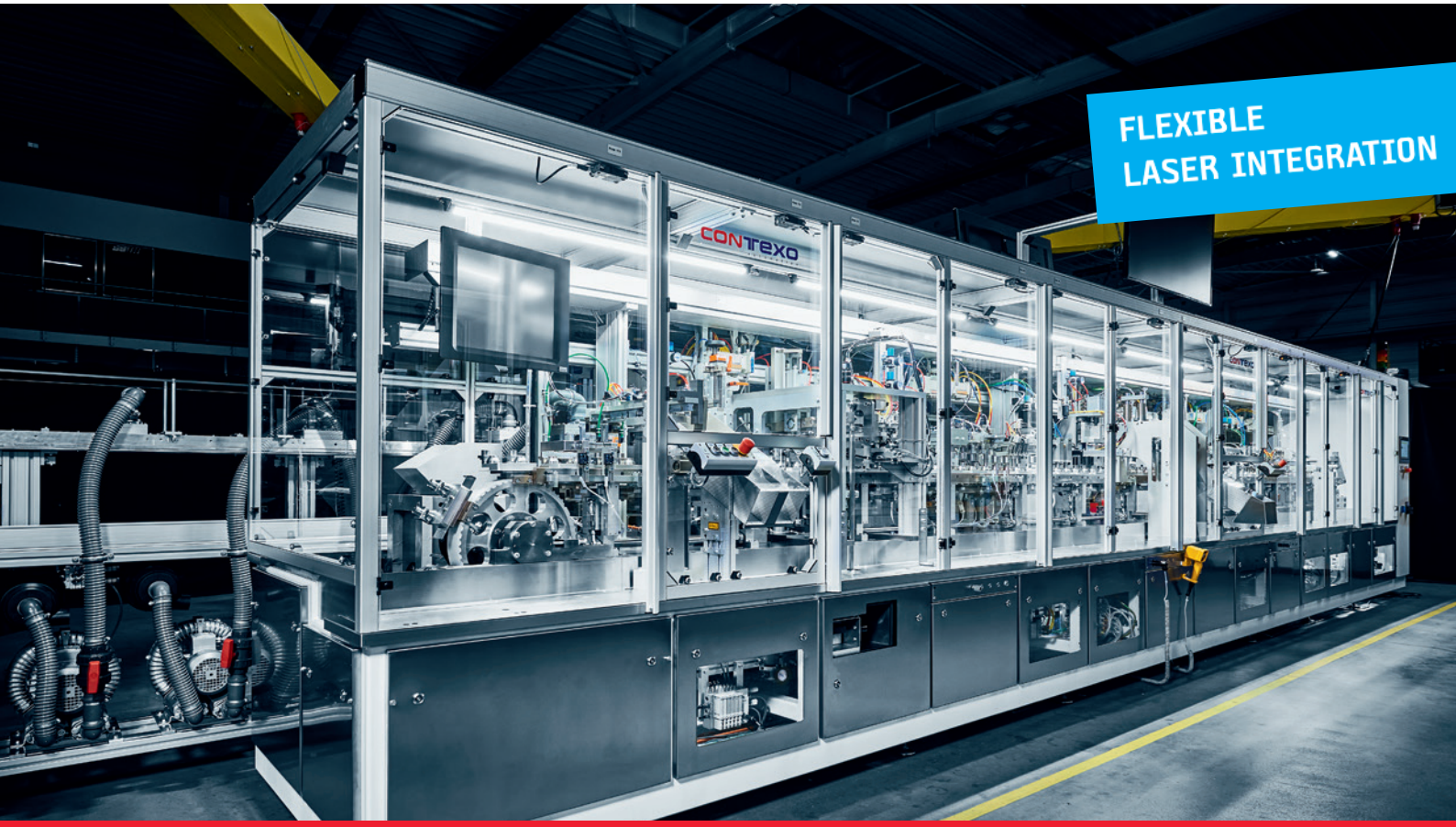

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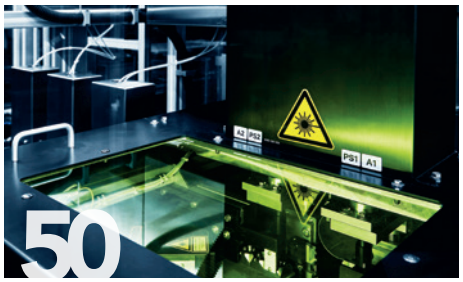

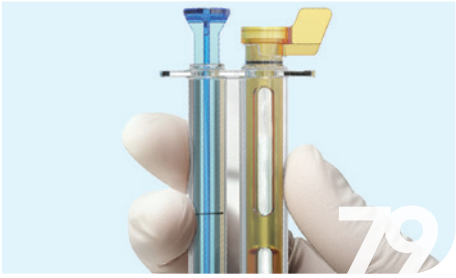

DUAL-CHAMBER DELIVERY SYSTEMS

ONdrugDelivery Issue N° 177, September 25th, 2025

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, "Barrel of the Credence Dual Chamber Syringe System", courtesy of Credence MedSystems, Inc. Reproduced with kind permission. (For more on the Credence Dual Chamber Syringe System, see this issue, Page 8.)

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Dual-Chamber Delivery:
New Solutions to Old Problems

In this issue of OndrugDelivery we present a brand new topic for the magazine – dual-chamber delivery systems. These systems represent a solution to two increasingly important challenges in the drug delivery industry – delivering combination therapies of multiple liquids and reconstituting lyophilised drug products simply and reliably. As this issue will discuss, the rising proportion of biologics in pharmaceutical pipelines has made both multi-drug therapies and lyophilisation more important tools for formulators dealing with challenging APIs, but the simultaneous desire to make therapies suitable for patients to use at home means that the complex and demanding routines required by traditional presentations of multi-drug and lyophilised products is no longer up to par. This clear gap in the market is being filled by innovative drug delivery systems and dual-chamber devices, many of which we cover in these pages.

First up we have an exclusive interview with Laxman Halleppanavar of **Credence Medsystems** (Page 8), discussing both Credence's own approach to dual chamber devices based on its signature *Innovation Without Change* approach, and how Credence is tackling the challenges presented by the lack of established fill-finish and production capacity for these new systems throughout the industry. Following that, **Stevanato Group** presents a novel approach to syringe bypass design (Page 14), enabling liquid bypass without introducing a bulge to the syringe; **Windgap Medical** puts forward its dual-cartridge system for multi-drug delivery as a challenge to the dual-chamber model (Page 20); and **SHL Medical** introduces its new Reunite™ dual-chamber three-step autoinjector platform (Page 26).

This issue also features multiple Expert View articles discussing the state of play in dual-chamber systems and the unmet needs they aim to fulfil. First, **Cambridge Design Partnership** provides an overview of the design considerations inherent to two-component injections (Page 32), then **Springboard (Sanner)** takes a deeper dive on lyophilisation and reconstitution approaches (Page 38) and **Lyophilization Technology** contributes further to this topic with extensive expertise in how dual-chamber systems can enhance lyophilised APIs for at-home use (Page 66).

We also present a pair of exciting Early Insights on new approaches in this field. First, **Pacifi** introduces DuoVIAL®, which brings dual-chamber technology beyond injectables and into the topical delivery space (Page 44); and second, **Ampulis** presents a novel configuration for dual-chamber systems that takes a lateral rather than concentric approach (Page 79).

Rounding out the issue, we have multiple contributors bringing supporting technologies for dual-chamber delivery into the spotlight. **BD** walks us through the design process for a novel valve component specifically designed to enable dual-chamber functionality in standard prefillable syringes (Page 54); **Vetter Pharma** takes a closer look at the lyophilisation process itself (Page 62); **Contexo** discusses the value that laser technology can bring to dual-chamber device manufacturing (Page 50); and **Phillips Medisize** presents a thorough discussion on how the administration of multi-component formulations can potentially be improved through the use of electromechanical delivery technology (Page 72).

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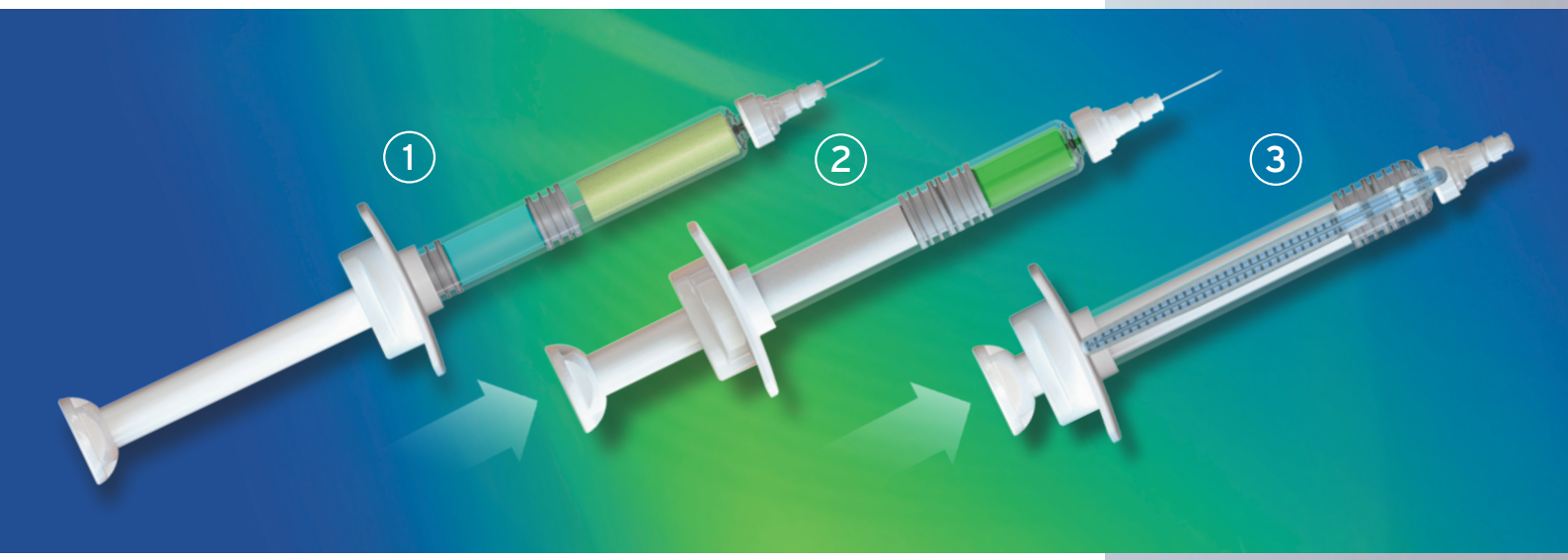

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Interview: Unlocking the Pent Up Demand for Dual-Chamber Delivery Systems

In this exclusive interview, **Laxman Halleppanavar** of **Credence MedSystems** and ONdrugDelivery's Guy Furness discuss industry trends and challenges with injectable delivery, and how Credence's dual-chamber devices provide solutions to address those challenges. Mr Halleppanavar goes into details of Credence's role in this increasingly important sector of the drug delivery market, explaining the company's approach to device design, development and overcoming the barriers posed by supply chain management.

Q To open, can you tell me what you see are the main industry trends and external environmental factors that are posing challenges to injection delivery systems?

A Starting with some general industry trends, the first ones that come to mind are pharma embracing heightened sustainability goals, patient-centric care and transitioning more treatment away from formal healthcare settings to at-home administration. This is pretty evident these days for many drug categories.

Another important trend stems from the rising use of biologics, including long-acting drugs, which is driving demand for higher delivery volumes and increasing concentration, impacting drug product viscosities. Furthermore, certain therapeutic areas have increasing requirements on higher dose accuracies with low volumes.

Something else you might have noticed is that manufacturing capacity constraints are having an impact at pharma companies' own sites, especially with glucagon-like peptide-1 receptor agonist (GLP-1) drugs. As a result, we're seeing significant movement of manufacturing towards CDMOs. These companies are having to expand to meet demand, which is driving higher lead times for equipment manufacturers.

Moving on to some key external factors that are posing challenges to injection delivery systems. The first one that springs to mind is increasing regulatory scrutiny and evolving guidelines – this has been particularly noticeable in the area of combination products over the last few years. Everybody's learning, including the regulators, so it's critical to pay attention to upcoming and draft guidelines and how they're impacting the industry. For example, EU Annex 1 compliance, which is focused primarily on drug filling, is putting pressure on the cost of drugs even as governments are trying to push the cost of medications down, creating both a push and pull simultaneously that the industry needs to navigate. There's an increased level of supply chain volatility that we're seeing due to geopolitical pressures, which is creating significant pressure on manufacturing costs.

Alongside that, you've got the question of upcoming intellectual property and patent cliffs, which increases the need for pharma companies to demonstrate product differentiation. Based on the current state of the market, this has to be one of the key considerations for pharma companies going forward.

"WHEN IT COMES TO MORE COMPLEX INJECTABLE THERAPIES, THE MOVE TO AT-HOME SELF-ADMINISTRATION DOES POSE INCREASED RISK TO LESS EXPERIENCED USERS BECAUSE EXISTING VIAL KITS CAN BE COMPLICATED AND UNINTUITIVE TO USE."

Q These are certainly changing times, presenting challenges but also opportunities and demand for innovative approaches, which leads us to the next question. What are the trends and challenges driving the need for dual-chamber syringe systems specifically?

A Well, there's an overlap with some of the general trends we've just discussed. But, focusing on dual chamber specifically, the critical drivers are the move from formal healthcare settings to at-home administration and the increasingly complex formulations being developed. The benefits of this move to the home are myriad and well-documented, both for patients and for healthcare systems. However, when it comes to more complex injectable therapies, the move to at-home self-administration poses increased risk to less experienced users because existing vial kits can be complicated and unintuitive to use, especially with therapies that involve multiple liquids or require reconstituting a lyophilised drug.

That neatly brings me to the other key trend related to dual-chamber devices – an increasing number of therapies are being developed as combinations with each other, leading to liquids that cannot be co-formulated but need to be co-administered. Simultaneously, we're seeing an uplift in the number of low-stability formulations packaged as lyophilised powders, which then require reconstitution at the point of care. These are both increasingly common practices, which is evident from the volume of vial kits being produced. These factors complicate the injection delivery process and introduce

significantly increased opportunities for user error compared with a single injection from a prefilled syringe (PFS) – add to that the increased regulatory pressure demanding that potential dosing errors and contamination be minimised and it becomes clear how a dual-chamber delivery system would offer significant advantages.

Last but not the least, we need to consider pharma's heightened focus on sustainability goals across the three ESG pillars – environmental, societal and governance – a major factor of which is waste reduction. This means eliminating the waste in terms of overfilling vials or needing to provide multiple vial kits to patients, each of which includes multiple vials, multiple syringes, multiple swabs, etc. Compare that with a single prefilled dual-chamber syringe and it is self-evident which option best aligns with sustainability goals.

Laxman Halleppanavar

Head of Portfolio Strategy and Management

E: lhalleppanavar@credencemed.com

Laxman Halleppanavar is the Head of Portfolio Strategy and Management at Credence MedSystems, leading the Injectable Device Portfolio Strategy and Management team for internal and external customer endeavours. Previously, Mr Halleppanavar was the Director and PharmSci Technical Team Lead at Pfizer. He came to Pfizer upon its acquisition of Hospira where Mr Halleppanavar was responsible for combination product development from early-stage development to manufacturing scale-up leading to commercial launch. Prior to Pfizer, Mr Halleppanavar was the Program Manager at GE Healthcare Monitoring Solutions leading development, manufacturing, service engineering and commercialisation of multiple medical devices and patient monitoring platforms – namely, patient-worn devices, blood pressure cuffs, bedside monitoring devices and networked central and remote monitoring stations.

Q What are the key features of the Credence Dual Chamber system and its adjacent technology offerings?

A The Credence Dual Chamber Syringe System offers four configurations – liquid-liquid sequential, liquid-liquid reconstitution, lyo-liquid reconstitution and powder-liquid reconstitution (Figure 1). Then, within those four main configurations, there is scope for multiple variations. That's the core of our technology.

Building on what we were discussing before, we've ensured that the Credence Dual Chamber is very simple to use, as the usability remarkably approaches that of a standard single-chamber PFS. With a simple push down on the plunger, you mix the contents in the syringe itself in a single step, eliminating the complexity inherent to vial kits. You don't need a lot of training there. Furthermore, there is an audible click at the end of the dose, with a simultaneous tactile sensation, to indicate that the complete dose has been delivered.

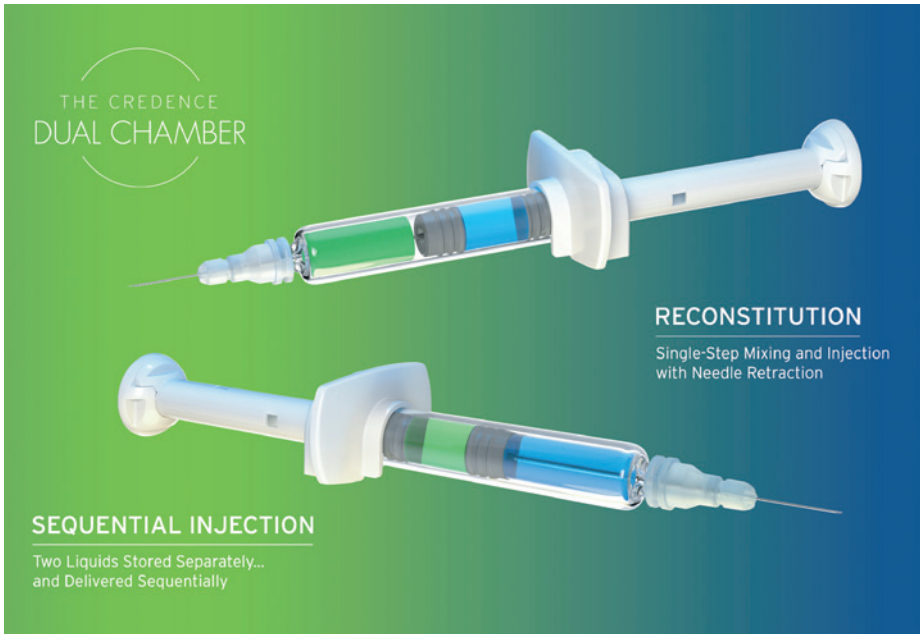

Figure 1: The Credence Dual Chamber System is available in four configurations – liquid-liquid sequential, liquid-liquid reconstitution, lyo-liquid reconstitution and powder-liquid reconstitution.

The Credence Dual Chamber uses standard ISO class syringe barrels offered by the leading manufacturers. Building on that, the Credence Dual Chamber is offered in two main formats – a retractable passive needle safety system and a standard Luer lock connection. The system is designed to work with a wide range of volumes, from 1 mL up to 100 mL, or even 200 mL in some extreme applications.

"THE CREDENCE DUAL CHAMBER IS OFFERED IN TWO MAIN FORMATS – A RETRACTABLE PASSIVE NEEDLE SAFETY SYSTEM AND A STANDARD LUER LOCK CONNECTION."

Another important facet to note here comes from the human factors (HF) studies that have been conducted comparing our Sequential Dual Chamber System with a standard single-chamber PFS. When you take a single-chamber PFS, you just push the plunger rod and the drug gets delivered – simple. The same is true of our Sequential Dual Chamber System, except two different liquids are delivered. What we've seen in our HF studies is that users have no preference for the single-chamber standard PFS compared with the Credence Sequential Dual Chamber Syringe. That's extremely significant, demonstrating that in this case, you get two liquids delivered for the 'price' of one.

We also have some key adjacent technologies, one of which is focused on giving the user more control of the injection. To address this, we're developing a Manual Injector, which essentially encapsulates a dual-chamber syringe in ergonomically friendly housing. The result is a system that performs many of the duties of an autoinjector, such as being user-friendly, needle guarding and end-of-dose cues, but maintains the control of the injection with the user and achieves more economical cost targets.

Complementary to that, we are developing a more traditional autoinjector that integrates with our Sequential Dual Chamber System. This is a collaboration with Cambridge Design Partnership (Cambridge, UK), and we are thrilled to say that the design won a Red Dot technology award for 2025 (Figure 2). Having a range of options all built off the Credence Dual Chamber – a PFS, manual injector and autoinjector – gives customers real flexibility in finding the dual-chamber solution that best fits their user needs, all while enabling faster development timelines and reduced cost.

Figure 2: Credence's Red Dot 2025 award-winning autoinjector, which integrates Credence's Sequential Dual Chamber System and 3 mL Companion Syringe.

"FORMULATION SPECIALISTS WITHIN THE PHARMA COMPANIES MAY NOT HAVE FULL EXPOSURE TO WHAT'S OUT THERE – IN MANY CASES THEY MAY NOT KNOW THAT THE IDEAL SOLUTION IS ALREADY AVAILABLE WAITING TO BE ADOPTED, SO IT'S CRITICAL FOR TECHNOLOGY DEVELOPERS TO INCREASE AWARENESS OF WHAT'S AVAILABLE."

Q What have been the barriers preventing pharma companies from adopting dual-chamber systems?

A One of the major barriers is that historical dual-chamber systems have not had the usability or the inherent safety to allow easy and proper administration of these medicines that require mixing at the time of use. The conventional approaches required a full autoinjector device around the primary package to allow use, and the number and complexity of use steps was still onerous. The devices weren't ready.

But neither was the infrastructure in the supply chain. Thus far, the industry hasn't had established "mainstream" dual-chamber fill-finish capabilities available to pharma manufacturers. I think it's fair to say that the understanding of the dual-chamber opportunity has in the last couple of years really started to gain significant momentum. In order to enable the opportunity for dual-chamber delivery systems to be unlocked, a broader availability of CDMO fill-finish capability is needed (Figure 3).

There also may be some unfamiliarity within broader pharma organisations regarding the advancements in drug delivery systems that the industry has been

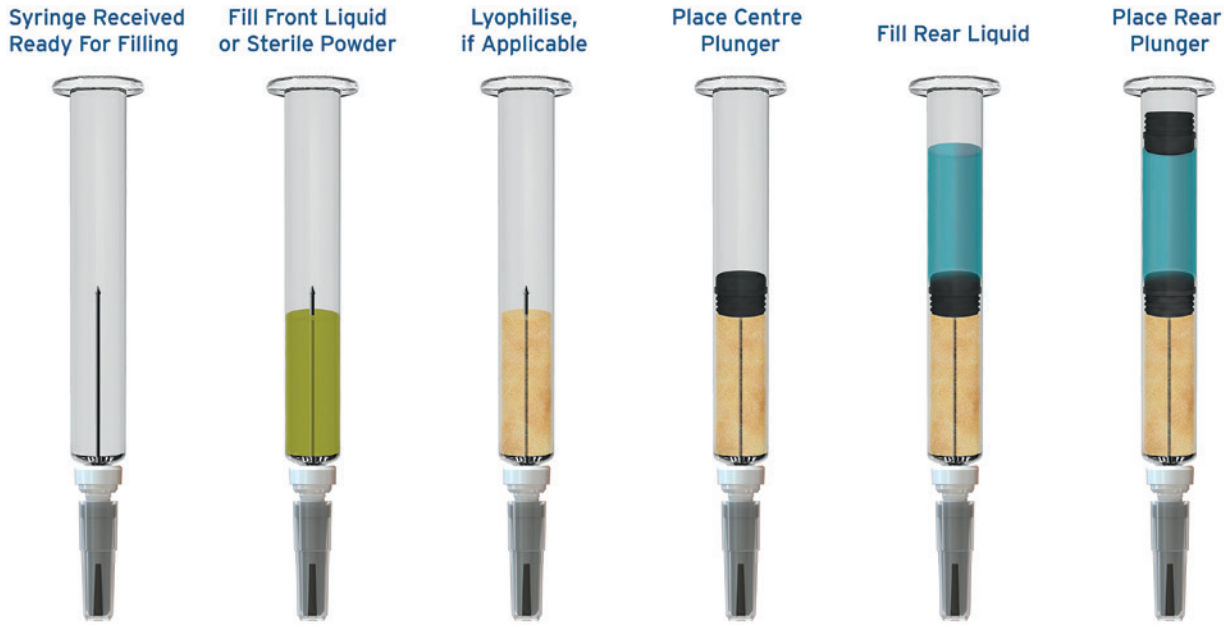

Figure 3: The Credence Dual Chamber Syringe enables broader fill-finish options from CDMO partners.

developing, and dual-chamber systems are no exception. Generally speaking, formulation specialists within the pharma companies may not have full exposure to what's out there – in many cases they may not know that the ideal solution is already available waiting to be adopted, so it's critical for technology developers to increase awareness of what's available. On top of that, pharma's conservative nature plays a role. The classic approach has led to lifecycle strategies where pharma progresses to initial approval and launch with an inferior delivery system, only considering advanced systems later, rather than implementing superior solutions, such as dual-chamber systems, initially.

If we're going to see wide-scale adoption of dual-chamber technologies, we're going to need to develop and demonstrate supply chain readiness – for pharma to proceed in the required investments to implement these systems, they will want to know that there is a direct and believable path with the device ready to go and the supply chain established and secure.

Q What role has Credence assumed in enabling dual-chamber solutions to address these unmet needs?

A At our core, Credence MedSystems is an innovator and supplier of problem-solving injectable drug delivery systems. So, our first role is in developing and providing a great dual-chamber platform that addresses the needs of our pharma customers and end-users.

But a delivery system without a means of turning it into a combination product is only half of a solution. Therefore, Credence is taking the lead in enabling development of the dual-chamber fill-finish supply chain readiness by engaging with leading equipment manufacturers and CDMOs (Figure 4). That's a key part of my role at Credence – I collaborate and partner with CDMOs and equipment manufacturers to make sure that dual-chamber capacity is being built up.

These kinds of partnership are critical for bringing pharma on board. By establishing partnerships and building up supply chain readiness, we're reducing the risk for pharma companies, which is one of the key barriers stalling pharma from implementing dual-chamber systems more broadly – it's a classic chicken and egg scenario.

Exactly to this point, we are so pleased to announce a collaboration with SMC Pharma Services (Cambridge, UK) for implementation of dual-chamber fill-finish readiness. The first focus is on implementing the capability for clinical supply, followed by commercial implementation. We will be ready to share more information soon. By taking on some of the initial investment and demonstrating the path to dual-chamber filling, we are making it that much easier for pharma to understand the business case. This approach also enables us to engage with multiple pharma companies, establishing what I call a syndicate relationship, where several partners come together for mutual benefit.

Credence's technology is focused on the concept of "Innovation Without Change". This means providing new solutions using existing infrastructure and components. Innovation Without Change is about enabling pharma to use their preferred off-the-shelf primary containers,

Figure 4: Credence is an enabling link for implementation of dual-chamber fill-finish.

which Credence then turns into dual-chamber systems. It is also about enabling these delivery systems to be filled by a network of CDMOs to unlock the potential in the market.

It's going to take successes from the early adopters to fully shift the dial. Once those products start gaining traction in the market, I think we'll see pharma's comfort expand. Then, when that awareness starts to build and other pharma see that dual chamber is here, there'll be a big shift towards dual-chamber solutions.

Q Finally, in summary, what would you say is the key takeaway message you'd like to send to pharma regarding adopting dual-chamber technology?

A First and foremost, Credence's dual-chamber systems are elegant and flexible solutions that simplify user steps, offer end-of-dose user cues, enhance dosing accuracy and provide safety features. Second, because the Dual Chamber employs very simple user steps, it promotes adherence and enables at-home administration of complex drugs and encourage patients to keep up with their treatment. This is not only better for patients but better for pharma, as it provides a key differentiator in a crowded market.

Furthermore, it's not just one product but rather a foundation for a series of presentations to support various use cases and lifecycle strategies. Credence offers a flexible range of adjacent technology solutions, including the manual injector and autoinjector. Looking to the future, we have the scope to expand this offering into additional technologies, such as connectivity. This means that we can meet a wide range of patient needs and tailor our technology to address the challenges of the specific application.

The last major takeaway is our collaboration with SMC that I touched on previously. This partnership is a great step in enabling pharma to implement dual-chamber solutions. We welcome pharma partners to collaborate with us in a joint partnership with SMC. It's a proud and exciting moment for us. All we have talked about is consistent with Credence's ongoing efforts to solve challenges facing injectable drug delivery, on behalf of our pharma customers and the patients and end users we all endeavour to help.

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TWO INTO ONE: SOLVING COMPLEX DRUG DELIVERY PROBLEMS WITH DUAL-CHAMBER CONTAINMENT SOLUTIONS

Enrico Barichello and **Valerio Ravazzolo**, both of **Stevanato Group**, describe how dual-chamber solutions ensure isolation, integrity and safety for managing lyophilised and liquid drugs. With innovative and customisable designs, these technologies improve drug delivery, reduce contamination risks and simplify complex therapies, addressing the evolving needs of both pharmaceutical industry and patients.

At the point of delivery, an injection is a fundamentally simple act – within a single process, the contents of a cartridge or syringe are expelled under force through a needle via the skin.

Advances in injectable technology have simplified this task further, in some cases even removing the requirement for administration to be carried out by a healthcare professional and handing responsibility to caregivers and patients themselves. By doing so, these methods enhance patient convenience and help to maximise the likelihood of sustained adherence to the dosing regimen.

However, not all injections are necessarily so straightforward. In some contexts, this process is complicated by a range of fixed parameters. For example, a drug might be lyophilised in the interests of shelf life and stability, but must undergo a process of reconstitution into suspension or solution before it can be injected. Alternatively,

"DEVELOPED IN EITHER CARTRIDGE OR SYRINGE FORM, DUAL-CHAMBER CONTAINERS PROVIDE A PLATFORM FOR ACCOMMODATING TWO INJECTABLE ELEMENTS THAT NEED TO BE KEPT SEPARATE UNTIL THE POINT OF USE."

in the case of combination therapies, multiple drugs might need to be delivered concurrently but are not co-formulated into a single integrated product. In these instances, the desire for accuracy in dosing, simplicity in delivery and even the possibility of self-administration remain constant, but important challenges must be overcome for these ideals to be realised.

A SINGLE CONTAINMENT SOLUTION FOR SEPARATE INJECTABLE ELEMENTS

A frequently effective solution to this conundrum is the use of dual-chamber containment systems. Developed in either cartridge or syringe form, dual-chamber containers provide a platform for accommodating two injectable elements that need to be kept separate until the point of use, whether in the form of liquid–liquid drug product combinations or lyophilised powders that need to co-exist with a diluent for reconstitution immediately prior to delivery. In either case, containing the two entities together enables the patient to undergo a coherent and measured injection process, making a potentially complex scenario far more simple, streamlined and convenient (Figure 1).

Demand for dual-chamber containment solutions has grown in line with advances in treatments for a wide range of indications, including growth hormone therapy, diabetes and schizophrenia.[1] The dominant growth area, however, is weight management, where the dynamic rise in glucagon-like peptide-1 (GLP-1) receptor agonists continues unabated and co-administered drugs offer the potential to further increase their efficacy.

Combination therapies of this type must accommodate a range of factors, from the chemical stability of different drugs to the timing of delivery and patient usability. In some cases, the obligation to satisfy these limiting parameters can lead to an undesirable situation where patients must receive two separate injections of products that serve a complementary purpose. Dual-chamber containment systems offer a way to reconcile these factors by enabling the two distinct components to remain physically separate within a single delivery container until the point of administration.

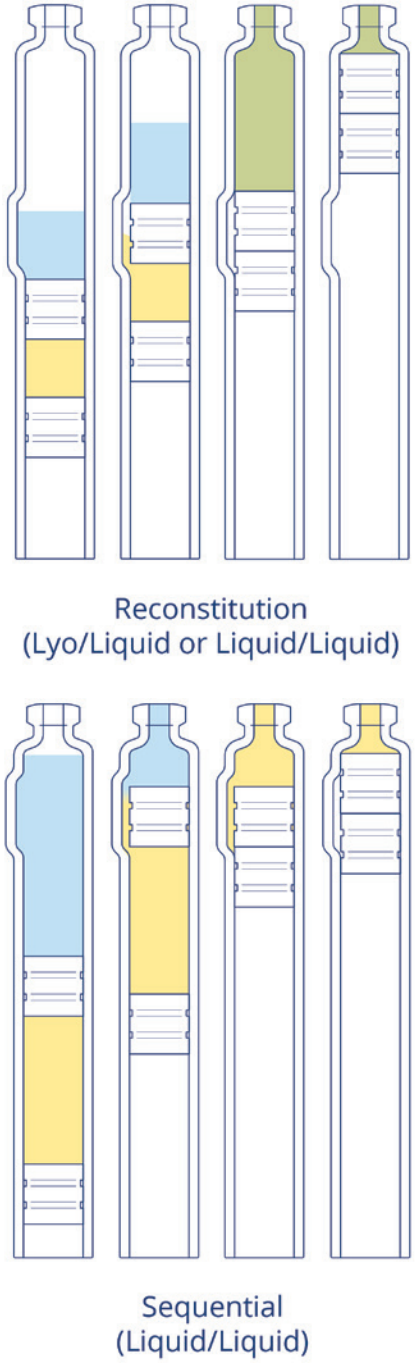

Figure 1: Dual-chamber containers can enable two delivery configurations: premixing and reconstitution of the drug product or sequential injection of two drug liquid products.

A PLATFORM FOR BYPASSING CO-FORMULATION AND SIMPLIFYING RECONSTITUTION

For combination therapies where two agents must be delivered simultaneously but cannot be co-formulated due to chemical incompatibility or regulatory constraints, dual-chamber formats enable drug integrity and efficacy to be maintained without the need for a patient to undergo multiple injections. At the same time, they effectively circumvent the co-formulation process, which, if it is even possible, can extend timeframes and result in higher costs.

> "EMPLOYING A DUAL-CHAMBER INJECTION SYSTEM SIMPLIFIES THE INJECTION BY INTEGRATING THE RECONSTITUTION STEP INTO A MORE COHERENT, MANAGEABLE AND UNIFIED PROCESS."

Alternatively, where drugs are formulated in a lyophilised format, the requirement for reconstitution requires that multiple additional steps are completed before a patient can be injected or self-inject. Lyophilisation can be crucial to ensure that stability and potency are protected throughout the shelf life of a drug, which might otherwise degrade in aqueous suspension – an issue particularly associated with delicate biologics. Reconstitution, however, introduces additional time, complication and risk to the injection process, which, in turn, can compromise patient acceptance, usability and adherence. Employing a dual-chamber injection system simplifies the injection by integrating the reconstitution step into a more coherent, manageable and unified process, making injections not only faster but also reducing the likelihood of administration errors on the part of patients or caregivers.

There are two main containment configurations that are typically used – dual-chamber syringes and dual-chamber cartridges. Each offers specific functional benefits depending on formulation type, delivery route and device integration. Syringes are typically employed for liquid–liquid self-administration scenarios, as might be the case for autoinjectors. Cartridges, meanwhile, are suited to lyophilised–liquid scenarios, as well as

liquid–liquid applications, and are ideal for pen systems and drug delivery platforms where repeated injections are required.

DESIGNED AND ENGINEERED ACCORDING TO DELIVERY REQUIREMENTS

In dual-chamber containment solutions, the design of the barrel structure is critical to the chosen injection process, and careful consideration must be given to both the position of the bypass that facilitates mixing and the position of the middle plunger that separates the two elements. When pre-mixing is required, the bypass is located in the middle of the cylinder barrel. Under pressure, the contents move along the container until the separating plunger aligns with the bypass "bulge". At this point, the first element can enter the bypass and combine with the second element nearest the needle. After mixing is complete, the combined formulation can then be injected as a single dose.

In sequential delivery, where two components must be injected one after the other without prior combination, the bypass is positioned as close as possible to the shoulder of the barrel. Here, the injection force pushes all contents along the container, first dispensing the full dose of the primary liquid. When this phase is complete, the separating plunger will be aligned with the bypass, thus enabling the secondary liquid to be forced around its side for subsequent delivery as part of a single action.

Whether in the case of sequential injection or pre-mixing, both configurations require meticulous engineering from a glass-forming perspective. Specific parameters, such as the volume of the chamber contents and plunger dimensions, will have an impact on the position and length of the bypass required. Factors such as drug viscosity, fluid pressure and glass stress must also be taken into account, as resistance forces will be higher in injection systems employing two plungers. In addition, there can be bespoke customer requirements around plunger selection to satisfy barrier performance and provide sterility assurance, specifically for the separating plunger in contact with two different products. Taken together, the multiplicity of these variables will require a degree of tailoring for the containment solution so that it precisely meets the needs of the application in question.

For lyophilised products, the lyophilised cake must remain physically and chemically isolated during storage, avoiding contact with liquid to prevent activation. As such, the glass barrel and plungers must together maintain a sterile barrier that can endure long-term storage and transportation.

Critical to performance is the seal integrity of each chamber and the ability of the internal plunger to pass through the container without compromising sterility. The reconstitution step must also be both effective and relatively effortless for the end user, while also avoiding the risk of contamination and ensuring even dispersion.

Figure 2: Stevanato Group's internal multi-bypass configuration facilitates transfer between the chambers through the inclusion of multiple, smaller-scale bypass channels.

"REGULATORY SCRUTINY ALSO UNDERLINES THE NEED TO MAINTAIN THE INTEGRITY OF BOTH CHAMBERS AND, INDEED, THE SYSTEM AS A WHOLE."

MAINTAINING INTEGRITY FROM POINT OF MANUFACTURE TO POINT OF DELIVERY

With these considerations in mind, a detailed appreciation of the fill-finish process is required in dual-chamber containment applications. Specifically, there is a clear need to maintain separation between either a lyophilised powder and liquid diluent or two liquid formulations, which can be a technically demanding task. Filling and sealing must also be completed with careful consideration of the potential for both cross-contamination of chamber contents and contamination by the external environment. This is a key reason why cartridges suit lyophilised material, as the container can be filled from the neck, isolating the drug from the activation liquid before freeze-drying takes place. Syringes, however, require filling via the plunger end of the cylinder, potentially bringing powder into contact with upper parts of the cylinder, which should be exclusively reserved for the activator liquid.

Regulatory scrutiny also underlines the need to maintain the integrity of both chambers and, indeed, the system as a whole. Assurances are required of the compatibility between materials and the avoidance of contamination risks, including from extractables and leachables. Dual-chamber systems must also guarantee performance throughout their shelf life, withstanding environmental stress, mechanical handling and prolonged storage while maintaining biocompatibility. In the case of prefilled syringes containing lyophilised drug and diluent, guidelines from the US FDA specifically highlight the importance of ensuring system integrity and undertaking comprehensive drug-device compatibility assessments.[2]

A DIVERSE SERVICE OFFERING DEDICATED TO DUAL-CHAMBER SYSTEMS

The breadth of Stevanato Group's service offering allows the company to address these requirements and manage such complexity via an integrated approach. While centred around the company's proprietary glass-forming technology, its offering is supported by deep expertise in drug containment, including analytical services to de-risk container and device selection, providing confidence from development though launch. The benefits of this approach are exemplified in Stevanato Group's development of a special container bypass design. This configuration complements the company's more traditional dual-chamber container offering, where the addition of the bypass channel manifests as a bulge, laterally extending the container profile. However, with the possibility that this asymmetric profile could add burden to handling and processing tasks in fill-finish, or that it could present issues of compatibility in device integration, Stevanato Group has engineered an internal multi-bypass configuration. This option maintains the symmetric, circular container profile while facilitating transfer between the chambers through the inclusion of multiple smaller-scale bypass channels (Figure 2).

These glass engineering capabilities are complemented by Stevanato Group's in-house manufacturing capability, which can accommodate production of bespoke container designs, enabling the company to develop cartridges and syringes in a range of configurations tailored to both drug characteristics and device integration needs. This includes options for liquid-lyophilisation and liquid–liquid formats, with full support for sequential or pre-mix delivery modes. Drawing on its expertise in modern fill-finish optimisation, Stevanato Group is also able to supply dual-chamber containers ready-to-use in its pre-sterilised EZ-fill® configuration. Taken together, these measures all contribute to a streamlining of downstream development, helping accelerate time to market.

TWIN BENEFITS: LIFE-ENHANCING THERAPIES PLUS PATIENT-CENTRIC DELIVERY

Indeed, it is with market-readiness in mind that Stevanato Group's dual-chamber containment offering has evolved to this point. The platform has been shaped not by purely scientific curiosity, but by direct collaboration with pharmaceutical partners navigating today's therapeutic frontiers, where ease of delivery remains paramount for patients in self-administration applications. However, it may be that reconstitution of a drug is required or that co-formulation of two drugs is chemically or temporally unviable.

"DRAWING ON ITS EXPERTISE IN MODERN FILL-FINISH OPTIMISATION, STEVANATO GROUP IS ALSO ABLE TO SUPPLY DUAL-CHAMBER CONTAINERS READY-TO-USE IN ITS PRE-STERILISED EZ-FILL® CONFIGURATION."

In these scenarios, dual-chamber containers offer an elegant, adaptable and pragmatic method for solving a potentially challenging equation. Consolidating multiple preparation steps into a single injection motion supports dosing accuracy, reduces errors and enhances adherence to therapies that might otherwise require clinical oversight. And, as care continues to shift increasingly towards personalised medicine and patient-centric delivery, dual-chamber solutions look set to play an ever more important role in enabling complex, innovative therapies to be matched by simple, safe and effective delivery at the point of need.

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Enrico Barichello

Enrico Barichello, Product Manager, Syringe Platform, Stevanato Group, holds a master's degree in Industrial Engineering from the University of Padua (Italy). Since joining Stevanato Group in 2017, Mr Barichello has worked closely with cross-functional teams to define and execute the roadmap for new products, including the Alba® platform. Since 2023, he has overseen the glass syringe platform, and as of January 2025, he also manages the polymer syringe platform, driving innovation and growth across Stevanato Group's syringe portfolio.

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Valerio Ravazzolo

Valerio Ravazzolo, Product Manager, Cartridge Platform, 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, 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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SOLVING COMPLEX DRUG DELIVERY PROBLEMS WITH DUAL CHAMBER CONTAINMENT SOLUTIONS

In drug delivery, every solution is a careful balance - efficacy vs toxicity, patient comfort vs dose volume, and so it goes on. These trade-offs often demand innovative approaches. That's why Stevanato Group offers a cutting-edge dual chamber platform for syringes and cartridges.

Designed to deliver liquid/liquid and liquid/lyo formulations, the platform ensures accurate, convenient administration - empowering pharma partners to meet complex therapeutic needs with confidence.

Ease of Use

Simple Administration

Increased Patient Safety

Stable Storage

Stevanato Group

MANAGING COMPLEXITY, DELIVERING VALUE

stevanatogroup.com

BEYOND THE BARREL: A DUAL-CARTRIDGE IMPROVEMENT TO TRADITIONAL DUAL-CHAMBER DEVICES

windgapmedical

Dr Brent Buchine of **Windgap Medical** explores how the company's devices transform dual-chamber systems with a modular, scalable and remarkably simple approach to reconstitution and complex drug delivery.

HAVE DUAL-CHAMBER DEVICES HAD THEIR DAY?

Monoclonal antibodies. Depot suspensions. Long-acting biologics. As R&D pipelines swell with increasingly complex injectable therapies, so does the need for delivery systems that can administer them safely, simply and swiftly at the point of care.

However, while drug formulations have advanced, many of the delivery systems supporting them have not. Once considered a breakthrough, traditional dual-chamber cartridges (DCCs) – glass barrels separated by stoppers with internal bypasses – are now becoming a bottleneck. Their rigid formats, intricate filling and assembly requirements and limited

"THE INDUSTRY IS AT A TURNING POINT. THE DELIVERY SYSTEMS THAT ONCE REDUCED COMPLEXITY ARE NOW INTRODUCING IT. FOR BIOPHARMA TEAMS ADVANCING THE NEXT GENERATION OF INJECTABLES, THIS SHIFT DEMANDS MORE THAN A RETROFIT."

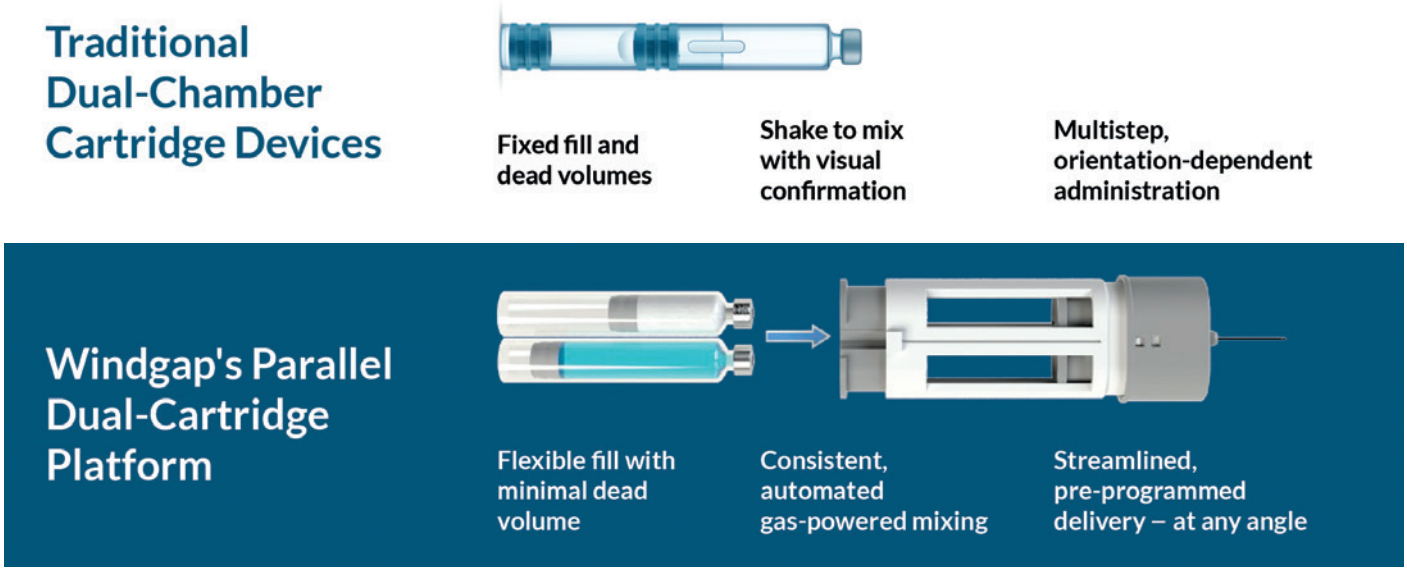

Figure 1: Side-by-side comparison of traditional DCC and Windgap dual-cartridge architectures.

capacity can slow down development, drive up costs and frustrate end-users.

At the same time, dual-chamber pens and autoinjector platforms face their own constraints, often requiring manual shaking, awkward orientations and complicated steps that introduce new risks for patients and providers alike.

The industry is at a turning point. The delivery systems that once reduced complexity are now introducing it. For biopharma teams advancing the next generation of injectables, this shift demands more than a retrofit. It calls for a fundamental reimagining of delivery architecture, designed to meet modern development demands and patient realities, side by side.

THE CASE FOR EVOLVING THE DUAL-CHAMBER STANDARD

Traditional DCCs were designed to solve a specific problem – shelf life. They do so by storing a lyophilised drug and diluent separately in a single container until the moment of administration. But as therapies grow more complex, this seemingly simple platform introduces friction at nearly every stage of the drug lifecycle.

- **Formulations Face Physical Limitations:** With drug and diluent housed end to end, teams must work within fixed volumes and ratios dictated by the cartridge's geometry. This restricts design options and can force compromises in concentration, viscosity, sequencing or dead volume – making difficult trade-offs common in early development.

- **Manufacturing Requires a Multistep Fill Process:** Where each chamber must be filled, lyophilised, stoppered, filled again and stoppered again, all within a single glass barrel. This sequence demands specialised equipment not widely available in most facilities in addition to uncommon tooling and stringent process controls, all of which extend production timelines and drive up the cost of goods.

- **Supply Chain Constraints Introduce Added Vulnerability:** Only a small number of vendors supply DCCs at commercial scale and even fewer are equipped to fill them. This scarcity, which shows no signs of abating, can further extend lead times and elevate risk, especially for lean teams managing global supply chains or scaling to commercial volumes.

- **The Device Itself:** To mix and deliver the drug, DCC-based devices must break internal stoppers and often rely on manual shaking and sometimes strict orientation requirements. When even minor complexity introduces risk, every additional step, component and second can detract from usability and adherence.

While DCCs have played a significant role in extending the application of injectables, the real challenge is the container, with the complexity extending to the formulation, filling and delivery of the drug.

THE PARALLEL DUAL-CARTRIDGE ADVANTAGE

Windgap Medical approaches this challenge from a new angle, literally and architecturally. Instead of filling two stacked substances into a single, complex primary drug container, Windgap uses two standard – and widely available – single-chamber cartridges positioned side by side (Figure 1).

By reimagining both the delivery system and the surrounding ecosystem, Windgap creates opportunities for innovation throughout the product lifecycle.

- **Formulation Freedom:** Side-by-side geometry removes the constraints of a single, fixed barrel. Teams can mix and match cartridge volumes, contents and timing to support a wide range of drug characteristics from high-viscosity biologics to staged or sequential therapies. This architecture enables flexible dosing, tailored reconstitution and novel delivery strategies that traditional DCCs cannot support.

- **Manufacturing Manageability**: Each cartridge can be filled independently, with diluents on standard liquid filling lines and lyophilised drugs via protocols similar to vial-filling operations. With fewer integrated steps and no need for custom DCC tooling, the fill-finish process is, by design, easier to validate, less expensive to operate and more adaptable for partners and production scales.

- **Supply Chain Flexibility**: Windgap's platform uses ISO-compliant cartridge formats available from multiple vendors, many being offered in ready-to-use configurations in a variety of sizes. This expands sourcing options, shortens lead times and streamlines scale-up across manufacturing partners and sites.

- **Smarter Device Mechanics**: Instead of relying on internal plungers, springs, or user effort, Windgap's gas-powered devices allow for reciprocated flow, controlled injection sequencing and instant reconstitution. Full reconstitution protocols can be validated without requiring shaking, swirling or visual guesswork.

Feature	Traditional Dual-Chamber Cartridge	Windgap's Parallel Dual-Cartridge
Cartridge Type	Complex dual-chamber glass cartridge	Two standard single-chamber cartridges. (1, 1.5, 3 & 5 mL)
Filling Complexity	High: fill, lyophilise, stopper-in-place, fill, stopper	Low: separate liquid fill and lyophilisation
Component Supply	Limited vendors, long lead times	Standard formats from multiple suppliers
Device Integration	Single-axis mechanics with complex timing and orientation issues	Parallel fluid paths, fewer moving parts
Reconstitution Flexibility	Low: fixed geometry	High: tuneable for diluent or cake geometry
Manufacturing Cost	Higher: complex processes and controls	Lower: standard lines, decoupled processes
Risk During Scale-Up	Higher: long validation cycles	Lower: modular assembly, standard inputs
Injection Force Efficiency	Constrained by inline geometry	Optimised for multi-cartridge force balance
Device Size	Long form factor due to single barrel	Compact layout with improved ergonomics

Table 1: Comparing technologies – Windgap dual cartridge versus traditional DCCs.

The result is a dramatically improved user experience. Completion and proper mixing can be validated. Drugs can be delivered in as few as two steps with no orientation constraints and with clear feedback on successful drug delivery. For patients and providers alike, the result is greater confidence, lower training burden and fewer opportunities for error. Table 1 presents a side-by-side comparison. The technology has pushed the boundaries of what is possible with formulations, feasibility studies and the potential of the platforms.

ARCHITECTURE MEETS APPLICATION

Windgap's parallel cartridge architecture powers a portfolio of delivery platforms, each purpose-built to meet distinct formulation and delivery needs.

DualFlo™: Simplified Sequential Dosing

DualFlo is designed for therapies that require two liquid components to be injected in a specific sequence that cannot be stored together in the same primary packaging. This compact, single-use device delivers the contents of both cartridges through a single needle, in a prescribed order, without requiring multiple devices, needle pricks or added user steps. DualFlo can also support high-volume injections, enabling a full 6 mL dose via two standard 3 mL cartridges in just one injection.

OneMix™: The Instant Solution™

Built for highly soluble lyophilised drugs that dissolve rapidly, OneMix is a true two-step autoinjector – simply remove the cap to mix and press the needle shield to inject. Its simplicity, compact size and single-use format make it ideal for field settings and self-administration of lyophilised therapies. Behind its intuitive simplicity is complex precision. OneMix's gas-powered mixing and plunger-speed controls are carefully tuned to the therapy and engineered into the device during manufacturing, ensuring consistent delivery of even shear-sensitive biologics, with reduced complexity for the user.

MultiMix™: Complex Mixing, No Shaking

MultiMix is built to handle difficult formulations – including high-viscosity biologics, long-acting injectables and depot suspensions. Its three-step design initiates a pre-set series of gas-powered reciprocation cycles between the two standard cartridges with no shaking required. Once mixing is complete, the device provides a clear signal that it is ready for injection – simply remove the cap and press the trigger against the injection site. By delivering complete, consistent and confident mixing in a fraction of the time, MultiMix eliminates guesswork, prolonged setup and the need for specialised training.

DuraMix™: Reusable, Reliable, Ready for What's Next

DuraMix brings the power of MultiMix into a reusable, electromechanical platform

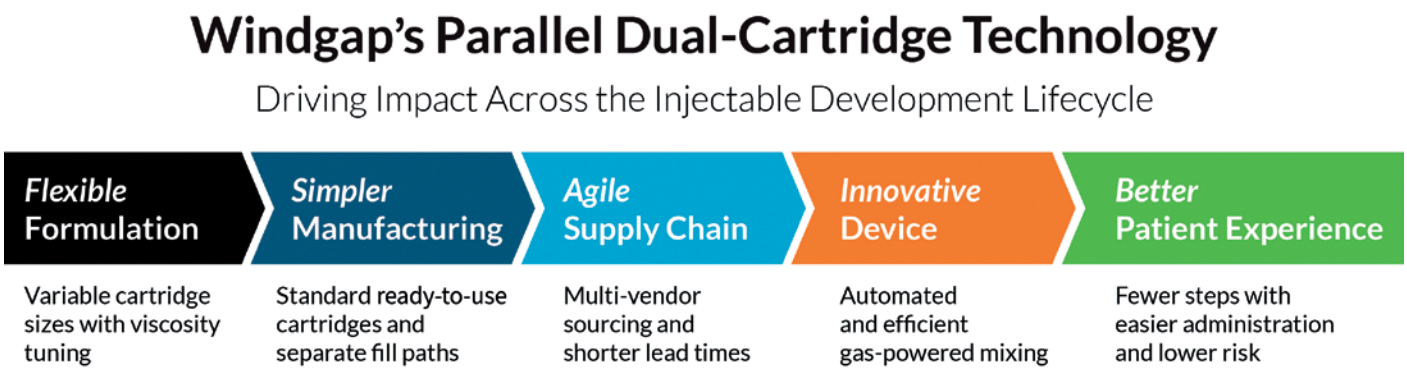

Figure 2: End-to-end advantages of Windgap's parallel dual-cartridge system.

designed for chronic care and digital health integration. With a durable outer housing and a replaceable dual-cartridge subassembly, it delivers a rare combination of flexible configuration, precise control and consistent performance across doses. DuraMix also supports data logging and connectivity – enabling integration with digital health systems, remote monitoring platforms and personalised care protocols.

Windgap's technology provided an unprecedented level of control and improvement, enabling the successful administration of a difficult-to-mix 75 cP suspension through a 29G XTW cannula. This reduced the combined mixing and delivery time by 99%. Such a level of efficiency will have significant implications for complex formulations.

THE SMARTER PATH FROM DEVELOPMENT TO DELIVERY

Windgap's dual-cartridge platform is not just a mechanical improvement – it is a lifecycle advantage, designed to reduce development and manufacturing friction from formulation to final dose (Figure 2).

"WINDGAP'S DUAL-CARTRIDGE PLATFORM IS NOT JUST A MECHANICAL IMPROVEMENT – IT IS A LIFECYCLE ADVANTAGE, DESIGNED TO REDUCE DEVELOPMENT AND MANUFACTURING FRICTION FROM FORMULATION TO FINAL DOSE."

- **Early Development – Flexibility and Forward Progress:** Standard cartridge formats allow formulation teams to iterate quickly and run preclinical studies without the need to lock complex packaging. Reconstitution steps can be validated early, accelerating regulatory filings and the path to first-in-human trials.
- **Manufacturing – Streamlined and Synchronised:** As drug and diluent are filled separately, teams can work across an established, trusted and validated supply base – easing co-ordination with CDMOs and minimising delays.
- **Commercialisation – One Format, Many Front Doors:** Having a common dual-cartridge platform makes it easier to launch device variants for multiple indications, dosing regimens and patient populations – without starting from scratch. This reduces the time to market, cost of goods, complexity and overall risk.
- **Patient and Provider Use – Simplicity that Scales:** Most importantly, these devices are designed with the end-user in mind. Both patients and healthcare providers benefit from fewer steps, shorter preparation times and less opportunity for error. This leads to lower risk and improved outcomes, whether they're at a clinic, a kitchen table, or anywhere in between.

Few platforms deliver measurable benefits across development, manufacturing and user experience. Windgap's does, by design.

CONTAINING COMPLEXITY: SOLVING THE NEED FOR MODULAR, SCALABLE AND SIMPLE

Modern injectable therapies are more viscous, more sensitive and harder to deliver than ever before – and the pressure to mix and administer them safely at the point of care is only growing.

Conventional thinking says rising complexity demands more complex devices. In fact, the more challenging the formulation, the more critical it becomes to have a system that simplifies delivery – creating new opportunities for formulation teams, patients and the industry as a whole.

The industry has long sought a platform that does more than deliver drugs. By rethinking the architecture at the core, Windgap's platforms show how a single innovation can streamline formulation, simplify manufacturing, improve sustainability and elevate the patient experience.

By building on the trusted principles of dual-chamber delivery, Windgap's platform evolves a familiar foundation into a modern solution, one designed to meet today's complexity and tomorrow's breakthroughs with greater ease, flexibility and scalability.

Dr Brent Buchine

Dr Brent Buchine is the Co-founder and Chief Business Officer of Windgap Medical. With over two decades of leadership across the life sciences and semiconductor sectors, he brings deep expertise in innovation, technology development and company building. At Windgap, he has played key roles in shaping the company's R&D and product strategy, leading cross-functional teams and establishing strategic partnerships across the pharmaceutical and biotech landscape. A materials scientist by training, Dr Buchine is known for translating breakthrough ideas into impactful products and fostering collaborations that shape the next generation of drug delivery innovation.

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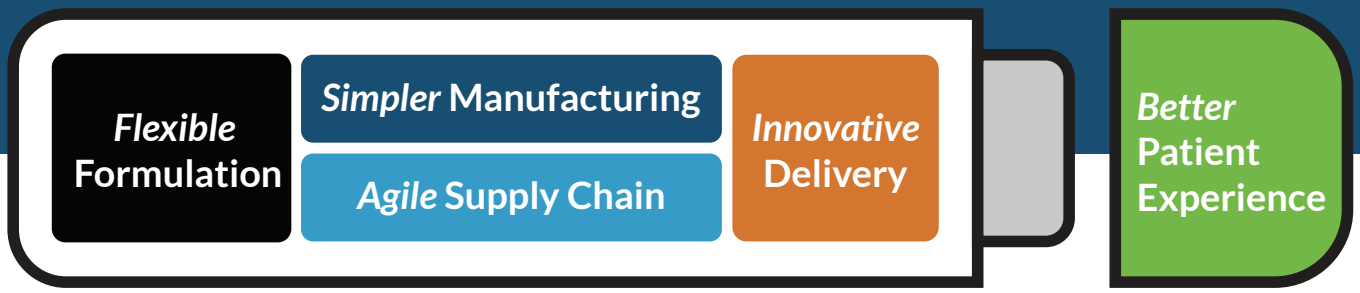
Revolutions start with a single shot.

Windgap's innovative **dual-cartridge** platform streamlines formulation, manufacturing, and delivery—with every device.



- Variable cartridge sizes with viscosity tuning
- Standard RTU cartridges and separate fill paths
- Multi-vendor sourcing and shorter lead times
- Consistent, automated gas-powered mixing and delivery
- Fewer steps with easier administration and lower risk

Discover the proven dual-cartridge difference at windgapmedical.com

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ADVANCING LYOPHILISED DRUG DELIVERY WITH REUNITE™: RECONSTITUTION MADE SIMPLE

SHL MEDICAL

Dr Nina Fetz at **SHL Medical**, introduces Reunite™, the first and only commercialised dual-chamber cartridge, three-step autoinjector featuring the company's Needle Isolation Technology. With automated reconstitution, Reunite enables reliable self-injection of lyophilised formulations, supporting home-based care models.

In today's injectable drug landscape, lyophilisation offers both scientific and strategic advantages. Lyophilisation is essential for the safe and effective use of several biologics and other novel therapies that are unstable in liquid form at their desired storage, shelf life and/or use conditions. A lyophilisation step during manufacturing preserves drug stability, extends the shelf life and maintains therapeutic efficacy.

THE EXPANDING ROLE OF LYOPHILISATION IN MODERN DRUG DEVELOPMENT

Today, approximately one-third of US FDA-approved parenteral medications are lyophilised products,[1] and the global lyophilised drug market is estimated to grow from US$371 billion (£274 billion) in 2025 to $683 billion by 2032[2] – a trend that reflects the continuing importance of lyophilisation in modern pharmaceutical development.

From a financial perspective, although they often involve higher initial manufacturing costs, lyophilised drug products offer long-term advantages.[3] Many liquid formulations depend on cold chain logistics, which account for up to 20% of pharmaceutical logistics costs and exceeded $12.6 billion globally in 2016,[4] creating ongoing operational burden and inventory risks (for example, product loss due to temperature excursions). Lyophilised formulations can reduce these dependencies, enable more flexible storage

and distribution, lower long-term costs and minimise supply chain vulnerabilities. This also brings sustainability advantages, cutting down on energy-intensive cold chain requirements and minimising the carbon impact of distribution.

CHALLENGES IN LYOPHILISED DRUG DELIVERY

Despite this growth and the strategic advantages, the delivery of lyophilised therapies has long been associated with significant usability challenges. Lyophilised products are traditionally presented in vial kits (Figure 1), often requiring separately packaged diluent and a transfer syringe for manual reconstitution. These vial kits typically involve many separate user steps, sometimes 12–15 or more.

The process of reconstituting a drug requires a high degree of knowledge, skill and technique to enable safe preparation and sterile injection. To correctly perform this long sequence, it can be complex, taxing and time-consuming, all of which increase the risk of user error. For these reasons, kits represent a practical barrier to self-administration, as patients may require additional training and healthcare provider (HCP) support.

Recent innovations aim to address these challenges by streamlining preparation. For example, prefilled diluent syringes/vial kits and similar solutions reduce the total number of preparation steps, but do not fully eliminate complexity, as manual reconstitution and handling of multiple components are still required in most applications. In parallel, regulatory bodies are placing growing emphasis on the performance of drug-device combination products, with particular focus on accurate dose delivery,[5,6] protection from sharps injury[7] and post-reconstitution stability.[8]

Figure 1: (A) Traditional vial kit for lyophilised products. (B) The new Reunite™ autoinjector.

To fully realise the potential of next-generation lyophilised therapies, the industry should seek to move beyond traditional multistep kits and manual HCP administration. This shift calls for innovative, patient-centred solutions that are easy to use, support accurate and reliable self-injection, and enable home-based care.

INTRODUCING REUNITE™, AN INTEGRATED APPROACH TO LYOPHILISED DRUG DELIVERY

SHL Medical has responded to these challenges with an integrated system approach, reimagining lyophilised drug delivery as a simple, safe and patient-centred experience.

This vision is realised in Reunite™ (Figure 1), the first autoinjector that integrates reconstitution and administration of lyophilised formulations in one device featuring SHL Medical's Needle Isolation Technology (NIT®).

Reunite became the first autoinjector of its kind to receive marketing authorisation (approved in the US in 2024 and subsequently in the EU, UK and Switzerland in 2025) for the subcutaneous delivery of a lyophilised monoclonal antibody targeting the IL-31 signalling pathway, a central mediator of chronic itch in prurigo nodularis and atopic dermatitis.

Reunite is built around a dual-chamber cartridge (DCC) and uses SHL Medical's proven NIT technology to enable automated reconstitution and injection. As a result, Reunite greatly reduces the total number of user steps, from 12 to 15 required to manually reconstitute down to just three: Unlock, Twist, Push. The autoinjector greatly simplifies the reconstitution process, removing the need for the precise manual technique required when using a traditional vial kit. Its enhanced usability features – which include a locking mechanism, needle safety shield and reduced number of steps – collectively minimise the risk of user error. This ensures more reliable self-administration and therefore greater patient independence. The unique internal design of the Reunite autoinjector is detailed in the next sections.

"REUNITE BECAME THE FIRST AUTOINJECTOR OF ITS KIND TO RECEIVE MARKETING AUTHORISATION FOR THE SUBCUTANEOUS DELIVERY OF A LYOPHILISED MONOCLONAL ANTIBODY TARGETING THE IL-31 SIGNALLING PATHWAY."

Inside Reunite: DCC and NIT

At the core of Reunite is the DCC that functions as the primary container, securely housing the lyophilised drug and its diluent in separate compartments (Figure 2). Upon user activation, a single spring mechanism drives an automated sequence that initiates reconstitution by mixing the contents of both chambers. The lower chamber contains the diluent, and the upper chamber contains the powder. When activated, the diluent moves through a bypass into the upper chamber. This design eliminates manual reconstitution steps, minimises cognitive demand, supports fixed-dose preparation and delivers consistent mixing prior to administration.

To complete the delivery sequence, Reunite features SHL Medical's proprietary NIT technology, which enables safe, automated needle attachment while maintaining full needle concealment before and after use (Figure 3). Integrated into the cap, the sterile cannula pierces the cartridge septum automatically when the cap is twisted off, opening the fluid path without requiring needle attachment by the user, eliminating the risk of needlestick injury and contamination.[9] NIT also provides the drug developer the option to change cannula gauge and length, without implication for long-term drug stability.

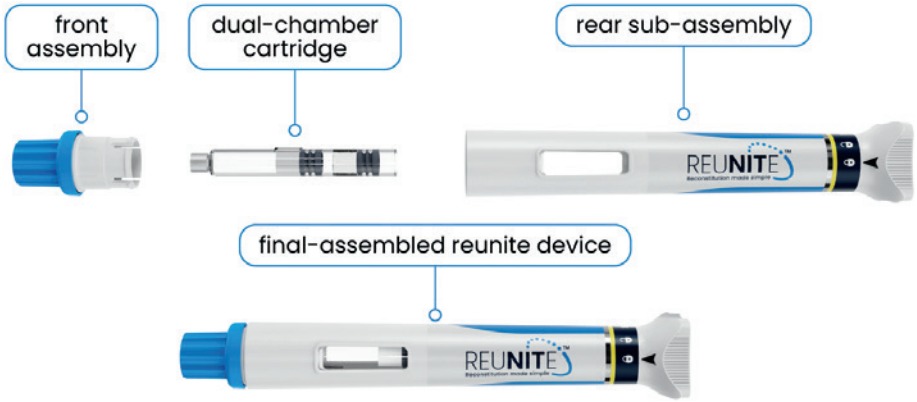


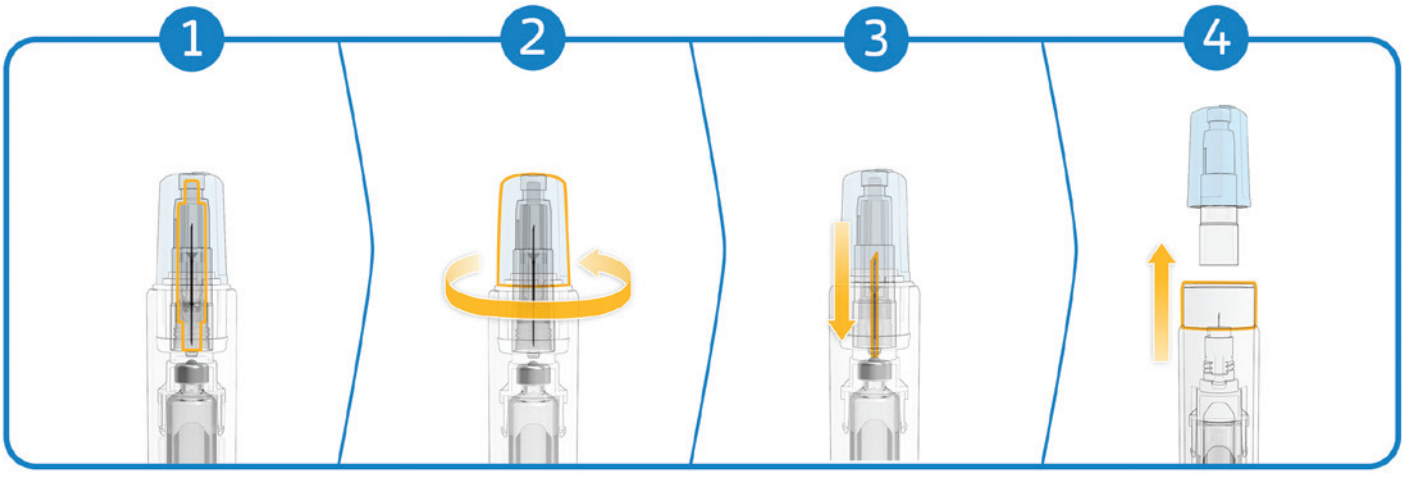
Figure 2: DCC containing lyophilised drug and diluent in separate compartments, enabling automated reconstitution at the point of use.

The first NIT autoinjector was developed for a suspension formulation for type 2 diabetes. First approved in 2017 and commercialised in 2018, it has delivered millions of doses to patients worldwide. In 2019, the NIT autoinjector was selected as the Gold Winner of the Medical Design Excellence Award in the drug delivery and combination products category.

"IN 2019, THE NIT AUTOINJECTOR WAS SELECTED AS THE GOLD WINNER OF THE MEDICAL DESIGN EXCELLENCE AWARD IN THE DRUG DELIVERY AND COMBINATION PRODUCTS CATEGORY."

Reconstitution Made Simple: The Reunite User Experience

By integrating a DCC and NIT into a single device, Reunite transforms the traditionally complex process of lyophilised drug delivery into a simple three-step experience (Figure 4). Upon unlocking the knob (Unlock), the user initiates an automated sequence: the internal spring mechanism drives reconstitution as the diluent mixes with the lyophilised drug. By twisting the cap in a second step (Twist), the user initiates priming and the sterile, pre-attached cannula engages to establish



The closed system.

Twist off the needle cap.

The non-patient end of the cannula moves backward to pierce the cartridge septum and open the fluid path.

Needle cap removed where the needle permanently stays hidden during the injection process.

Figure 3: NIT keeps the needle concealed before and after use, enabling safe, automated needle engagement and drug delivery.

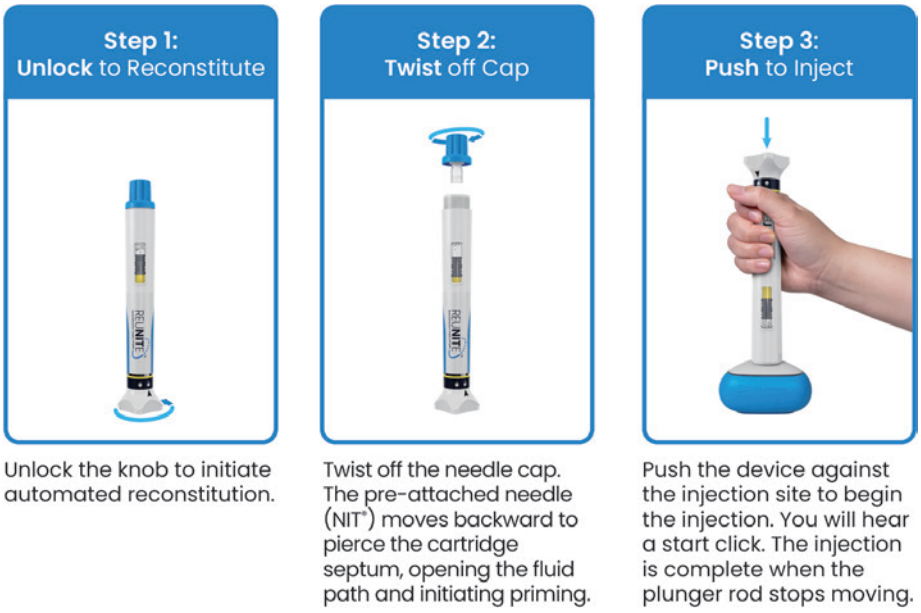


Figure 4. Reunite™ enables a simple three-step user experience: unlock, twist, push. In parallel, the device performs its own drug delivery sequence: reconstitute, prime, inject.

the fluid path. As a final step, the user presses the device against the skin to activate the injection (Push).

Each step has been carefully engineered for simplicity and reliability. There are no separate components to assemble, no manual mixing steps and no exposed needles. Audible feedback at the start of the injection guides the user through the different stages, providing clear reassurance and supporting proper handling.

PARTNERING WITH LYOTECH FOR STREAMLINED PROCESSES

Just as Reunite integrates reconstitution and delivery within a single device, the successful commercialisation of lyophilised therapies depends on the integration between formulation, filling and final assembly processes. Recognising this, SHL Medical has collaborated with leading CDMOs offering lyo-liquid formulation and filling, including Lyophilization Technology, Inc (Ivyland, PA, US). Building on the company's extensive experience in process development for lyophilised products and DCC filling of lyo-liquid combinations, the partnership of SHL Medical with Lyophilization Technology, Inc accelerates the path from formulation to launch while reducing development risks.

THE STRATEGIC VALUE OF REUNITE

Reunite offers pharmaceutical companies a strategic platform to unlock the potential of lyophilised therapies by combining drug stability with simplified self-administration and integrated commercialisation pathways. Built around a DCC and featuring SHL Medical's proprietary NIT, Reunite is the first commercialised dual-chamber, three-step autoinjector to support automated reconstitution and injection in a single device. It delivers value across drug formulation, patient experience, supply chain and time to market. Key advantages include:

- **Expanding Access to Lyophilised Therapies:** Reunite removes historical barriers to the use of lyophilised drugs, such as the need for multicomponent vial kits, manual reconstitution and clinic-based administration, thus driving the commercial viability of therapies that require lyophilisation for stability.
- **Empowering Patient-Centric Self-Administration:** Designed as a three-step autoinjector, Reunite delivers a safe and intuitive user experience. The integrated design reduces total handling steps, conceals the needle, and provides visual and audible cues, empowering patients to self-administer their medication with confidence and minimal training at home.
- **Enhancing Operational Efficiency and Supply Chain Resilience:** Lyophilised stability reduces dependence on cold chain logistics, minimises inventory risks and strengthens the supply chain.
- **Accelerating Development and Reducing Risks:** SHL Medical's expertise in device development and its partnership with LyoTech, an expert in process development for filling lyophilised drugs helps pharmaceutical partners to streamline development timelines, reduce risks and accelerate time to market.

Together, these capabilities position SHL Medical as a strategic partner for pharmaceutical companies seeking to deliver novel therapies safely, efficiently and with a greater focus on the patient experience, making Reunite the platform of choice for lyophilised drug delivery.

"REUNITE OFFERS PHARMACEUTICAL COMPANIES A STRATEGIC PLATFORM TO UNLOCK THE POTENTIAL OF LYOPHILISED THERAPIES BY COMBINING DRUG STABILITY WITH SIMPLIFIED SELF-ADMINISTRATION AND INTEGRATED COMMERCIALISATION PATHWAYS."

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Dr Nina Fetz

Nina Fetz, PhD, is the Senior Customer Solutions Manager at SHL Medical, bringing over eight years of experience in the pharmaceutical and medical device industry. Her expertise spans product development, engineering and strategic management of ready-to-use packaging and drug delivery solutions. Previously, she held key roles, including Global Product Manager for Polymer Solutions, where she strategically managed prefilled sterile syringe systems made from polymer. She holds a Doctor of Natural Sciences in Chemistry from Johannes Gutenberg-Universität Mainz (Germany) and completed an internship at Caltech (CA, US) in Solid State Chemistry. Her research contributions include work on nano-porous cathode materials and crystal structures of inorganic materials. Dr Fetz has been a supporting scientist at leading research institutions, including ESRF and Diamond Light Source.

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Reunite is an **easy-to-use dual-chamber cartridge autoinjector** featuring SHL Medical's **Needle Isolation Technology (NIT®)**, designed to support the **automated reconstitution** and **delivery of lyophilized formulations.**

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DELIVERING COMPLEXITY: DEVICE CONSIDERATIONS FOR TWO-COMPONENT INJECTABLE FORMULATIONS

María FM Balson at Cambridge Design Partnership weighs up strengths and limitations when developing devices for lyophilised injectables, exploring their growing demand and the impacts of formulation, device type and design on the feasibility for bringing a device to market to deliver these essential therapies.

Since the 1980s, when modern-day prefilled syringes (PFSs) and intravenous (IV) bags became prevalent, injectable drug delivery has steadily moved towards ready-to-use formats and integrated devices – as evidenced by the widespread adoption of self-injection devices such as autoinjectors and pen injectors.

Human factors considerations, now recognised as integral to safe and effective use of such drug-device combination products, have driven a clear trend towards simpler, more automated solutions with fewer use steps. This shift has enabled at-home care for more therapies than ever before – a key development given the growing strain on healthcare systems.

Nevertheless, the delivery of certain drugs, such as lyophilised injectables, often remains burdensome and dependent on administration by specially trained professionals. As injectable therapies evolve and become more complex, unique challenges and opportunities have emerged.

TWO-COMPONENT INJECTABLES ON THE RISE

Let's define two-component formulations as those consisting of two parts that, for stability or other reasons, must be kept separate throughout the product's shelf-life, and are delivered together at the point of administration. The two constituent parts may be a solid drug and a liquid

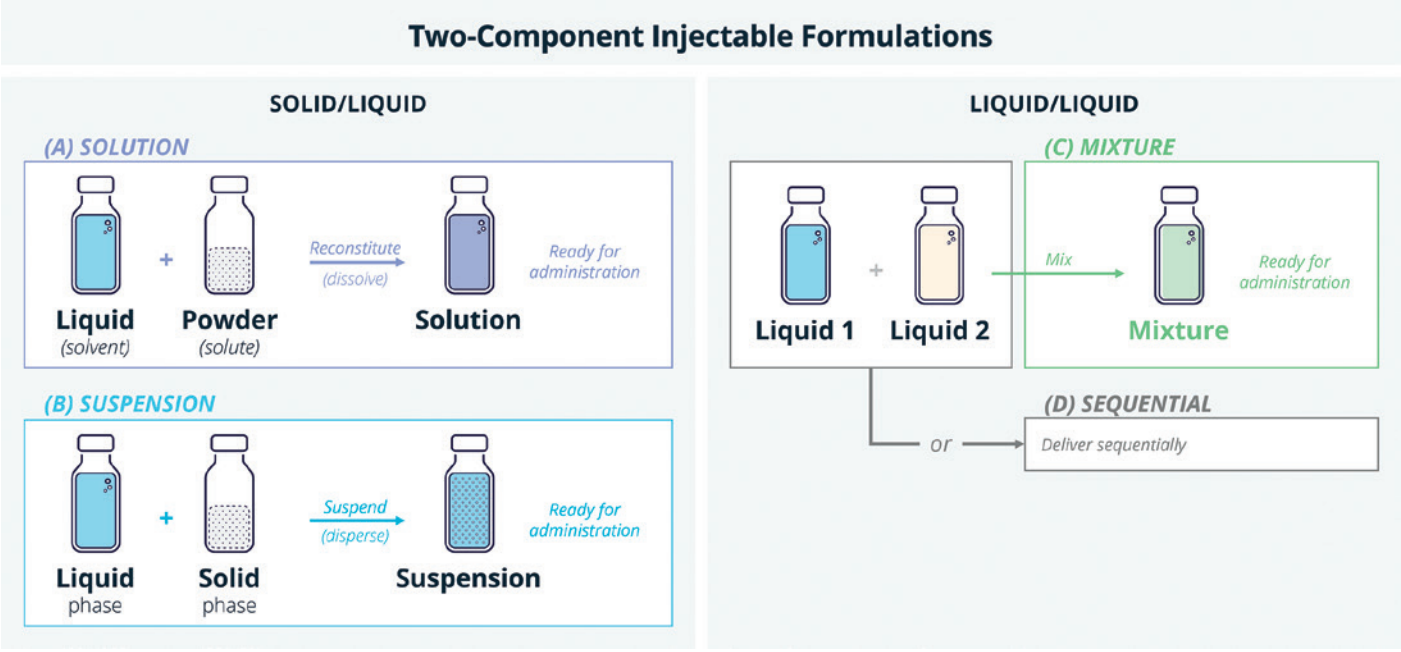

Figure 1: A simplified model of two-component injectables, classified according to the state of matter of constituent parts.

"LYOPHILISED FORMULATIONS NOW REPRESENT OVER 30% OF ALL FDA-APPROVED PARENTERAL MEDICATIONS – AND DEMAND FOR LYOPHILISED PARENTERAL PRODUCTS IS INCREASING."

solvent or diluent (e.g. sterile water for injection) that must be mixed thoroughly before use. Alternatively, both constituents may be liquid, in which case they may either require mixing prior to delivery or be delivered sequentially (Figure 1).

The Archetype: Solid/Liquid Reconstitution

Reconstitution is the process of adding a liquid solvent to a solid medication to dissolve it and form a solution. This may be required, at point of use, when a drug is unstable in liquid form and must therefore be stored dry. In such cases, the formulation is often filled as a liquid and then lyophilised (freeze dried) *in situ*. Alternatively, it may be manufactured and handled as a powder.

Freeze drying is an effective way to increase formulation stability. For small molecules, it can eliminate the need for cold-chain storage. For biologics (especially those that are large, complex or prone to aggregation) it can be a necessity in order to achieve an acceptable shelf-life.

Lyophilised formulations now represent over 30% of all US FDA-approved parenteral medications[1] – and demand for lyophilised parenteral products is increasing, as evidenced by past drug approvals (~35 such drugs were approved by the FDA each year over the past decade, compared to ~12 per year in the decade prior[2]). Considering lyophilised parenterals approved in 2023, oncology and infectious disease indications represented the largest share, together accounting for ~75% of total approvals.[2]

As lyophilisation is on the rise, so too are devices to simplify reconstitution. A wide range of solutions are available beyond the well-established vial-and-syringe method – from primary container adaptors to dual-chamber systems.

Solid/Liquid Suspensions

Suspensions are a dosage form in which insoluble solid particles are mixed into a liquid medium. They enable delivery of insoluble drugs and can be used to formulate long-acting injections. Suspensions may be supplied as separate wet and dry components (in which case the liquid phase is added to the solid phase and mixed prior to administration) or in a single primary container that is shaken to resuspend.

While solutions can readily be reconstituted with gentle swirling, suspensions usually need a greater energy input to achieve even mixing – the required amount varies greatly depending on the chemical and physical properties of the formulation. In some cases, vigorous shaking is insufficient and benchtop equipment, such as a vortex mixer, must be used.

Given sufficient energy input, the particles will be uniformly dispersed within the liquid, however the resulting mixture will be heterogenous and unstable; it will eventually settle. Therefore, suspensions must be thoroughly mixed immediately before use. Inconsistent dispersion can lead to inaccurate dosing or needle clogging – persistent challenges for device integration.

Injectable suspensions are becoming more prevalent, particularly for severe chronic conditions such as schizophrenia and HIV,[3,4] where extended-release formulations are of particular value and which are often reliant on a suspension format to produce a long-acting depot. When formulated as separate wet and dry components, these products largely rely on vial-and-syringe or vial-adaptor workflows, with the occasional exception, such as Eligard's (leuprolide acetate, Tolmar) reciprocating syringes, or the Abilify Maintena (aripiprazole, Otsuka) dual-chamber syringe.[3,4]

Liquid/Liquid Mixtures

Injection of two-liquid mixtures is rarer but not unheard of. Two liquids may be mixed and delivered together out of:

1. **Necessity:** When a formulation consisting of two fluid phases is unstable in mixed form, but must be mixed prior to injection in order to achieve the intended therapeutic effect (e.g. API and polymer solutions that mix to form a long-acting depot).
2. **Convenience:** If two liquid formulations are frequently administered together, such as in combination vaccines, pharma companies may choose a dual-chamber presentation over developing a coformulation, such as with Vivaxim (typhoid and hepatitis A, Sanofi).[6] In this case, mixing isn't necessary but rather a side effect of leveraging mature dual-chamber systems (which mix the two liquids prior to administration) rather than betting on more niche sequential delivery technology.

Sequential Delivery of Two Liquids

Sequential delivery of two different liquids through a single needle or injection port has been proposed for combination therapies, as well as for IV drug administration through a vascular access device (with the drug preceded, or followed, by a catheter flush).[7]

While there are several delivery technologies in development that might enable these use cases, only one combination product in this category is on the market at the time of writing, according to data from PharmaCircle. The DuoDote emergency-use autoinjector (Meridian Medical Technologies, St Louis, MO, US), based on a custom primary container, sequentially injects atropine and pralidoxime chloride. It is approved for treatment of nerve agent or insecticide poisoning.

CHOOSING THE RIGHT DEVICE

Choosing the right device for a two-component injectable is often an exercise in trade-offs, highly dependent on the

"CHOOSING THE RIGHT DEVICE FOR A TWO-COMPONENT INJECTABLE IS OFTEN AN EXERCISE IN TRADE-OFFS, HIGHLY DEPENDENT ON THE PROPERTIES OF THE FORMULATION ITSELF, INDICATIONS FOR USE AND THE STAGE OF DEVELOPMENT."

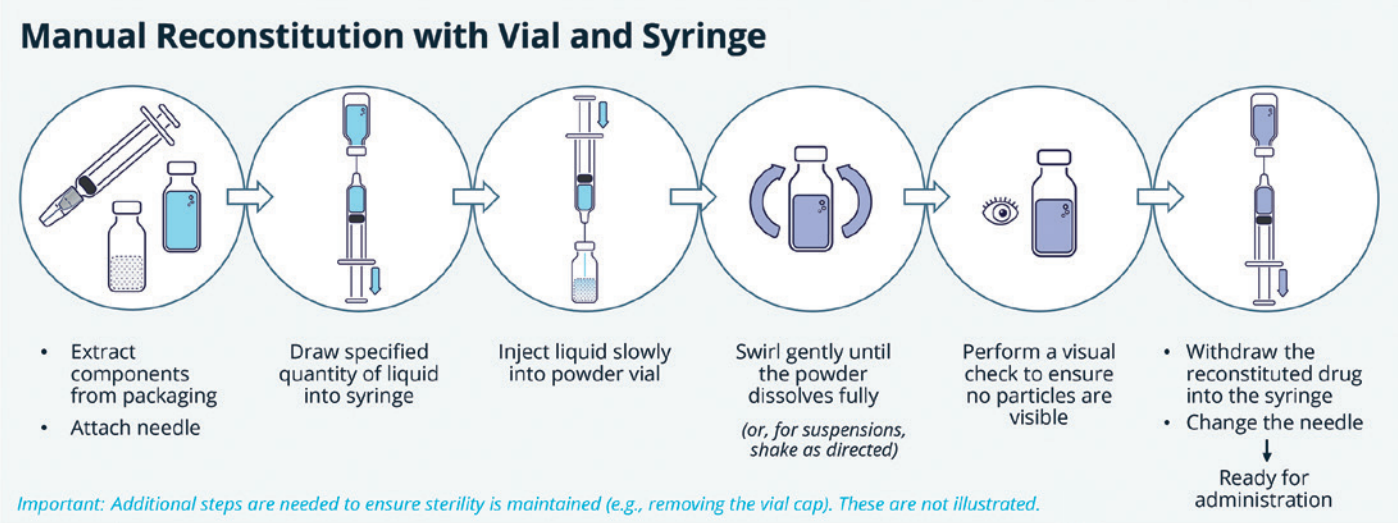

Figure 2: A summary of steps required for manual reconstitution using vials and syringes.

properties of the formulation itself, indications for use and the stage of development. Hereafter, this article will assume that a two-component injectable consists of separate wet and dry constituents that are reconstituted prior to injection, unless otherwise stated. This section will briefly cover the range of available technologies, and factors to consider when it comes to device selection.

Vial and Syringe: Trusty but Burdensome

Two-component injectables are often supplied in vials, with off-the-shelf (OTS) needles and syringes used for fluid transfer and subsequent injection (Figure 2). By leveraging mature primary containers and fill-finish technologies, this approach benefits from low unit cost and a robust supply chain. It is also extremely versatile, with fewer restrictions on formulation volume and viscosity compared with alternatives, the ability to accommodate different doses in a single stock keeping unit, and no need for device-specific training.

On the other hand, the process is onerous and a high degree of technical expertise is required to perform all steps correctly. Dose accuracy is highly dependent on the user, and there is a greater risk of contamination and sharps injury compared with other methods, meaning that this type of system is typically limited to trained staff in clinical settings. Moreover, some drug wastage is inevitable, with vials often overfilled by 10–20% to ensure that a full dose can always be drawn.

Devices to Simplify the Reconstitution Process

Given the growing prevalence of two-component injectables and the limitations of the established vial-and-syringe method,

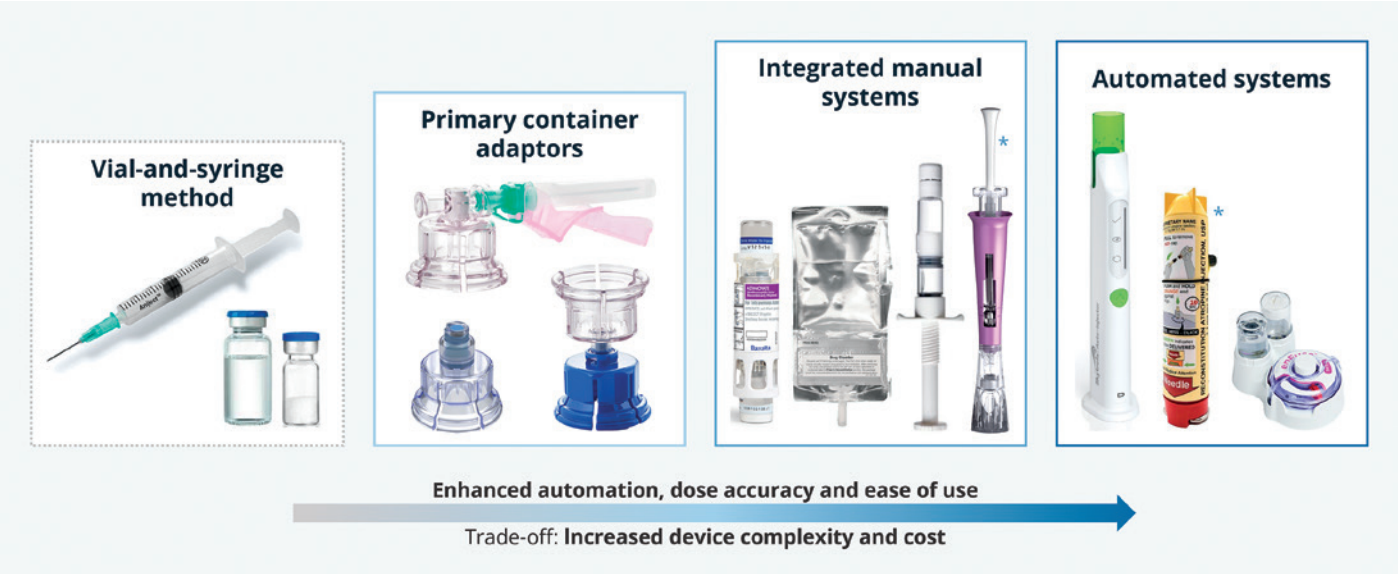

Figure 3: Examples of reconstitution devices for intravenous, intramuscular and subcutaneous administration. Devices marked with an asterisk are in development at the time of writing; the others are on the market. Note that prefilled dual-chamber systems can fall within the "integrated manual" or the "automated" categories, depending on device function.

"IT IS NO SURPRISE THAT A WIDE RANGE OF SPECIALIST DEVICES HAVE BEEN DEVELOPED TO AID RECONSTITUTION."

it is no surprise that a wide range of specialist devices have been developed to aid reconstitution. Figure 3 illustrates some of the solutions available.

- **Primary Container Adaptors:** Co-packaged with standard prefilled primary containers, these allow for drug components to be accurately pre-dosed during manufacturing, while maintaining low device and fill-finish costs.

- **Integrated Manual and Automated Systems:** Some of these leverage standard OTS containers, while others are designed around bespoke primary containers (e.g. dual-chamber cartridges).
  - Integration of device components reduces the number (and sometimes complexity) of use steps, reducing the burden of use and the likelihood of errors.
  - Automated devices take this further by incorporating mechanisms in the design (such as springs or electronics) to enable reconstitution and/or delivery with minimal user input.

Horses for Courses: Different Drugs Have Different Needs

When choosing a device, key trade-offs include cost, time to market, dose accuracy and ease of use. Consider:

- **Properties of the Formulation:** All reconstitution devices have their strengths and limitations; the choice of device must be compatible with the needs of the formulation. For example, dual-chamber PFSs are limited to products with relatively low volumes that reconstitute readily.

- **Use Case and Dose Accuracy:** The choice should be made with the final user in mind; integrated and automated systems greatly simplify usage, making accurate reconstitution accessible to users with less technical expertise (e.g. patients in the home setting).

- **Supply Chain Implications:** The choice of primary container is the single most important factor influencing development timeline and manufacturing cost of the device. Dual-chamber fill-finish is highly complex; expertise is rare and CMO capacity limited.

- **Stage of Drug Development:** Priorities differ depending on the stage of development. For example, a novel drug in clinical trials may benefit from the use of vials, since they offer flexible dosing and use only OTS components, whereas more integrated systems may be introduced post-launch to encourage wider adoption.

DUAL-CHAMBER DELIVERY SYSTEMS

Prefilled dual-chamber systems (DCSs) are "all-in-one" devices built around bespoke primary containers, designed to simplify the reconstitution and delivery of two-component injectables. This final section delves deeper into this device category – strengths, limitations and key design considerations.

Anatomy of a Dual-Chamber System

In a DCS, the primary container consists of a barrel (typically made of glass) divided into two chambers by a central stopper. This barrier keeps the drug components separate from each other throughout

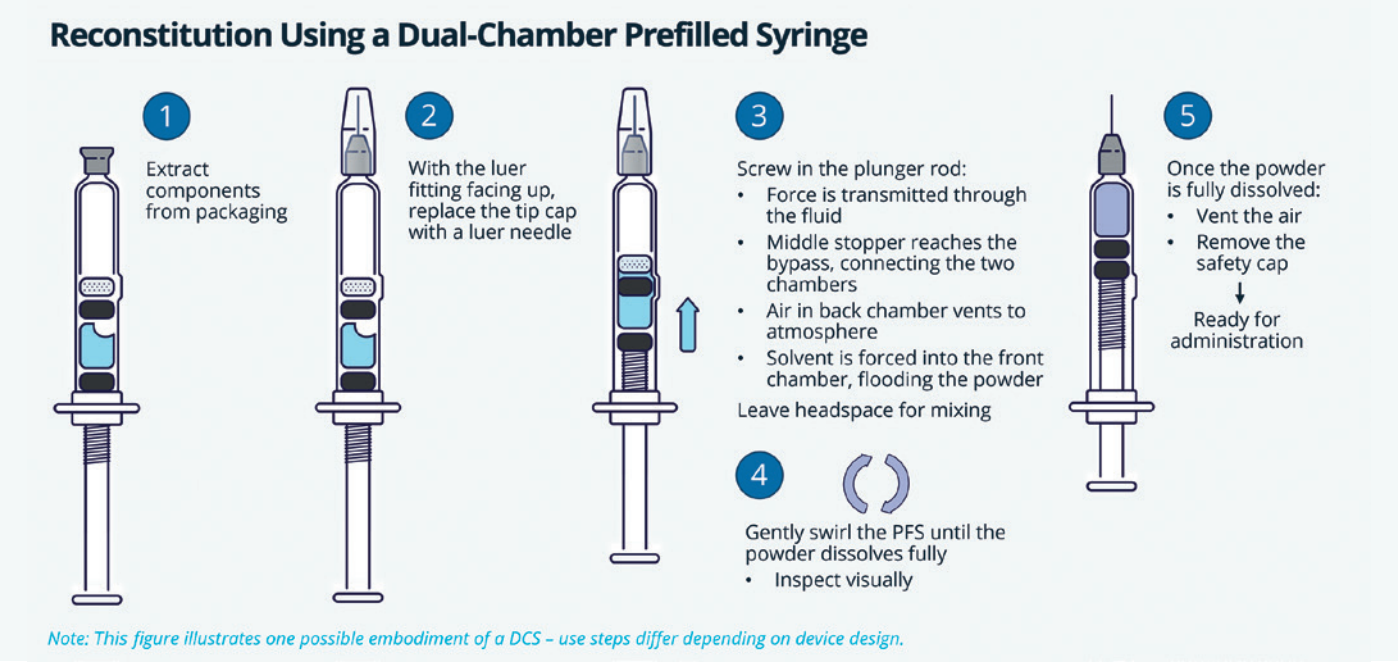

Figure 4: Use steps and function of a typical DCS embodiment. Note that the linear application of force causes the bypass mechanism to activate, opening a fluid path that connects the two chambers.

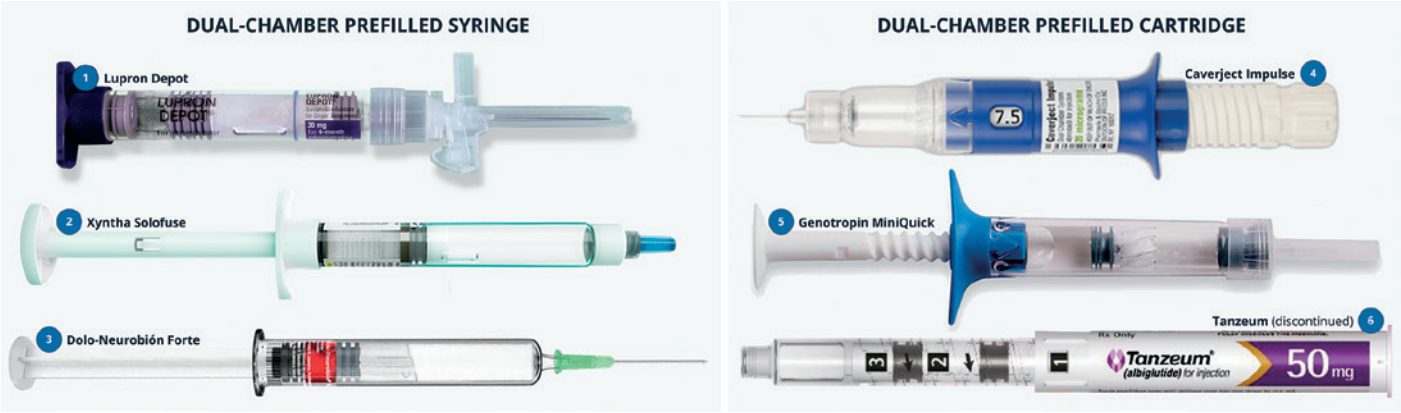

Figure 5: Approved DCS products (all marketed, bar Tanzeum (albiglutide, GSK), which has been discontinued). Left: dual-chamber prefilled syringes. Right: integrated injection devices built around dual-chamber cartridges. Device 1 contains a lyophilised suspension; Devices 2, 4, 5 and 6 contain lyophilised solutions; and Device 3 contains two liquids for co-administration.

storage. Once the DCS is activated, a bypass mechanism allows fluid to flow from the back (wet) chamber into the front (typically dry) chamber (Figure 4).

DCSs vary in type of closure and bypass:

- The closure can be PFS-style or cartridge-style (Figure 5).
- The bypass is usually external (a blister bypass), but can also be internal (such as the multi-groove design of the Genotropin MiniQuick (somatropin, Pfizer) – Figure 5, Device 5). Note that an internal bypass allows the use of standard syringe or cartridge tubs, which is advantageous for manufacturing. Emerging designs, such as Credence MedSystems' (Menlo Park, CA, US) fenestrated needle bypass, also have the additional benefit of being compatible with OTS syringes.

Bespoke Primary Containers: A Double-Edged Sword

Like other specialist reconstitution devices, DCSs make administration of two-component injectables accessible to a wider range of users and care settings. They require less technical expertise to use accurately and consistently, with fewer and simpler handling steps, pre-measured drug components and reduced sharps exposure.

However, their unique strength lies in their form factor – the single barrel with a bypass that can be activated with a co-linear application of force (so both mixing and delivery are done by pushing on the rear plunger in a straight motion). Thanks to this design, DCSs can readily be integrated into devices with enhanced usability and/or advanced features. For example:

- Xyntha Solofuse (antihemophilic factor, Pfizer), an easy-to-use device with a simple finger flange (Figure 5 Device 2).
- Caverject Impulse (alprostadil, Pfizer), an integrated manual system with dose selection capability (Figure 5 Device 4).
- The reusable Skytrofa autoinjector (lonapegsomatropin-tcgd, Ascendis), pictured in Figure 3 with the green needle guard.

The flip side of the form-factor coin is that complexity is pushed into the manufacturing and filling process. Fill-finish for these devices requires specialist equipment and know-how (as noted above, expertise is rare and capacity is limited) and lyophilisation is inherently less efficient in the dual-chamber geometry compared with vials (smaller batches, poorer energy transfer, longer cycle times[6]). It all adds up to greater up-front investment and time-to-market, higher unit cost and a restricted supply chain.

For this reason, DCSs have so far been limited to premium value products, such as those used to treat rare diseases (e.g. haemophilia, growth hormone deficiency) or those that solve complex or critical clinical challenges (e.g. unmet needs, home care).[6]

"THANKS TO THIS DESIGN, DCSS CAN READILY BE INTEGRATED INTO DEVICES WITH ENHANCED USABILITY AND/OR ADVANCED FEATURES."

Design Considerations

Current marketed DCSs have inherent technical limitations that impact formulation compatibility and device design. For example:

- **Capacity is Limited to ~4 mL Total Reconstituted Volume:** Headspace in the front chamber must be sufficient to accommodate the initial plunger stroke required to open the bypass, both drug components and additional room for swirling and mixing. Therefore, there is a limit to how much can be delivered with these devices before they become too large to be practical.

- **Venting and Orientation are Important:** There usually needs to be a path to atmosphere during mixing to avoid pressure build-up in the front chamber (if there is a large amount of headspace in the powder chamber, this may not be required). In all cases, excess air must be vented prior to injection, which can be challenging and requires careful handling, as the device must be kept upright whenever there is a path to atmosphere to avoid drug spilling through the needle.

- **Plunger Motion Must be Well-Controlled:** When the bypass opens, the pressure in the system drops sharply. Unless

the plunger's forward motion is well-controlled, there is a risk of prematurely locking out the fluid path, which would prevent the liquid in the back chamber from being fully incorporated into the mixture. To prevent this, many devices incorporate a screw mechanism that enforces a slower twist-to-mix action.

- **They Are Best Suited to Lyophilised Formulations That Are Readily Reconstituted with Gentle Swirling:** Suspensions can only be delivered if the energy required to suspend is low. In addition, sequential delivery is not possible without specialised valve design (some mixing will always take place with the currently marketed DCSs). Finally, very particular considerations apply to the delivery of liquid/liquid mixtures – space is at an even greater premium, venting becomes critical and mixing performance varies widely depending on the specific device and formulation.

LOOKING AHEAD

Meeting the next generation of injectable delivery challenges will demand the best of device innovation, alongside advances in formulation and process development. As therapies grow more complex, the need for close cross-functional collaboration becomes increasingly critical.

Developers of combination products will continue to face trade-offs between usability, flexibility, cost and manufacturability. To navigate these successfully, device and formulation experts must work hand-in-hand with clinical, regulatory, commercial and access stakeholders. Working together, medicines can be delivered that are fit for purpose today and ready to meet the needs of tomorrow.

ABOUT THE COMPANY

Cambridge Design Partnership is a design and engineering consultancy with R&D centres in the UK and the US. The company creates breakthrough products and services for global brands and ambitious startups across the healthcare, consumer and industrial sectors. The company's drug delivery team innovates solutions for parenteral, respiratory, nasal, sublingual, transdermal and novel delivery routes, such as ocular, brain and direct-to-organ delivery. With deep subject-matter expertise and a focus on close client collaboration, Cambridge Design Partnership is well positioned to help pharmaceutical and biotechnology companies address the next generation of injectable delivery challenges.

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María FM Balson

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POWDER TO THE PEOPLE: ACCELERATING ACCESS TO LYOPHILISED THERAPIES

Kristien De Clercq and **Dr Alex Vasiev** of Springboard discuss the challenges and recent advances in drying and reconstitution technologies, as well as how, while dual-chamber primary packaging offers a potential solution for simplifying reconstitution, it remains underused due to usability concerns and a prevailing industry preference for vial-based lyophilisation over alternative drying methods such as spray drying and powder filling.

"WHEN REFORMULATION IS IMPRACTICAL, A LYOPHILISED DRUG CAN BE PAIRED WITH A RECONSTITUTION DEVICE. THESE DEVICES STREAMLINE PREPARATION, REDUCE TRAINING REQUIREMENTS, IMPROVE PATIENT CONFIDENCE AND MINIMISE THE ERRORS ASSOCIATED WITH MANUAL MIXING – DELIVERING MANY USABILITY BENEFITS WITHOUT ALTERING THE DRUG ITSELF."

LYOPHILISATION IN DRUG DEVELOPMENT

Lyophilisation, or freeze drying, is a widely used formulation strategy in drug development, particularly for biologics such as monoclonal antibodies, peptides and nucleic acids. These molecules often exhibit limited stability in liquid form, making lyophilisation an attractive solution. By removing water, the primary mediator of many degradation pathways, this process can dramatically extend shelf life, reduce storage constraints and simplify transport across diverse climates by minimising or eliminating cold-chain requirements.

In this low-temperature dehydration process, the product is first frozen and then exposed to reduced pressure, causing frozen water to sublimate directly from solid to vapour. If well controlled, this gentle method preserves the structural integrity and biological activity of sensitive compounds. Lyophilisation can be implemented at virtually any scale, allowing seamless progression from early laboratory experiments to clinical development batches and, ultimately, large-scale commercial production.

Liquid Versus Lyophilised Formulations

The decision to transition from a lyophilised product to a stable liquid formulation is commercially driven. Many companies launch with a lyophilised version to accelerate regulatory approval and establish a revenue stream. Later, if justified by market demand, they may invest in ready-to-use liquid formats or prefilled syringes as part of a lifecycle management strategy.

Liquid formulations simplify use by eliminating the reconstitution step, which is particularly valuable for home-use scenarios where mixing can be perceived as cumbersome or prone to error. However, developing a stable liquid formulation carries significant technical and regulatory risks. It requires extensive formulation research, stability ("stress") testing, manufacturing process validation and sometimes additional clinical trials. For certain molecules, inherent instability in liquid form makes this route technically or commercially unfeasible.

When reformulation is impractical, a lyophilised drug can be paired with a reconstitution device. These devices streamline preparation, reduce training requirements, improve patient confidence and minimise the errors associated with manual mixing – delivering many usability benefits without altering the drug itself.

Challenges of Manual Reconstitution

For self-administered therapies, manual reconstitution can be difficult or frustrating for patients and caregivers. Typical steps include cleaning components to ensure sterility, connecting and disconnecting fluid paths, swirling or rolling to mix and judging whether or not the final dose is fully reconstituted. These long, complicated processes create many opportunities for use error, which can lead to incorrect dilution or incomplete reconstitution, directly affecting treatment efficacy.

Faced with these challenges, users may turn to shortcuts such as skipping steps that they don't think are important or using the injection needle to access the vial, exposing them to further potential harms. All of these challenges are further multiplied if the patient population suffers from manual dexterity issues or other comorbidities that may affect their ability to complete the reconstitution process.

Drug	Company	Route	Primary Pack	Device	Year of Approval
Humatrope (somatropin)	Eli Lilly	SC	Cartridge	HumatroPen (Ypsomed)	1987
Genotropin (somatropin)	Pfizer	SC	Cartridge/Syringe	Genotonorm or Miniquick (Ypsomed and Pfizer, respectively)	1995
Cardizem (diltiazem)	Bioavial Pharmaceuticals	IV	Syringe	Lyo-Ject (Vetter)	1996
Saizen (somatropin)	Merck Serono	SC/IM	Cartridge	One-click pen (Haselmeier)	1996
Edex (alprostadil)	Schwarz Pharma	IC	Cartridge	Edex Injection Device (Schwarz)	1997
NeoRecormon (epoetin beta)	Roche	SC	Cartridge	Reco-Pen (Ypsomed)	1997
Caverject (alprostadil)	Pfizer	IC	Cartridge	Caverject Impulse (Pfizer)	2002
Xyntha Solofuse (antihaemophilic factor)	Pfizer	IV	Syringe	Lyo-Ject (Vetter)	2008
Tanzeum (albiglutide)	GSK	SC	Cartridge	LyoTwist® (Ypsomed)	2014
Abilify Maintena (aripiprazole LAI)	Otsuka Pharmaceuticals	IM	Syringe	Dual-Chamber Syringe (Arte/Otsuka)	2014
Bydureon (exenatide extended release)	AstraZeneca	SC	Cartridge	LyoTwist® (Ypsomed)	2014
Skytrofa (lonapegsomatropin-tcgd)	Ascendis Pharma	SC	Cartridge	Skytrofa Autoinjector (Phillips Medisize)	2021

Table 1: Non-exhaustive list of devices using dual-chamber primary packaging.[1,2] (SC – subcutaneous, IV – intravenous, IM – intramuscular, IC – intracavernous)

DUAL-CHAMBER DEVICES

Dual-chamber devices (DCDs) offer a significant advantage by performing aseptic fluid transfer and reconstitution inside the primary packaging (syringe or cartridge), thereby eliminating the risks of leakage and contamination during preparation. Several regulator-approved devices already incorporate this technology (Table 1).

Despite these benefits, DCDs present their own usability challenges. While these devices may reduce the number of use steps in the preparation process, they may still contain tasks that could be confusing for users, such as combinations of pushing and screwing actions where use errors can still occur.[3] Further to this, the larger size of some dual-chamber syringes may be daunting for patients.

From a product-design perspective, ensuring long-term moisture protection for a lyophilised cake places high demands on the stopper-to-container interface – requirements that are intensified in cartridge-based systems with more sealing points. After activation, the lyophilised powder must dissolve completely within a practical timeframe and without undesirable effects, such as foaming, particle formation or incomplete mixing. This makes certain device platforms unsuitable for formulations with inherently slow dissolution rates.

Transferring a validated vial-based lyophilised formulation to a cartridge or syringe format introduces additional regulatory and chemistry, manufacturing and control (CMC) hurdles, requiring new stability studies and manufacturing validation. Moreover, manufacturing DCDs adds complexity at the fill-finish stage – dedicated processing lines and specialised transport fixtures are needed, and freeze-drying performance in these formats has historically been limited by inconsistent

"TRANSFERRING A VALIDATED VIAL-BASED LYOPHILISED FORMULATION TO A CARTRIDGE OR SYRINGE FORMAT INTRODUCES ADDITIONAL REGULATORY AND CMC HURDLES, REQUIRING NEW STABILITY STUDIES AND MANUFACTURING VALIDATION."

heat transfer due to product residing too far from the heat-transfer surface and unfavourable surface-area-to-volume ratios.

These factors can prolong drying cycles and make it harder to achieve uniform cake quality.[1] Specialised fixtures are necessary to support syringes during freeze drying, and cycle optimisation is essential to prevent cake collapse or loss of structure. Although technological advances have improved freeze drying in cartridges and syringes, industry experience and data remain more extensive for vial formats.

ALTERNATIVE TECHNOLOGIES

There are, however, a number of promising device and process technologies that, combined or in isolation, have the potential to reduce user burden when reconstituting drugs and usher in a new generation of combination products. Their successful adoption will require a multidisciplinary approach, as novel combination product development relies on a fundamental understanding of formulation, biopharmaceutical processing, reconstitution physics and fill-finish and device expertise.

Spray Drying

Another, though less widely used, approach to drying therapeutics is spray drying, which offers exceptional control over the dissolution properties of dry formulations by engineering particles through the kinetics of the drying process.[4] Unlike freeze drying, spray-dried particles can be solidified in an amorphous state, improving the stability of fragile molecules and accelerating dissolution.

The particle structure can also be influenced by the balance between solvent evaporation and solute diffusion, described by the Péclet number:

- **Low Péclet Number:** Solutes remain evenly distributed, producing solid particles
- **High Péclet Number:** Solvent evaporation outpaces solute diffusion, resulting in surface enrichment and the formation of a shell.

Proteins and polymers tend towards the high Péclet number scenario, but this can be adjusted using other process parameters (Figure 1). By controlling solvent-drying kinetics, selecting appropriate excipients and adjusting spray-drying parameters, manufacturers can fine-tune

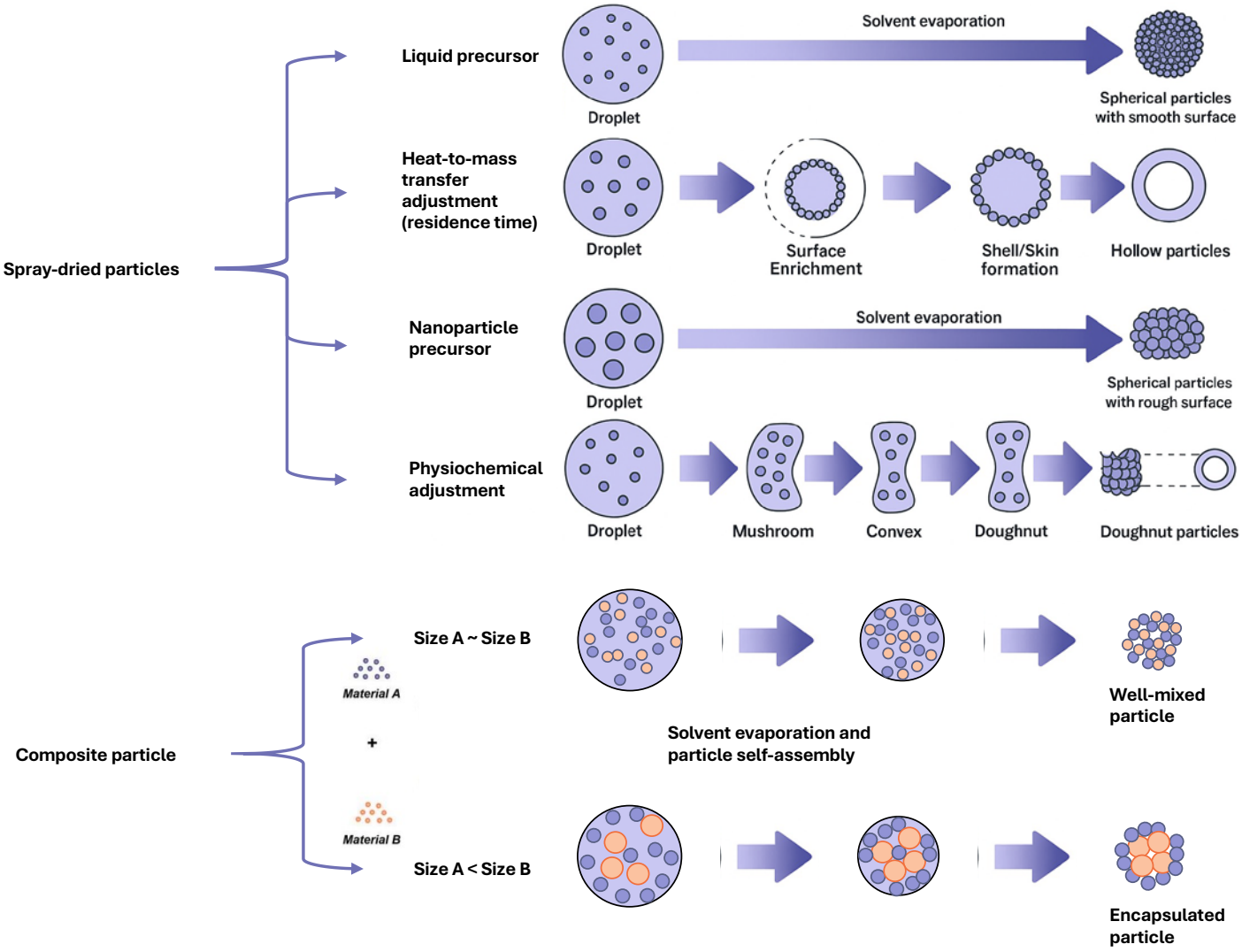

Figure 1: Illustration of the level of control possible over particle morphology using spray-drying process design.[4]

several key characteristics:

- Particle surface area
- Stabilisation of an amorphous state (useful for both stability and dissolution)
- Particle density (e.g. solid, foamed or hollow)
- Barrier- or surface-modifying coatings
- Powder dispersibility and flowability
- Controlled drug-release profiles.

When optimised, spray drying can reduce reconstitution times from several minutes to mere seconds.[5] This has the potential to significantly improve usability and adherence, even with existing device technologies, by removing some of the difficulties users face.

Because it is perceived as a harsher process than freeze drying, spray drying has traditionally been used for small-molecule drugs. However, it has been shown to be suitable for biologics, including complex biomolecules, such as immunoglobins and viral capsid proteins, due to evaporative cooling and the use of protective excipients, such as trehalose.

Aside from unfamiliarity, adoption for injectable formulations has been limited by practical challenges, including the availability and maturity of aseptic spray drying and powder handling, high cost of physical losses at small scale (up to 50%), and the limited number of CDMOs available with experience in this area.

Today, some of these barriers, such as aseptic handling and powder filling, are gradually diminishing, increasing the accessibility of this technology. However, as with lyophilisation, spray drying requires the development of an appropriate formulation – a process that can be time-consuming and demands specialised expertise.

Alternative Reconstitution Device Technologies

A different approach to simplifying and standardising the process of reconstitution is to design around the issues. Several novel drug-device combination platforms aim to achieve this by automating some or all preparation steps. These systems reduce user burden, lower the risk of use errors and improve overall usability compared with more manual methods.

"SEVERAL NOVEL DRUG-DEVICE COMBINATION PLATFORMS AIM TO ACHIEVE THIS BY AUTOMATING SOME OR ALL PREPARATION STEPS. THESE SYSTEMS REDUCE USER BURDEN, LOWER THE RISK OF USE ERRORS AND IMPROVE OVERALL USABILITY COMPARED WITH MORE MANUAL METHODS."

Windgap Medical's (Watertown, MA, US) Large Volume Dual Cartridge platform employs a side-by-side configuration of two standard single-chamber cartridges – one containing the diluent and the other the lyophilised drug product. Reconstitution occurs through cyclic fluid transfer between the cartridges, ensuring thorough mixing prior to administration. Two variants are offered – a touch-activated design and a compressed-gas-driven version, the latter capable of delivering large volumes and handling highly viscous formulations.

Eveon's (Montbonnot-Saint-Martin, France) Intuity® Ject MX also uses cartridges as primary packaging and achieves reconstitution via cyclic fluid transfer between two containers. However, it replaces manual or gas-driven actuation with an electromechanical mixing mechanism. This automation standardises the mixing process and allows for connectivity features that enable data capture and adherence monitoring. Additionally, Eveon offers the Intuity® Mix, a piston-pump-based, non-portable, fully automated system intended for clinical or pharmacy use.

Enable Injections' (Cincinnati, OH, US) EnFuse® system follows a different approach. While currently marketed versions are designed for liquid formulations, such as Empaveli® (pegcetacoplan, Apellis Pharmaceuticals, Waltham, MA, US), a variant exists that performs reconstitution immediately before pump filling. This method bypasses the challenges associated with *in situ* lyophilisation and container compatibility by connecting directly to a standard lyophilised powder vial. EnFuse uses an internal mechanical pumping system for fluid transfer and mixing, enabling it to handle a wide range of formulation viscosities.

Some systems address specific aspects of vial usability by automating diluent transfer but without automating mixing, transfer or delivery. Their vial-based format is generally bulkier than cartridge-based platforms and offers fewer opportunities for delivery device integration. However, it provides flexibility in dosing and route of administration, making these systems well suited to formulations with straightforward dissolution profiles or varied dosing regimens, while being less appropriate for tackling challenges such as high viscosity.

Baxter's BaxJect III®, marketed for use with ADYNOVATE® (PEGylated antihaemophilic factor, Takeda Pharmaceuticals), uses two standard vials: one for diluent and one for lyophilised powder, connected via a sterile transfer device. Reconstitution is driven by a pressure differential between the vials, without an active mixing mechanism. The user must manually withdraw the prepared solution into a syringe through a side port.

DuoJect's (Bromont, Canada) INTERVIAL™ family of devices, including PENPREP EVO™, approved for use with SAIZEN® (somatropin, Merck), combines the diluent and lyophilised powder within a single device. Mixing is manual, and the user then draws up the dose after reconstitution is complete.

Pfizer's Act-O-Vial® offers a simple mechanical method to simplify reconstitution. It integrates the diluent and lyophilised drug in a single vial assembly separated by a rubber stopper. Pressing the stopper releases the diluent into the powder chamber, allowing mixing before withdrawal for injection.

Innovation in this space benefits most from partnerships that bridge formulation science, human factors expertise and engineering design into a single integrated development. By combining deep understanding of the drug product with insight into user needs and awareness of enabling technologies, it is possible to streamline reconstitution, reduce

complexity and unlock the next generation of combination products. With unmet market need still evident, this remains a fertile area for innovation and a compelling opportunity for growth.

CONCLUSION

Lyophilisation remains the preferred solution for stabilising sensitive biologics, offering substantial benefits in shelf-life extension, storage flexibility and global distribution. However, the shift from traditional vial formats to integrated, patient-friendly delivery systems is an area rich with innovation. Dual-chamber primary packaging and in-device reconstitution platforms promise simpler preparation and fewer use errors, yet they bring their own user and technical challenges, such as larger size, potentially confusing use steps, freeze drying within constrained geometries, ensuring rapid and complete dissolution and maintaining long-term stability.

Emerging alternatives, such as spray drying, present new opportunities to tailor powder characteristics and enhance reconstitution efficiency. Still, historical barriers, including the complexity of aseptic powder filling and high material losses at small scale, have limited broader adoption. Advances in device technology are also driving progress, with platforms that aim to automate some or all steps of the reconstitution and delivery process.

Ongoing innovation in both drying and delivery technologies is fuelled by the need to improve patient convenience, adherence and therapeutic outcomes. The widespread adoption of on-device reconstitution will depend on carefully balancing formulation stability, manufacturing feasibility and human factors. The potential reward is significant – expanding access to complex biologics in formats that are both highly effective and intuitive to use across diverse markets and therapeutic areas. Achieving this will require multidisciplinary collaboration, less-siloed development approaches and strategic partnerships that unite expertise in formulation, engineering, and user-centric design.

ABOUT THE COMPANY

Springboard is a technology and design consultancy, which creates and develops new products and technology, including products in the field of medtech and drug delivery devices, assisting companies in resolving technical challenges and decreasing time to market. Springboard is part of the Sanner Group, which provides high quality, agile and cost-effective manufacturing for medical devices, including drug delivery devices.

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Kristien De Clercq is a Principal Engineer and Project Lead at Springboard with expertise in medical device innovation. She has contributed to the development of wearable injectors, autoinjectors, soft-mist inhalers and reconstitution devices. Ms De Clercq is passionate about biomimicry and takes a perceptive, holistic approach to product innovation, combining technical rigour with a clear focus on commercial objectives. She holds an MSc in Mechanical Engineering from Delft University of Technology (The Netherlands) and applies her expertise to deliver robust, market-ready technologies.

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Early Insight

DuoVIAL® – PROTECT, MIX AND DELIVER

DUO VIAL by Pacifi

Gareth Pearce of **Pacifi** introduces the company's DuoVIAL® primary packaging technology for topical lyophilised formulations – a minimalist dual-chamber drug delivery system that enables safer, easier and more cost-effective reconstitution, while retaining the proven materials, formats and filling processes well established in the pharmaceutical sector.

With a growing pipeline of biologics, lyophilised formulations can provide the necessary stability to help support drug efficacy. It is, however, worth recognising that it is not only parenteral drug products that benefit from lyophilisation. Within topical therapies, there are now live biological products (LBPs) for treating inflammatory skin conditions undergoing clinical trials. Notably, the end user is not a skilled healthcare professional, and meeting the challenges of reconstitution in a non-clinical environment requires serious consideration of the packaging format and delivery mechanism.

The global lyophilised drugs market is estimated to be valued at US$371 billion (£275 billion) in 2025 and is expected to reach $683 billion by 2032, exhibiting a compound annual growth rate of 9.1% from 2025 to 2032. By packaging type, it is expected that the vial segment will continue to lead the lyophilised drugs market in 2025, with a projected contribution of 40.5%.[1] While the majority of lyophilised drug products will be processed in traditional tubular glass vials, dual-chamber syringe and cartridge formats are anticipated to see continued growth, due to increased end-user convenience. While bulk lyophilisation in trays, milling and transfer of powder into specialist packaging is established, a more exciting lyobead technology appears to be able to achieve increased productivity, reduced costs, lower cycle times and easier handling.[2]

RISK MANAGEMENT

The technologies underpinning Pacifi's innovative approach were conceived in response to an ampoule sharps injury complaint, frustration by market acceptance of the status quo and acknowledgement of the inertia of a conservative pharmaceutical industry. In cases where ampoules and vials are the assumed packaging of choice for ease of use and safety, there are a number of accessories that are usually recommended to supplement them. However, human nature and convenience often mean these accessories are treated as optional; for example, using a blunt filter needle to draw product from an ampoule to mitigate the risk of glass particles and needlestick injuries, or with a vial to mitigate particles from coring the rubber stopper entering the drug product.

> "IT OFTEN FEELS LIKE THESE ADDITIONAL COMPONENTS, COMPLEXITIES AND COSTS ARE A STICKING PLASTER THAT DO NOT ADDRESS THE FUNDAMENTAL FLAWS IN TRADITIONAL PRIMARY PACKAGING FORMATS."

Figure 1: Ampoule + Vial = DuoVIAL®.

Vial-to-vial reconstitution can benefit from the use of sophisticated vial adaptors that incorporate double particle filters, visual cues, and functional and ergonomic features that can help to mitigate sharps injuries, particles, user errors and non-aseptic technique. However, it often feels like these additional components, complexities and costs are a sticking plaster that do not address the fundamental flaws in traditional primary packaging formats. Alternatively, there are proprietary dual-chamber syringe and cartridge solutions that may be easier and safer, but are typically only commercially viable for premium drug products.

Meanwhile, regulatory hurdles continue to increase; the US Pharmacopoeia has evolved to enable a more considered approach to drug delivery device innovation based upon assessing risk and resolving it through suitable design solutions and systems. Notably, in the past, glass flakes arising from delamination, driven by the incompatibility of specific formulations, process conditions and glass material, led to studies and proposals to use vial adaptors incorporating filters.[3] Not every administration route has the acceptance quality limits specified for sterile injectables – topical and oral therapies are aligned with fitness for purpose when it comes to inspection and particles.

FORM FACTOR

Is it a vial? Is it an ampoule? No, it's DuoVIAL® (Figure 1). Combining the functional advantages of ampoule and vial into a dual-chamber system, enhanced by laser technology, Pacifi's innovation brings DuoVIAL® to market, a unique, patented primary packaging system.[4]

The benefits are that the primary materials, manufacturing processes, form factors, filling and sealing remain broadly similar to those for vials and ampoules, with the exception of introducing a unique laser process – Lasered Annular Cleave Ring (LACR™) – to modify and pre-weaken the glass membrane in a much more precise and controlled way than traditional scoring. The form is also relatively scalable, in terms of diameter, length and chamber ratio to accommodate unit- and multidose and mix-ratio variations.

Simplistically, a single-piece tubular glass form incorporates a LACR'd glass membrane separating the two chambers. The openings at each end can be formed with their respective finish, be it a flange (stopper and seal), thread (screw cap), cylinder (piston) or flared ampoule opening (flame sealed). The vial end, having the smaller inner chamber, may contain the lyophilisate and be extended for increased fill volume, while maintaining a standard neck finish diameter. This minimalist form, produced on relatively conventional glass-forming lines is cost effective, while also delivering an advantageous new format for lyophilised formulations.

The ampoule end may have a thin-wall flared finish, typical of ampoules, enabling a hermetic glass seal through flame sealing. Advantageously, the diluent is only ever in contact with the relatively inert glass during storage. No butyl rubber or siliconisation is required, mitigating the formulation compatibility challenges arising from leachables or silicone oil. This patented packaging system is equally applicable to both glass and polymers, enabling a broader choice of materials, whether driven by barrier performance, formulation compatibility, cost, situational usage, functional features or sustainability drivers.

LACR & SIFT – ENABLING TECHNOLOGIES

During manufacture, specialist LACR technology is applied to the glass membrane to enable the clean-cleave detachment of a contact lens-like disc, wherein any intrinsic sub-visible particles are managed through the Sintered Integral Filter Technology (SIFT™). Notably, this means that all products dispensed from DuoVIAL® are filtered before administration.

LACR is a unique process applied through a clean, non-contact, high-speed, focused beam of light modifying the material. This confidential patented process is light years ahead of traditional glass pre-weakening, ampoule scoring, one point cut, colour break ring or ablation processes. As a highly scalable process, it is both efficient and cost effective in volume production. Having applied and proven the LACR process with Type 1 borosilicate glass samples, further studies are to be conducted with the DuoVIAL® technology. In particular, the aim is to assess transparent polymers, where the injection and associated blow-moulding processes can enable enhanced features, an extended range of form factors and a broader range of applications.

In surgical adhesive and wound care applications, there are medical devices that incorporate glass "onion skin" ampoules to protect liquid formulations in storage with the glass capsule crushed to release the liquid immediately prior to use. In these devices, a filter to ensure that the sterile liquid being applied is fit for purpose and compliant with regulations is integral to the device flow path. Pacifi's SIFT approach is very similar, with value-added design in the form of special SIFT.2K™ applicator tips, incorporating filtration, aesthetic and ergonomic form to apply product to the skin, along with venting to enable flow from the container.

Figure 2 shows a DuoVIAL® 2.5 mL cartridge incorporating a SIFT tip protruding through the glass membrane, having opened a pathway between the powder and liquid chambers, through transfer of force to cleave the disc. The SIFT.2K applicator tip emphasises the aqueous liquid (blue) wicking to the domed surface to be applied to the skin, in contrast with the vent (white) mitigating vacuum and enhancing flow. Having been activated, the clean-cleaved membrane hole has an aesthetic "frosted" surface, a positive consequence of the LACR process. The X-Ray computed tomography image of the cleaved disc emphasises the results of this unique precision process, where the cleaved frosted surface (green, Ra < 1µm), combined with the rounded rim, presents a smooth form, similar to weathered pieces of glass washed up on a beach.

PROTECT

The primary objective of DuoVIAL® is to maintain the stability of the lyophilised drug product from moisture degradation. Glass, being uniquely impermeable and transparent, remains the ideal material for this purpose; alternatively, transparent polymers may also be used. With a first application in topical probiotic therapy, consisting of a lyophilised LBP and aqueous diluent prebiotic, the DuoDERM™ system was conceived as a single-use glass cartridge. The ampoule end is hermetically flame-sealed similar to standard ampoules and the vial end is sealed with aluminium foil by induction.

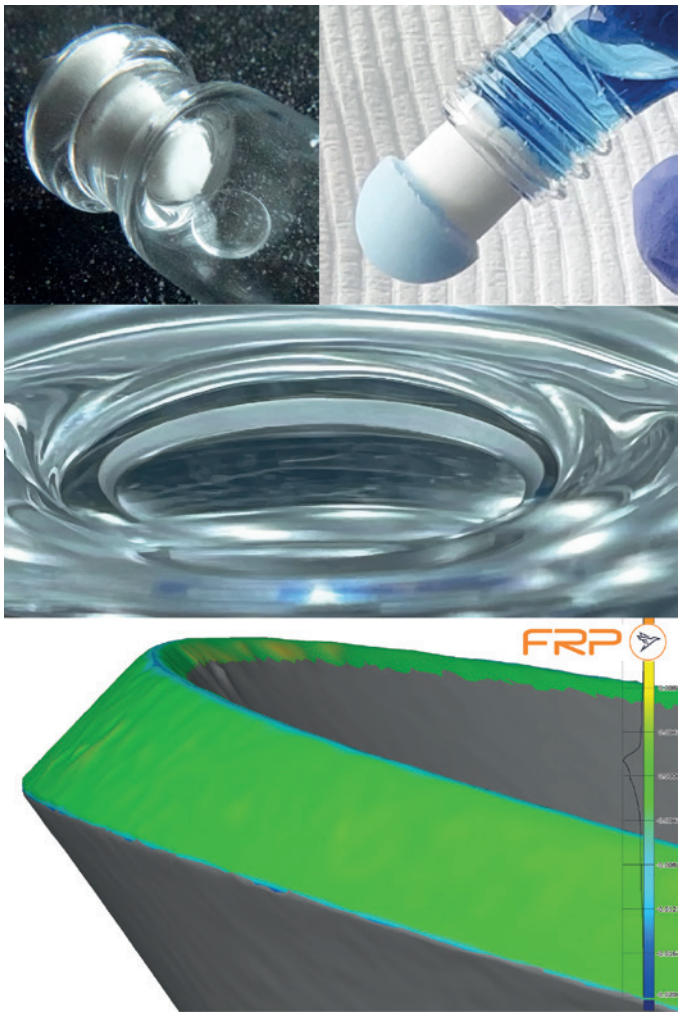

Figure 2: LACR and SIFT technologies – cleavage and filtration.

"THE PRIMARY OBJECTIVE OF DUOVIAL® IS TO MAINTAIN THE STABILITY OF THE LYOPHILISED DRUG PRODUCT FROM MOISTURE DEGRADATION. GLASS, BEING UNIQUELY IMPERMEABLE AND TRANSPARENT, REMAINS THE IDEAL MATERIAL FOR THIS PURPOSE; ALTERNATIVELY, TRANSPARENT POLYMERS MAY ALSO BE USED."

Accelerated stability studies were conducted on a DuoDERM 2.5 mL cartridge containing bacteria preserved in lyophilised powder form over an eight-week period at 40°C and 75% relative

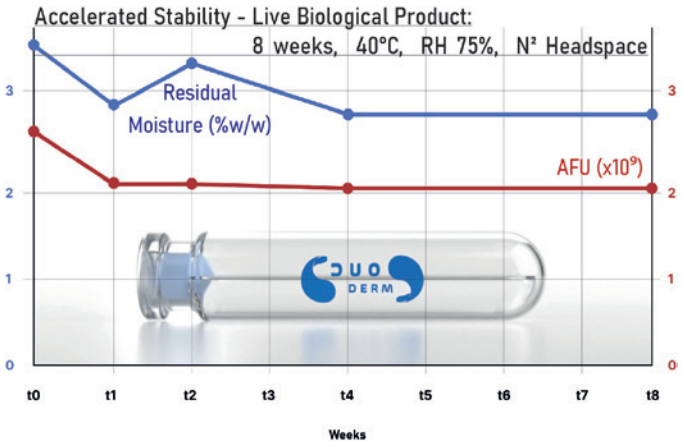

Figure 3: PROTECT – accelerated stability in a DuoDERM cartridge.

humidity, equivalent to two years of real-world conditions (Figure 3). The headspace was filled with nitrogen to displace the atmospheric air. Samples were analysed, confirming a moisture level stabilising at <3% water by weight. Subsequently the live bacteria were reconstituted and analysed to determine the cell survival rates, which remained consistently high.

Protecting the patient, healthcare provider and planet are also potential benefits achieved through DuoVIAL®. The technology ensures administration of safe drug product, mitigates sharps injuries and reduces packaging logistics, material use, waste and costs.

Figure 4: MIX – lyobeads and diluent combined.

MIX

DuoVIAL®'s integral glass membrane is 100% impermeable, keeping the lyophilisate dry and the diluent wet. While there are some attractive dual-chamber systems on the market where frangible polymer membranes are used, some of the common challenges they face include:

- A deliberately thinner wall section, which undermines the intended moisture barrier function
- All polymers are permeable to a greater or lesser degree.

These need to be taken in context – depending upon a formulation's sensitivity to moisture degradation, specific polymers may be fit for purpose. One solution to these challenges is to incorporate a desiccant in the lyo-chamber; however, this approach has both a finite moisture capacity and also draws moisture from the liquid chamber, increasing the liquid formulations' viscosity, lessening its ability to mix and pour. This complex matrix of materials also undermines recyclability initiatives.

For DuoDERM, The LACR'd membrane being pre-weakened allows the disc to be displaced, opening a porthole in the membrane, which allows the liquid and lyophilisate to combine and reconstitute. Agitating the container enhances the mixing process. Figure 4 shows a DuoDERM 2.5 mL cartridge with incorporated lyobeads, alongside an aqueous diluent, separated by the transparent membrane. Aluminium foil is induction-sealed to complete the impermeable lyo-chamber, while the trio of 2.5 mL cartridges contain a lyophilised milled powder and the aluminium foil seal secures the lyophilisate, with the diluent hermetically sealed by flame.

DELIVER

Each formulation is tailored to its administration route and therapy, presenting individual challenges in terms of dosing, whether it be unit-dose or multidose; aqueous-, alcohol- or oil-based; or a solution, emulsion or suspension. In all cases, a key consideration is viscosity. To manage this and provide dispensing flexibility, DuoDERM can incorporate different applicator tips and dispensing mechanisms. In its simplest form, the base is a flame-sealed dome, whilst opposite is a SIFT.2K domed form that filters and wicks the solution to be applied directly to the skin. Alternatively, an airless pump format may be desirable to help protect the formulation from environmental contamination and degradation once activated and during the period of use. Another option is a syringe format with graduations, where the end-user depresses the plunger rod to dispense product via a cannula-like nozzle.

"TO MANAGE THIS AND PROVIDE DISPENSING FLEXIBILITY, DUODERM CAN INCORPORATE DIFFERENT APPLICATOR TIPS AND DISPENSING MECHANISMS."

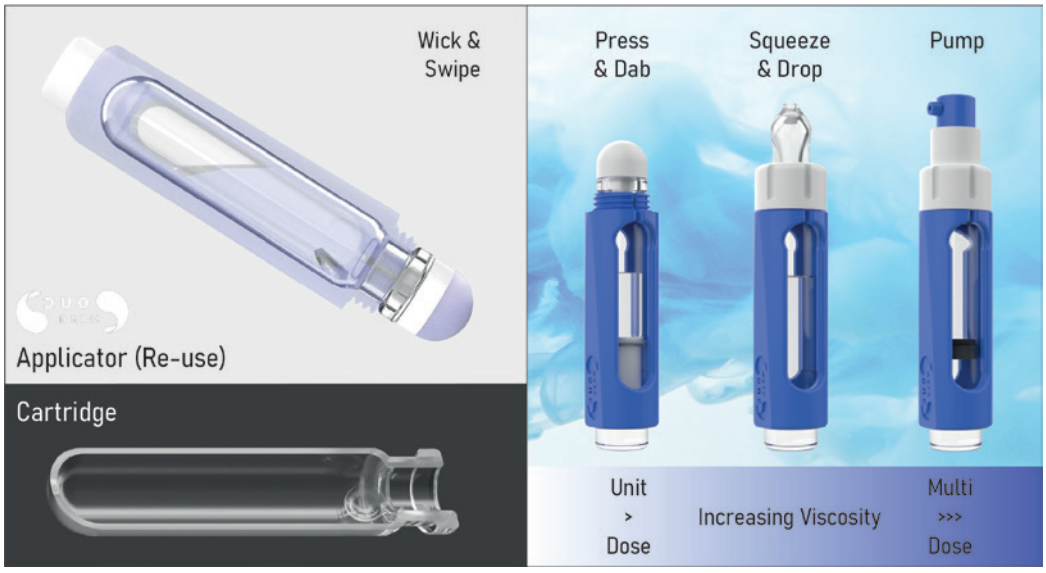

Figure 5: DELIVER – topical applicator portfolio.

Figure 5 shows the DuoDERM system in its simplest cartridge form, incorporating the DuoVIAL® packaging technology, including a reusable applicator for activation and administration of therapies contained in single-use cartridges. The SIFT.2K tip transfers user-applied cap torque, cleaving the glass membrane, enabling reconstitution, while wicking the solution to the tip where it is applied to the skin.

Although DuoVIAL® offers benefits across sectors from diagnostics to cosmetics, its primary focus is healthcare, with broad therapeutic and administration potential. The long-term goal is parenteral vaccines; however, the initial focus is topical therapies. In dermatology, conditions such as atopic dermatitis, eczema and acne affect large populations, where conventional small-molecule treatments, such as steroids, carry undesirable side effects.

An emerging alternative – restoring skin microbiome balance via topical applications of commensal live bacteria are advancing through clinical trials. Like vaccines, these LBPs benefit from lyophilisation for stability. In this case, an unskilled consumer is required to reconstitute their medication in a non-clinical environment and apply as prescribed. However, existing pharmaceutical packaging is often unsuitable or carries unacceptable consumer risk. DuoDERM, incorporating DuoVIAL® technology, addresses these challenges, providing a safe and easy-to-use packaging system.

ABOUT THE COMPANY

Pacifi commercialises healthcare packaging solutions that mitigate end-user frustration, error and injury. DuoVIAL® is the company's core primary packaging technology, enabling a portfolio of applications to protect, mix and deliver as part of a safer, easier to use and more cost-effective system.

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Gareth Pearce

Gareth Pearce, Founder and Director of Pacifi, began his career developing and commercialising prefilled syringe-based drug delivery systems, and he has worked across all administration routes, including complex respiratory devices. Broad experience of the main pharmaceutical packaging components, materials and processes, combined with exposure to market and end-user safety challenges led to him develop the DuoVIAL® packaging technology. With an initial focus on topical applications, he won Pharmapack 2022's "High Commendation" packaging innovation award for DuoDERM. Real-world industry experience has led him to focus on innovation and establishing healthcare packaging solutions that minimise frustration error and injury.

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20 YEARS ON drugDELIVERY

HIGH SPEED LASER ASSEMBLY – FLEXIBLE MACHINE CONCEPTS WITH FULL LASER INTEGRATION

CONTEXO automation

Matthias Müller of **Contexo** discusses the advantages of including laser technology in drug delivery device manufacturing, covering the various ways in which this technology can be applied and used to provide efficient, cost-effective and clean processes at high throughput rates.

Modern laser technology is conquering more and more industry sectors. What seemed unthinkable only a few years ago is now possible. It therefore makes sense to integrate this technology into product assembly in a targeted manner. The pharmaceutical industry, specifically, is faced with a particular challenge – it must strike a balance between costs, time and efficiency while also taking sustainability and patient-centric goals into account.

With access to all relevant laser manufacturers and technologies, Contexo can provide comprehensive solutions and find the perfect fit for a given machine. The company can provides full support throughout the product development process. If included early on, Contexo's valuable know-how can accelerate the development process, generate solutions and help ensure efficient production.

Integrating laser processes enables fast, cost-effective manufacturing with consistent results and a consistently high level of quality. Since laser operations are contactless, they are vibration-free and permit a high degree of geometric freedom.

> "SINCE LASER OPERATIONS ARE CONTACTLESS, THEY ARE VIBRATION-FREE AND PERMIT A HIGH DEGREE OF GEOMETRIC FREEDOM."

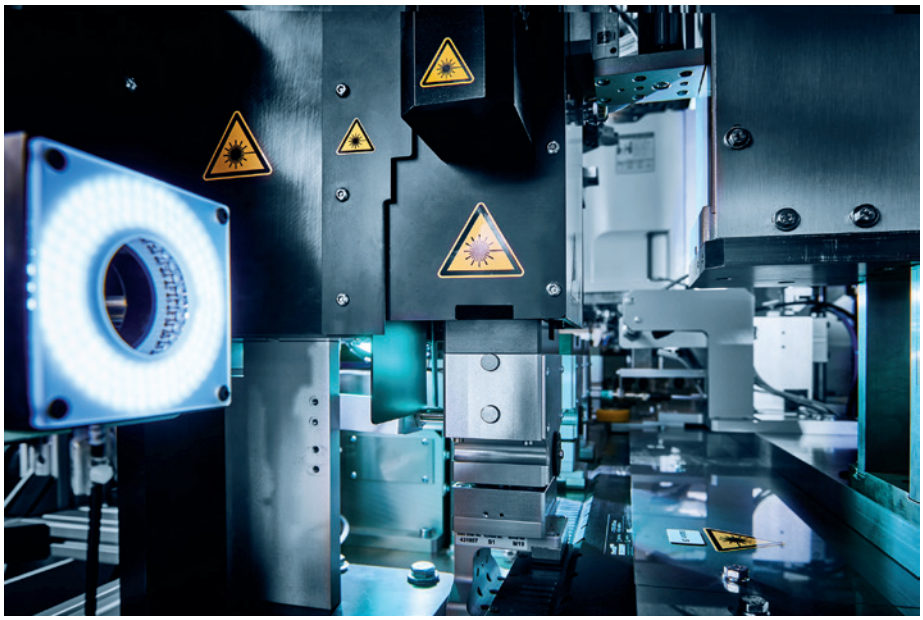

Figure 1: High flexibility – for product variants.

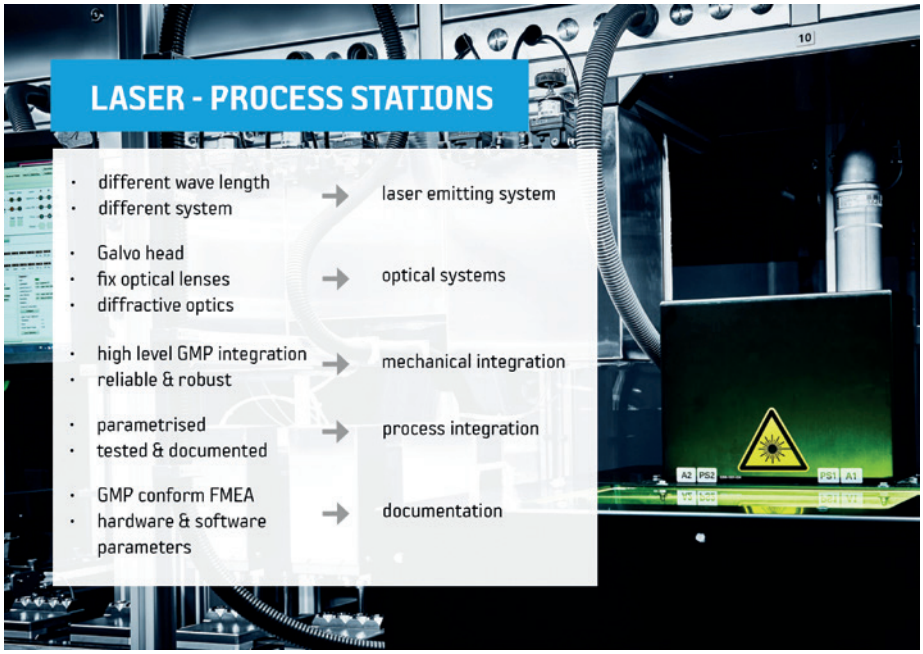

Figure 2: Laser integration – flexible and precise processes.

In addition to extraordinary precision and short cycle times, flexibility is another decisive factor when selecting the right processes, for example for product variants (Figure 1).

Lasers facilitate the rapid, uniform and protective movement of materials in high-speed automation processes. The parts are presented to the laser in precisely repeated operations to ensure the highest possible quality. The solid, durable design of Contexo systems and the fine process control of laser technology can ensure safe, clean and reliable production.

Contexo has extensive knowledge of laser integration and assembly technology (Figure 2), be it for safety syringes, eyedroppers, nasal devices, caps, novel syringe systems or others. In all areas, a good development partner should play a central role, offering professional project management assistance at every stage.

"LASER PLASTIC WELDING IS IDEAL FOR APPLICATIONS WHERE HIGH DEMANDS ARE PLACED ON WELDING AND PROCESS RELIABILITY."

LASER INTEGRATION: FLEXIBLE AND PRECISE PROCESSES

Four common technologies are regularly incorporated into Contexo assembly systems – laser welding, laser drilling/perforation, laser cutting and laser marking.

Laser Welding

Laser plastic welding is ideal for applications where high demands are placed on welding and process reliability. Contexo uses different processes to ensure particle-free production and safe, hygienic conditions, including:

- Simultaneous
- Quasi-simultaneous
- Rotative
- Contour
- Mask.

Both the movement of the source and the movement of the product are possible. This makes it ideal for seal welds, container welds and more.

Laser Drilling/Perforation

Micro-holes in plastics and nozzle openings in the micrometre range can be efficiently integrated using innovative laser technology. High reproducibility with narrow tolerance limits is guaranteed. The methods used include:

- Single pulse
- Percussion
- 5-axis trepanning.

These methods are ideal for tamper evidence (TE) functions, predetermined breaking points and flow holes.

Laser Cutting

Laser cutting is an energy-efficient method of cutting plastics that produces precise edges. The parts can be processed flexibly, precisely and without wear. The process remains clean thanks to efficient air purification. The methods used include:

- Fusion cutting
- Sublimation cutting.

This is ideal for achieving high edge quality and for working with very thin materials, fragile and heat-sensitive parts, TE functions and predetermined breaking points.

Laser Marking

Laser marking has developed into one of the most important labelling methods. Thanks to ongoing advancements, plastics can now be labelled, engraved or modified using lasers. The result is permanent legibility and high-quality laser labelling. The methods used include:

- Foaming
- Discolouring
- Engraving
- Ablation.

Laser marking is ideal for data matrices, unique device identification coding, tracking and tracing, functional declarations and technical prints.

Figure 3: Assembly machine – mini-laboratory for diagnosing infection diseases.

"THANKS TO ONGOING ADVANCEMENTS, PLASTICS CAN NOW BE LABELLED, ENGRAVED OR MODIFIED USING LASERS."

APPLICATION

Whether it's 800,000 diagnostic kits or 1.2 million insulin doses per day, Contexo designs and builds cleanroom machines for producing complex medical devices in large quantities. Contexo designed and built a highly innovative mini-laboratory for diagnosing infectious diseases (Figure 3), marking a milestone in molecular medical technology. Needless to say, production of medical applications takes place in cleanroom conditions and in accordance with international regulations.

Contexo uses highly efficient, space-saving machine systems with standardised modules for assembly, sealing, stamping, welding and inspection, with laser and other process steps flexibly integrated (Figure 4). Precise processes and controls ensure that all medical devices satisfy the strictest requirements. This means that one machine concept can be operated efficiently in the long term, even in the event of product modifications or additions.

As an example, Contexo was faced with the challenge of assembling an analysis cartridge (Figure 5). The task was to assemble seven components, perform laser welding and quality control on five criteria, then reach a production rate of 10 million parts per year. To implement this, Contexo used linear indexing with a one- and two-lane layout and 36 stations,

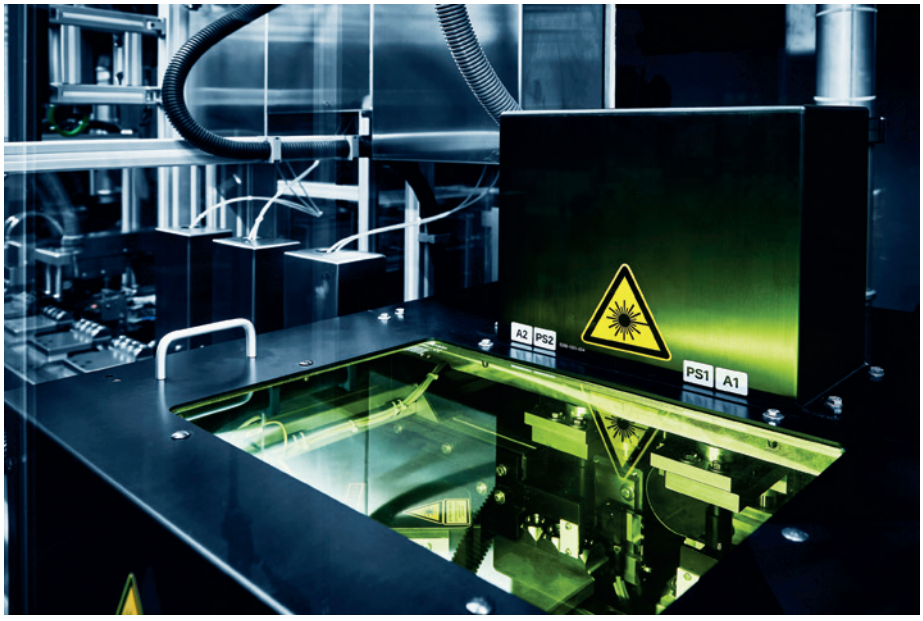

Figure 4: Fully integrated laser system.

with direct chaining and a tray packing portal. The line can produce 30 parts per minute and features three product formats; two integrated lasers; an integrated leak test for the chambers; inline vision inspection; and a change from Type 1 to Type 2 in under five minutes with no mechanical refit required.

Laser plastic welding is always the most economical solution when high demands are placed on welding and process reliability. No other process is safer, more hygienic or faster. Even complex, three-dimensional designs are no obstacle. This is how ideas become products.

FULLY AUTOMATED PRODUCTION WITH LASER INTEGRATION

The following are the key advantages and benefits of fully automated assembly systems, which enable fast time-to-market and reliable production for years to come:

1. High output quantities, perfectly suited to mass production
2. Efficient assembly and precise lasering
3. Quality control – 100% inline with no time loss
4. The maximum number of processes can be integrated
5. Cleanroom environment
6. Full laser integration
7. Flexible machine concepts
8. 64 process steps with up to 80 cycles per minute
9. Complex parts can be manufactured cost-efficiently
10. An ideal platform for innovative products.

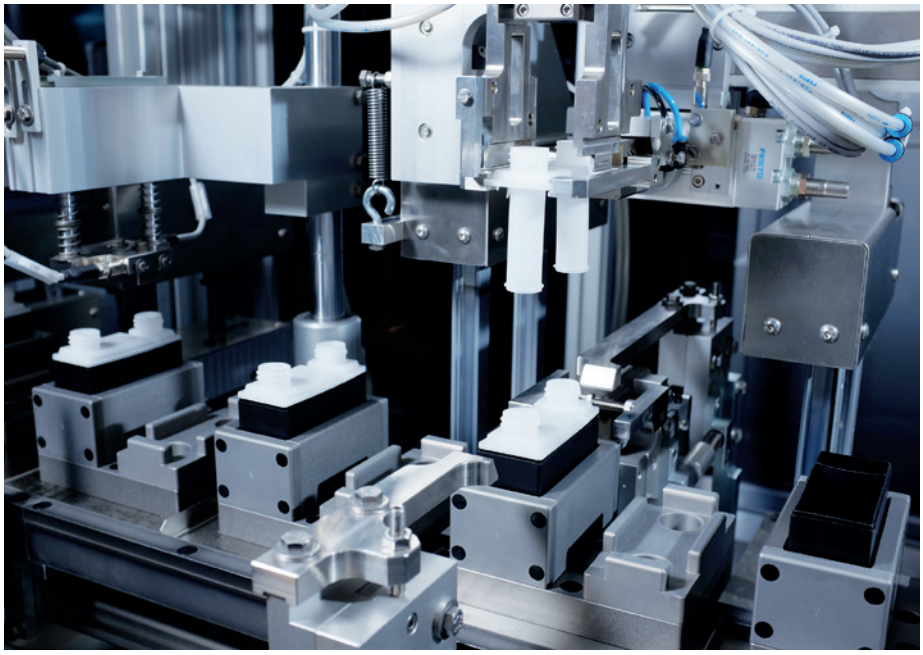

Figure 5: Analysis cartridge assembly.

Matthias Müller

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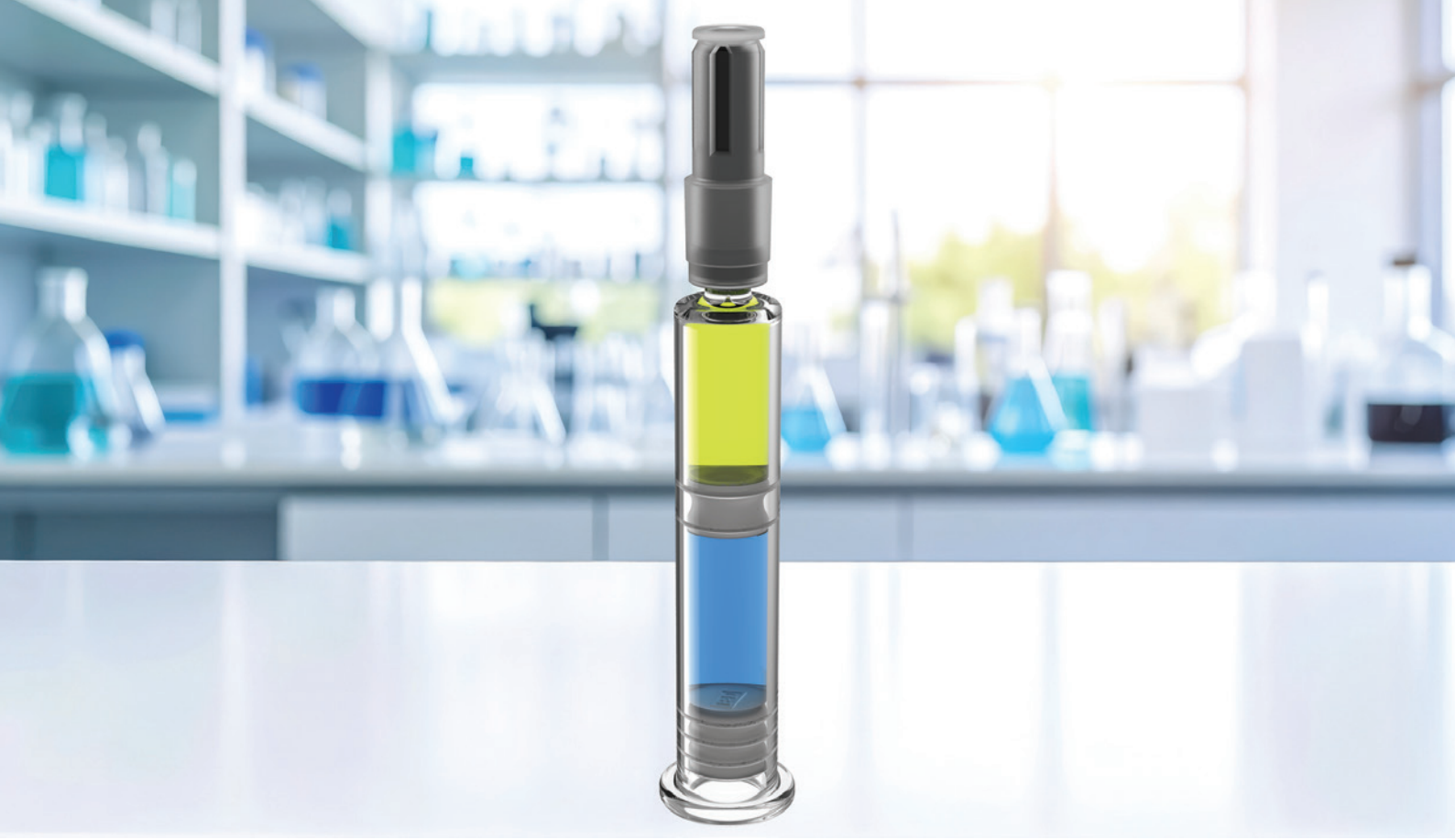

REIMAGINING DUAL-CHAMBER INJECTION: DE-RISKING A NOVEL VALVE COMPONENT FOR USE WITH STANDARD SYRINGE SYSTEMS

BD
Advancing the world of health™

Marc Flippe and **Sophie Lelias** of **BD** introduce a novel valve component designed to enable dual-chamber functionality within standard syringe and autoinjector platforms. Developed through a comprehensive modelling and development framework, the BD dual-injection syringe system provides a scalable solution to dual-chamber injection that reduces the burden of change by preserving compatibility with established container formats and device architectures.

As the pharmaceutical industry continues to explore innovative drug formulation and delivery strategies, the co-formulation of drugs has emerged as a compelling approach, particularly for fixed-dose combinations of synergistic therapies targeting distinct mechanisms of action. While this strategy is well established for small molecules in areas such as infectious disease, diabetes and neurological diseases, its application to biologics is currently gaining momentum.[1,2] The 2020 US FDA approval of the first co-formulated monoclonal antibodies marked a significant milestone, opening the door to broader application of co-formulated drugs across the global development pipeline.

Such co-formulations can offer multiple advantages, including enhanced therapeutic efficacy, reduced adverse effects, fewer required injections, cost efficiencies and intellectual property protection.[1–3] For example, using a combination of antibodies could offer a more effective therapeutic intervention, as multiple epitopes can be addressed within a single drug product.[3] However, these complex mixtures may also introduce significant development risks, including cross-reactivity, physical and chemical instability, safety concerns and complex analytical characterisation.[1–3] This may be especially true for protein formulations with different pHs, excipient types and ionic strengths.[1]

An alternative to co-formulation may be dual injection, allowing for co-administration of two liquid drugs while maintaining separation until use. This

approach may avoid the risks associated with the interaction of two drug formulations prior to use while preserving the benefits of combination therapies. 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 standard container and device platforms and increasing drug-device development complexity.

To address these challenges, 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 prefillable syringe and autoinjector devices. Using an incremental innovation approach, this solution builds on known materials and device architectures to minimise risk for pharmaceutical developers. The BD dual-injection valve features an external shape designed to support compatibility with existing syringe systems, and integrates a novel slitted valve engineered to maintain separation of two liquid drugs in a standard syringe until use.

To de-risk the development and integration of this novel component into existing delivery platforms, BD employed a comprehensive modelling and simulation framework. This approach confirmed that dual-chamber functionality can be achieved with the BD dual-injection valve within standard prefillable syringe systems without requiring changes to the primary container, or major changes to the delivery device components or established processes, offering a streamlined and de-risked solution for pharmaceutical developers pursuing dual-injection delivery.

"THE BD DUAL-INJECTION VALVE FEATURES AN EXTERNAL SHAPE DESIGNED TO SUPPORT COMPATIBILITY WITH EXISTING SYRINGE SYSTEMS, AND INTEGRATES A NOVEL SLITTED VALVE ENGINEERED TO MAINTAIN SEPARATION OF TWO LIQUID DRUGS IN A STANDARD SYRINGE UNTIL USE."

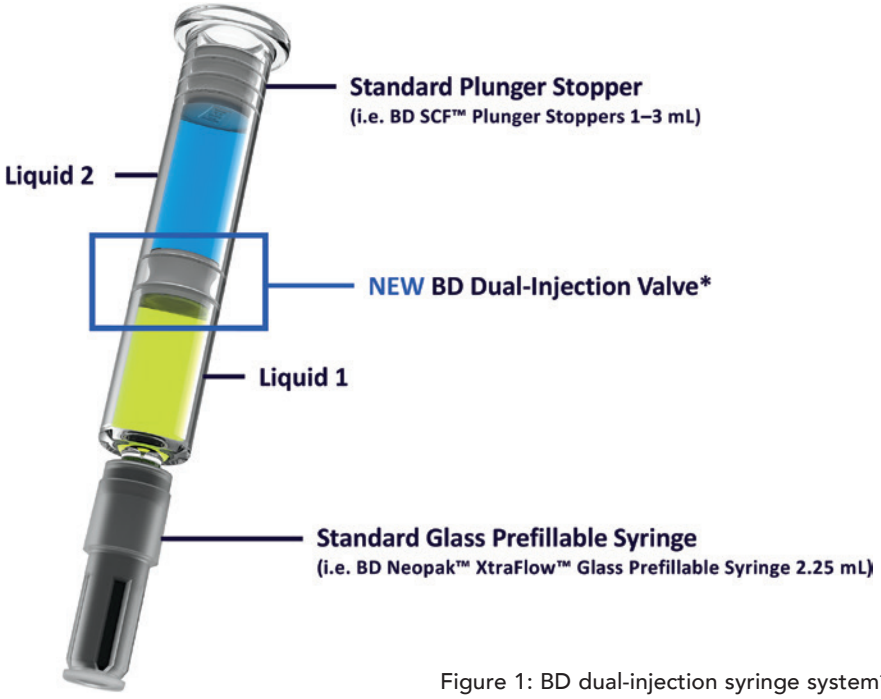

Figure 1: BD dual-injection syringe system*.

OVERVIEW OF THE BD DUAL-INJECTION SYRINGE SYSTEM

As a global leader in prefillable syringes and drug delivery systems, BD has drawn on its extensive expertise to develop the BD dual-injection syringe system (Figure 1). This system is designed to enable dual-injection delivery of two liquid drug formulations while maintaining compatibility within standard prefillable syringe and autoinjector systems.

At the core of this system is a novel valve component that maintains physical separation of the two liquids within a single syringe until use. Upon activation, Liquid 1 and Liquid 2 are administered, with Liquid 2 passing through the valve. This enables complete dual injection without the need for a bypass channel or specialised container geometry, meaning that it can be used in standard glass prefillable syringe, such as the BD Neopak™ Glass Prefillable Syringe platform.

The dual-injection valve component is designed with an external shape that eases syringe system integration and processing on existing pharmaceutical manufacturing lines. It is designed to provide dual-chamber functionality to a syringe system, isolating the two drugs prior to delivery, and incorporates a central slitted valve (Figure 2), engineered to open during injection, allowing for a controlled flow. Uniquely, the valve component is functionally symmetrical, simplifying orientation during automated handling. Furthermore, it uses well-characterised materials and validated packaging and sterilisation processes, thereby reducing the regulatory and operational risks typically associated with adopting a new component.

Figure 2: Top view of the BD dual-injection valve*.

DE-RISKING DEVELOPMENT WITH MODELLING AND SIMULATIONS

A critical objective in the development of the BD dual-injection valve and syringe system was to ensure reliable dual-chamber functionality without requiring any significant changes to the primary container platform, standard autoinjector systems or existing fill-finish operations. To achieve this, BD applied a rigorous design approach grounded in advanced modelling, simulation and iterative analyses (Figure 3).

The development framework began with the definition of key input parameters, including material properties, design geometry, customer-process parameters and manufacturing tolerances. These inputs were used to drive a suite of physics-based simulations, ranging from finite element analyses to fluid dynamics to seal integrity and assembly modelling. Together, these tools enabled BD to predict and optimise system design and behaviour under a wide range of real-world conditions.

By integrating these models into a unified framework, BD was able to evaluate key performance metrics, such as injection forces, valve actuation, fill volume accuracy and robustness, across various environmental and mechanical stressors. This predictive capability was essential for de-risking the design and ensuring that the BD dual-injection valve and syringe system could deliver reliable, reproducible performance while maintaining compatibility with existing manufacturing processes and autoinjector platforms.

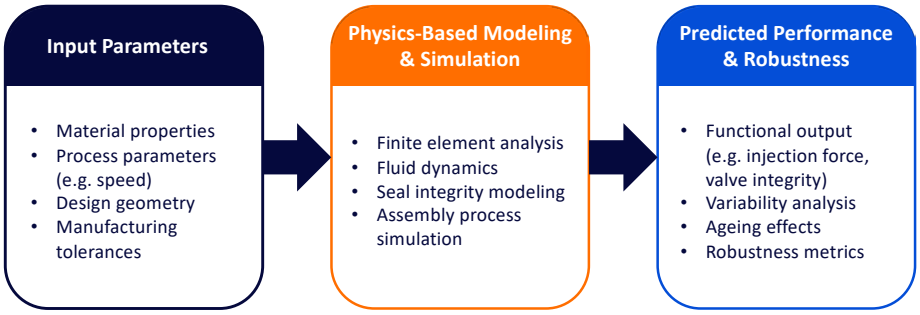

Figure 3: High-level design approach to de-risk BD dual-injection valve design.

Fill-Finish Modelling

To de-risk the fill-finish processability of the BD dual-injection valve and syringe system, BD implemented a comprehensive stack-up modelling approach that integrated both dimensional and functional design parameters. This methodology incorporated variability assessments to define maximum injectable dose and required fill volumes, including overfill margins, accurately by triangulating finite element modelling inputs.

The modelling also enabled precise prediction of the positions and dynamic movements of both the novel valve (Figure 4) and the plunger stopper throughout the anticipated drug-device combination product lifecycle. Furthermore, it accounted for environmental changes, including pressure and temperature variations, during fill-finish operations or during air shipment, ensuring robust system behaviour under real-world conditions.

Additionally, the framework supported key integration calculations, such as the plunger stopper's position before and after injection, reinforcing confidence in system performance from filling to transport and final injection.

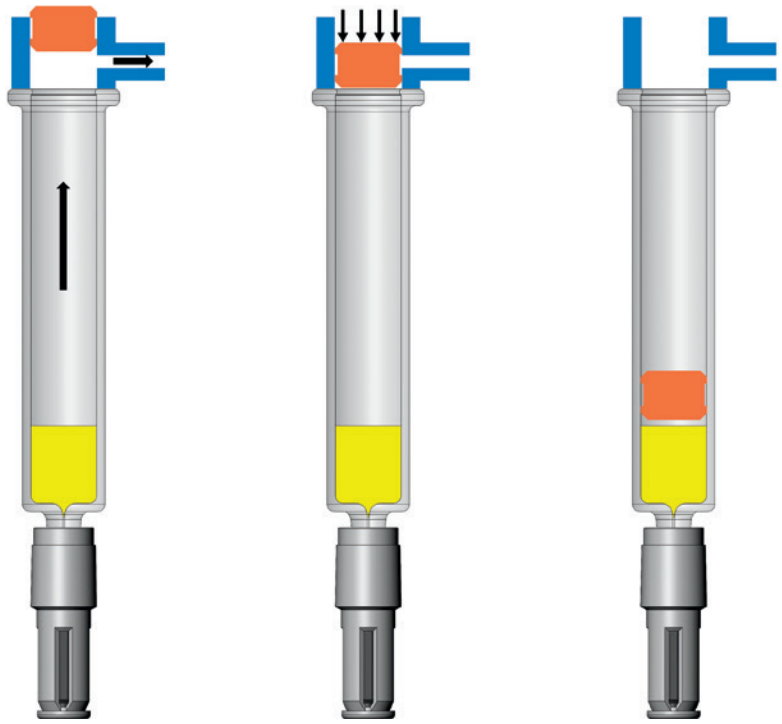

Figure 4: Schematic view of the dynamic movement during the stoppering step for the BD dual-injection valve component.

FEA Simulations

Finite element analysis (FEA) simulations were employed to analyse and optimise the design within a defined space, ensuring that functional performance is maintained throughout the final drug-device combination product lifecycle. The accuracy of these simulations was verified by BD through targeted physical testing, providing a high level of confidence in the predictive outcomes.

This approach enabled detailed characterisation of component behaviour within the prefillable syringe system and its interaction with the final delivery device, such as a standard disposable autoinjector. These finite element simulations were particularly critical for sizing and evaluating the novel valve component, where certain behaviours may be difficult to observe or quantify through conventional testing alone.

Fluidic Modelling

Fluidic modelling was used to analyse flow dynamics and backpressure behaviour throughout the valve featuring complex, pressure-driven geometry. This approach enabled detailed evaluation of the valve's performance across the full range of product use conditions, such as during autoinjector-based injection. The modelling captured the entire sequence, from initial pressure buildup on the valve surface, through valve opening to complete liquid transfer (Figure 5). This modelling proved to be essential for optimising the valve geometry and ensuring consistent performance under varying mechanical pressures.

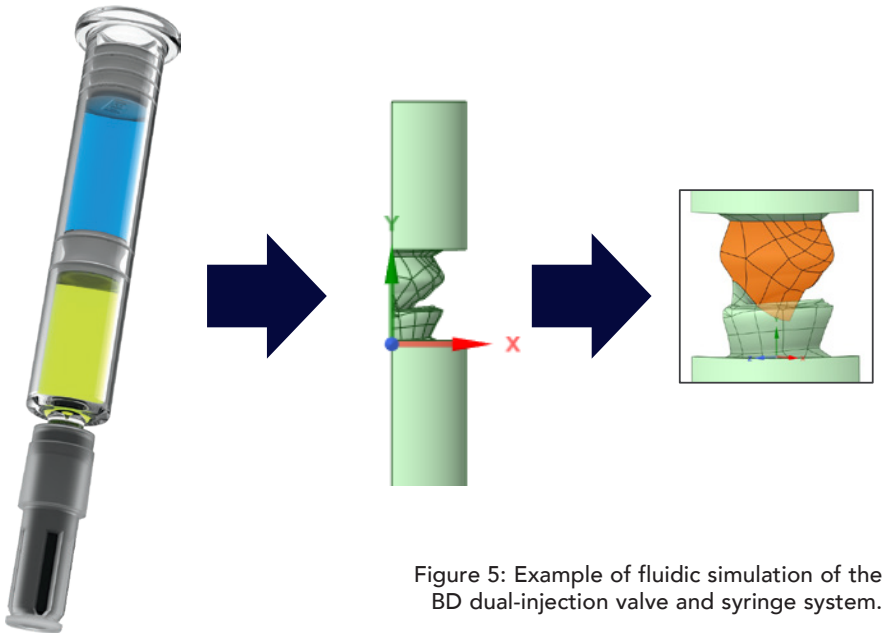

Figure 5: Example of fluidic simulation of the BD dual-injection valve and syringe system.

Rubber Tightness and Valve Integrity Modelling

BD is able to draw on decades of expertise in rubber component development and optimisation across its vast product portfolio, which gives it a robust understanding of the physical drivers that govern slitted valve and component integrity throughout the product lifecycle. By embedding various key inputs into physics-based simulations, BD can anticipate how the tightness of a valve evolves with time and under stress, ensuring reliable valve integrity from fill-finish through final use at point of delivery.

"BD IS ABLE TO DRAW ON DECADES OF EXPERTISE IN RUBBER COMPONENT DEVELOPMENT AND OPTIMISATION ACROSS ITS VAST PRODUCT PORTFOLIO, WHICH GIVES IT A ROBUST UNDERSTANDING OF THE PHYSICAL DRIVERS THAT GOVERN SLITTED VALVE AND COMPONENT INTEGRITY THROUGHOUT THE PRODUCT LIFECYCLE."

To assess valve tightness, BD applied Persson's multiscale contact mechanics theory, which enables analysts to predict the sealing behaviour of a given interface, considering the materials' mechanical properties, the roughness of both surfaces and the interface geometry.[4–6] This approach enables accurate prediction of interfacial stress distributions and separations, which are critical for evaluating leakage risk (Figure 6). The valve's slitted geometry and surrounding ribs are modelled to reflect deformation behaviour, incorporating material properties and surface roughness profiles.

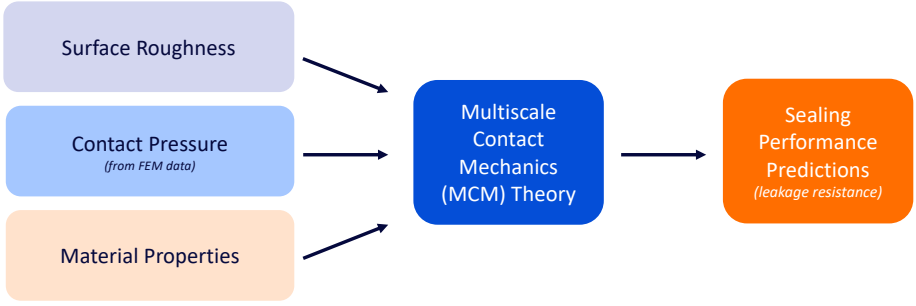

Figure 6: High-level theoretical approach leading to sealing performance predictions of a given interface.

By embedding use-case and operational parameters into the simulation, BD can anticipate how valve tightness changes over time and under mechanical or thermal stress. This includes predicting the onset of deformation and its impact on seal integrity. The modelling also supports design optimisation by identifying critical thresholds for leakage and ensuring the valve maintains reliable separation and delivery performance from manufacturing to final use.

Autoinjector Integration Modelling

With extensive experience in prefillable syringe and autoinjector system integration, BD employs a comprehensive, end-to-end modelling approach for de-risking and predicting injection performance. This modelling framework predicts key functional parameters, such as injection force and injection time, based on potential physical properties of the filled drug, including viscosity and density. The injection model developed by BD can support single- and dual-drug configurations, accounting for various

secondary device parameters, enabling pharmaceutical developers to anticipate performance across a range of scenarios (Figure 7).

Importantly, this model is interconnected with other BD simulation domains, including FEA and fluidic modelling, allowing for a holistic understanding of autoinjector system behaviour. This integrated approach may help to ensure that system performance can be reliably anticipated in real-world situations, enhancing confidence in device functionality and the end injection experience (Figure 8).

The result is a predictive capability that confirms the BD dual injection system maintains a similar performance profile compared with standard single-chamber prefillable syringes in an autoinjector format. This ensures streamlined integration into existing autoinjector platforms, minimising the need for design changes and supporting efficient development of combination products.

CONCLUSION

The BD dual-injection valve and syringe system was created in response to the ever-evolving pharmaceutical development pipeline, particularly in the context of biologics. As co-formulated and co-administered therapies continue to gain traction for their potential to improve efficacy, reduce the burden of injections and enhance patient outcomes, they may also introduce formulation and delivery challenges, especially when facing incongruent or reactive excipients, pH profiles or stability requirements. Dual injection, where two liquid drugs are kept physically separated until use, offers a compelling alternative to co-formulation.

"IMPORTANTLY, THIS MODEL IS INTERCONNECTED WITH OTHER BD SIMULATION DOMAINS, INCLUDING FEA AND FLUIDIC MODELLING, ALLOWING FOR A HOLISTIC UNDERSTANDING OF AUTOINJECTOR SYSTEM BEHAVIOUR. "

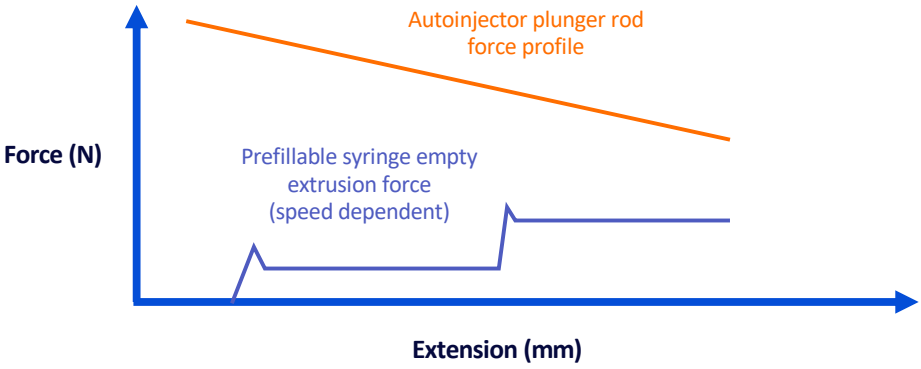

Figure 7: Graph representing the BD dual-injection syringe system force profiles in a mock autoinjector.

The BD dual-injection valve integrates dual-chamber functionality into a standard syringe format, supporting efficient manufacturing and straightforward compatibility with existing autoinjector platforms, allowing for reliable drug delivery. By enabling pharmaceutical developers to use existing container and device systems, this innovation supports de-risked, adaptable, accelerated and scalable drug-device combination product development.

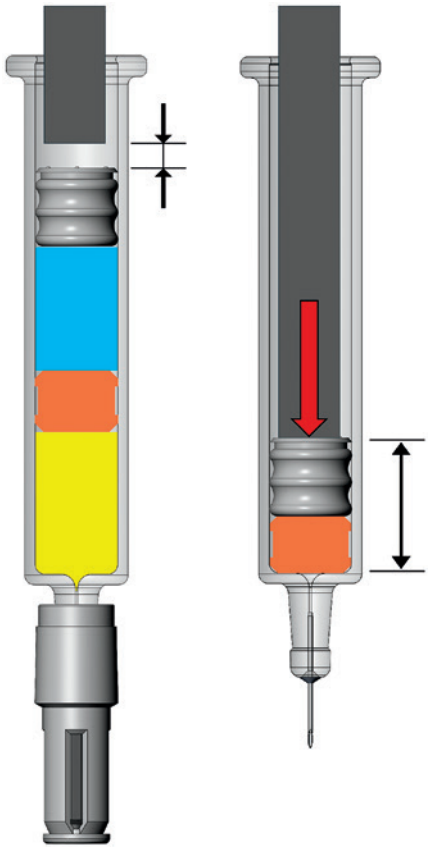

Figure 8: Simulation of BD dual-injection syringe system before and after injection.

To inform and de-risk the BD dual-injection valve design, BD applied a rigorous product development pathway, using cutting-edge modelling, theories and simulation methods. Combined with extensive product expertise built on over 125 years of purpose-driven innovation, BD remains committed to delivering innovative drug delivery solutions that help its pharmaceutical partners meet the demand of today's pipeline and tomorrow's possibilities. To fully realise this potential, continued collaboration across the pharmaceutical ecosystem, such as with machine makers, CDMOs and autoinjector suppliers, is essential. BD invites these "partners of partners" to join in shaping the future of drug delivery and accelerating access to differentiated therapies for patients worldwide.

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

ACKNOWLEDGEMENTS

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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, leveraging 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 a Senior Marketing Manager, Global Marketing at BD, where she leads strategic portfolio marketing for the Biologics Prefillable Syringe portfolio, including BD Hypak™ for Biotech and BD Neopak™ Glass Prefillable Syringe platforms. She collaborates closely with global and regional teams across multiple markets to deliver innovative and value-driven solutions for biologic drug delivery. Throughout her career at BD, 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) and is passionate about advancing patient-centric innovation in drug delivery.

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2026 Event Calendar

PharmaED RESOURCES, INC

Cleaning Validation Summit 2026
February 24-25, La Jolla, CA

Connected Devices & Digital Health 2026
March 24-25, Philadelphia, PA

Extractables and Leachables 2026
April 14-15, Raleigh, NC

Combination Products Summit 2026
May 13-14, Philadelphia, PA

Microneedle & Transdermal Delivery Forum 2026
September 16-17, Philadelphia, PA

Aseptic Processing Summit 2026
October 27-28, Philadelphia, PA

Extractables & Leachables West 2026
November 4-5, La Jolla, CA

Pre-filled Syringes & Injection Devices 2026
December 9-10, La Jolla, CA

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BD offers an integrated Prefillable Syringe system approach, backed by a comprehensive portfolio of syringes, stoppers and other drug delivery solutions.

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The latest addition to the BD Neopak™ Glass Prefillable Syringe platform is our BD Neopak™ XtraFlow™ Glass Prefillable Syringe.

Featuring a shorter (8mm) needle length and thinner wall cannula, the BD Neopak™ XtraFlow™ Glass Prefillable syringe has been designed to optimize subcutaneous delivery of higher viscosity drug formulations >15cP.[3,*]

The BD Neopak™ Glass Prefillable Syringe Platform can be leveraged with our BD SCF™ PremiumCoat® Plunger Stopper, available in 1mlL and 1-3mL sizes.

BD SCF™ PremiumCoat® supports:

- Improved functional performance due to reduced glide force and glide force variability**[5,6]
- Container Closure Integrity with guarantee of no ribs not touching[7,8]
- 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

ADVANCING LYOPHILISED DRUG DEVELOPMENT IN DUAL-CHAMBER SYSTEMS

Dr Markus Neumeier of **Vetter** details the lyophilisation process and the range of elements that need to be examined for a dual-chamber system undergoing freeze-drying, while also laying out the quality control processes to conduct when transitioning from the laboratory to industrial-scale operations.

The injectable drug market is continuing to evolve in response to the growing demand from pharmaceutical and biotech companies for innovative delivery systems that improve patient convenience and safety. Prefilled systems offer a streamlined, user-friendly alternative that provides advantages in terms of safety, dosing accuracy and lifecycle management.

Dual-chamber systems provide a packaging and delivery system that can offer significant added value to parenteral drug products. These systems contain both the lyophilised drug and its diluent in a single device, separated by a middle stopper. This innovative system is an alternative to traditional vial-and-syringe combinations and greatly simplifies the administration process, reduces the risk of contamination and effectively minimises drug overage (Figure 1). However, the lifecycle of a drug product, from a lyophilised vial to a dual-chamber system, faces a variety of technical and regulatory challenges.

PROCESS DEVELOPMENT FOR LYOPHILISED DRUG PRODUCTS

The successful development of a lyophilised product in a dual-chamber system requires an in-depth understanding of the formulation's properties, the packaging materials and the parameters of the manufacturing process and equipment. A robust lyophilisation cycle is founded on the thermal characterisation of the unique API formulation. Once these elements have been identified, they undergo a holistic,

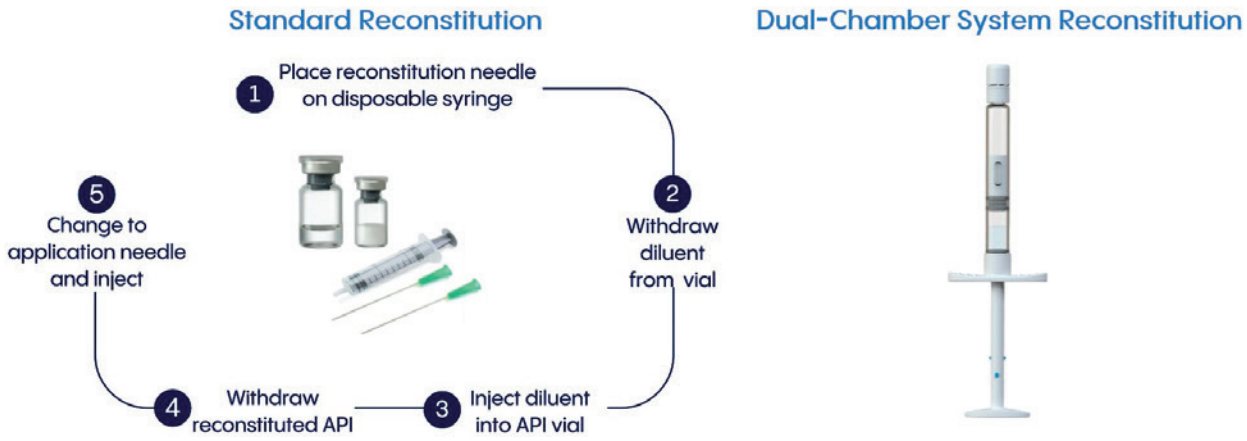


Figure 1: Comparison of traditional vial syringe versus dual-chamber system reconstitution (example shown is Vetter Lyo-Ject® syringe).

"THE UNIQUE GEOMETRY AND SILICONISATION OF THE PACKAGING COMPONENTS INFLUENCE THE FREEZE-DRYING PROCESS."

small-scale development process to create a strong package. Completion of this process leads to a successful qualification of a lyophilised product in a dual-chamber system.

The lyophilisation cycle is usually divided into three phases: the freezing phase, primary drying and secondary drying. Each phase requires specific input parameters, such as shelf temperature and chamber pressure, which must be correlated with output parameters, such as product temperature and sublimation rate. Using a "Design of Experiments" approach involving different temperature and pressure combinations can help to establish a product specific design space and specification limits.

Packaging Materials

The transition from a lyophilised vial to a dual-chamber system requires careful evaluation of the packaging components. A typical dual-chamber syringe consists of a siliconised glass barrel, middle and end stoppers and a closure part. Compared with vials, the glass barrel for a dual-chamber system is longer and has a smaller inner diameter, affecting heat transfer during lyophilisation.

The unique geometry and siliconisation of the packaging components influence the freeze-drying process. The design of the dual-chamber glass barrels results in a sublimation process that is separate from direct shelf contact. Unlike vials, dual-chamber systems require magazine-based processing to maintain an upright position throughout the manufacturing process. Additionally, the sealing must occur under atmospheric pressure as opposed to under partial vacuum to prevent stopper movement.

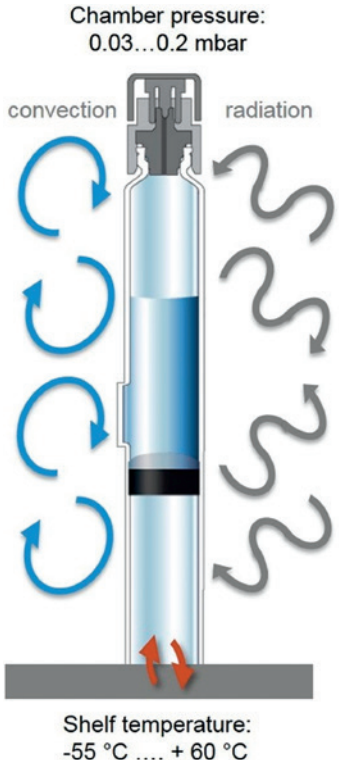
Thermal Product Properties

Compared with lyophilisation in a vial with direct contact to the freeze dryer shelves, the drying process in dual-chamber systems is governed by different driving forces – primarily by convection and radiation rather than direct heat conduction from the shelves. These altered heat transfer dynamics necessitate closer scrutiny of sublimation behaviour. Key parameters such as fill volume, cake height and mass concentration directly affect product resistance and drying performance.

Therefore, it is essential to monitor product temperature and drying time, as these are linked to output parameters such as cake appearance and residual moisture levels. These factors must be evaluated alongside critical quality attributes during drug product stability studies to validate the lyophilisation cycle.

Heat Transfer Mechanisms in Freeze Drying

During lyophilisation, heat transfer in a dual-chamber system occurs via conduction, convection and radiation. The sum of all three mechanisms determines the overall heat transfer rate (dQ/dt), which can be derived using the formula shown in Figure 2.



$$\frac{dQ}{dt} = A_v K_v (T_s - T_p)$$

Figure 2: Heat transfer mechanisms during freeze drying in a dual-chamber system.

It uses the following variables: (Ts – Tp) for the difference between the shelf temperature and the product temperature; Av for the cross-sectional area of the glass barrel; and Kv for the heat transfer coefficient. In a dual-chamber system, convection dominates during the freezing phase due to atmospheric pressure, while radiation becomes the primary mechanism during primary and secondary drying under vacuum conditions. This is a major difference compared with lyophilised vials.

As the product is not in direct contact with the shelf, its temperature is only indirectly influenced by the shelf temperature. This makes drug products in dual-chamber systems more susceptible to edge effects, regardless of formulation or fill volume. Understanding these dynamics is crucial for designing a robust lyophilisation cycle.

Sublimation Rate Considerations

The sublimation rate, a key determinant of drying efficiency, is governed by the total resistance within the system, including:

- Resistance from the container
- Resistance from the drug product
- Resistance from the freeze dryer itself.

The dimensions of the glass barrel and the design of the closure part significantly influence the resistance of the container. The resistance of the drug product depends on the drying surface, fill height, formulation and maximum mass concentration.

The driving force behind the sublimation process in a lyophiliser is the gradient in water vapour pressure between the sublimation front and the chamber pressure. As the fundamental principle of freeze drying, water vapour is drawn into the condenser to create a sublimation flow. A detailed look inside the freeze dryer shows a heterogeneous distribution of flow, with water vapour pressure having a strong effect on sublimation of the drug product. Although the opening of the glass barrel can restrict vapour flow into the lyophilisation chamber, the main factor influencing sublimation is still the vapour pressure from the condensed phase of the drug product.

"THESE TARGETED EXPERIMENTS OFFER VALUABLE INSIGHTS INTO BOTH THE FORMULATION AND THE INTENDED MANUFACTURING PROCESS, HELPING TO ESTABLISH A SOLID FOUNDATION FOR FURTHER DEVELOPMENT."

Process and Equipment Parameters

A thorough understanding of the properties of packaging and equipment, heat transfer and sublimation behaviour are essential for developing a lyophilisation cycle. This theoretical knowledge must be combined with the product-specific properties of the formulation. Determining the glass transition temperature of amorphous formulations and the eutectic temperature of crystalline formulations provides relevant parameters with which to evaluate the design space for lyophilisation cycle development (Figure 3). Thermal analysis techniques, differential scanning calorimetry and freeze-drying microscopy help to identify critical formulation parameters.

Small Scale Development

Lab-scale studies play a crucial role in thoroughly characterising each phase of the lyophilisation cycle. These targeted experiments offer valuable insights into both the formulation and the intended manufacturing process, helping to establish a solid foundation for further development. As they require only minimal quantities of the API, they are not only cost-effective but also highly adaptable to changing conditions. Their flexibility allows for rapid variations of process parameters and facilitates the early identification of potential failure points. This, in turn, supports the design and refinement of product-specific lyophilisation cycles tailored to the unique properties of each formulation.

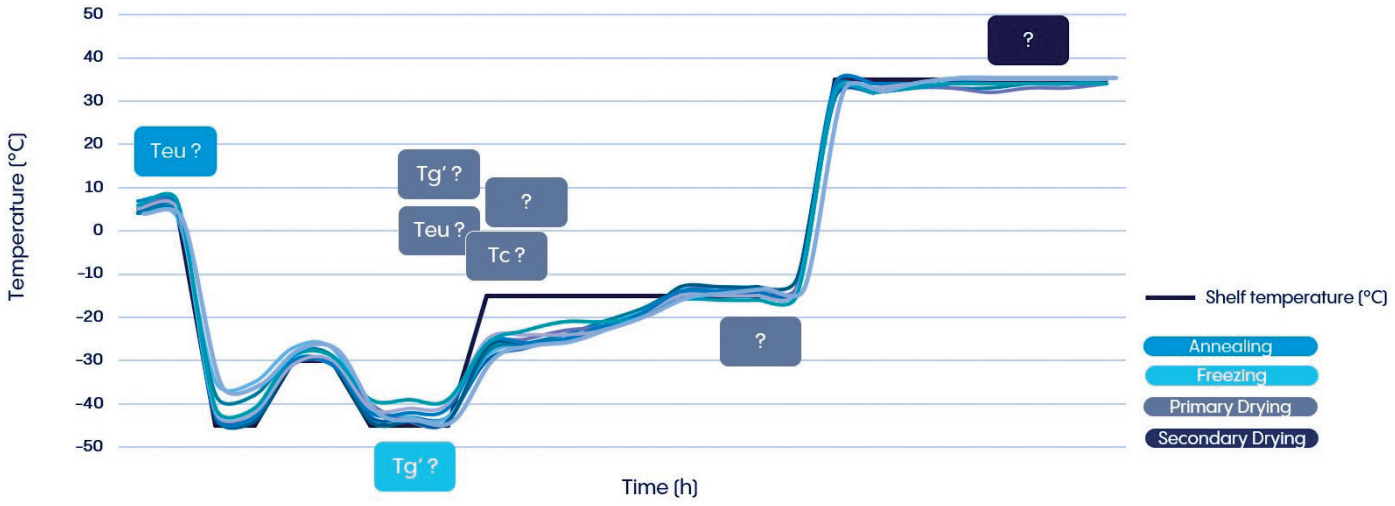


Figure 3: Illustration of freeze-drying cycle development – considering the relevant parameters for each phase during lyophilisation cycle design (Teu – Eutectic temperature; Tg' – Glass transition temperature; Tc – Collapse temperature).

Once the lyophilisation cycle has been successfully optimised at the laboratory scale, established scale-up factors can be applied to transfer the process to commercial manufacturing environments (Figure 4). This allows for consistency and reproducibility across production batches, helping to maintain product quality and regulatory compliance.

QUALIFICATION OF LYOPHILISED PRODUCTS

Lab-scale development results form the foundation of a risk-based control strategy for commercial production, and engineering runs on the intended commercial filling line and freeze dryer serve as the starting point for the overall validation strategy of the drug product freeze-drying cycle. The intended strategy is also supported by a bracketing approach, which covers minimum and maximum loads, the use of multiple lyophilisers and varying fill volumes.

The success of the lyophilisation cycle qualification depends on thorough equipment qualification. Spatial uniformity of product temperature and critical quality attributes are assessed using a star-pattern mapping technique. These data identify hot and cold spots, providing essential information for understanding the specific heat transfer coefficient of the shelf and freezer dryer, which enables the impact of these elements on the critical quality attributes of the drug product to be evaluated further on a more case-specific basis. Authorities often require this star mapping to identify the worst positions of the freeze dryer.

Process analytical technology systems are used to monitor the product temperature in relation to the shelf temperature at each individual position. Samples taken from distinct positions confirm the consistency of critical quality attributes, thus validating the lab-scale findings and supporting a reproducible manufacturing process.

MANAGEMENT OF LYOPHILISED DRUG PRODUCT LIFECYCLE

Dual-chamber systems offer clear advantages over traditional vial-and-syringe combinations and represent a further step in lifecycle management. However, developing a lyophilised drug product in a dual-chamber system is challenging and requires comprehensive expertise and know-how.

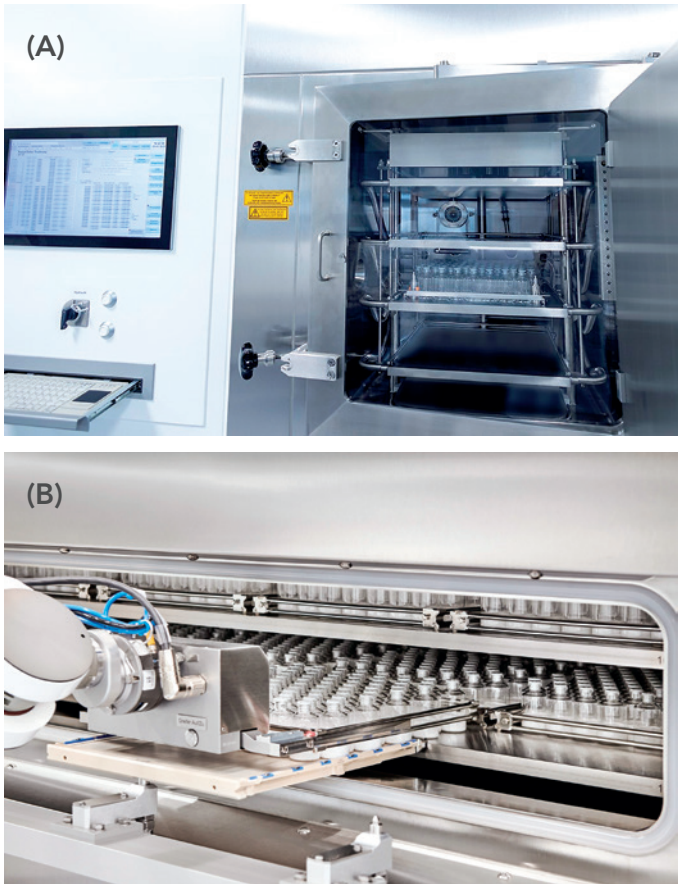


Figure 4: Scale-up – (A) from lab lyophiliser for small-scale studies to (B) automated, commercially operated lyophiliser.

Risk-based development within a defined design space demonstrates that the duration of both primary and secondary drying phases is dependent on product temperature, as confirmed through the design of experiments. This science-driven approach results in a robust data package. By integrating thermal analysis, small-scale experimentation and robust qualification strategies, pharmaceutical manufacturers can design a lyophilisation cycle that meets the critical quality attributes and regulatory expectations of drug products.

Dr Markus Neumeier

Markus Neumeier, PhD, Team Lead Technology & Process Transfer at Vetter Pharma, studied molecular biology and earned a doctorate degree in Natural Science at the University of Regensburg, Germany, in 2008. He focused his studies on basic research on liver function in the context of metabolic disorders Dr Neumeier began his career at Vetter in 2013 as Manager Technology & Process Transfer and was named Team Lead Lyophilisation and Dual-Chamber Systems in 2016. In this position, he and his expert team are responsible for the development and implementation of pharmaceutical processes on lyophilisation and filling of dual-chamber systems.

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Expert View

FROM HOSPITAL TO HOME HEALTHCARE: ADVANCES IN LYOPHILISED PRODUCT DELIVERY

Edward Trappler, **Denise Miller** and **Michael Thomas**, all of Lyophilization Technology, Inc., discuss the challenges for lyophilised products and consider the role of dual-chamber devices in simplifying reconstitution, particularly for at-home healthcare products, and go on to look at how future advances in delivery devices are providing safe solutions for self-administration while improving patient adherence.

Lyophilised products have been available since the mid-1930s, with plasma being one of the earliest applications of freeze-drying.[1] Since then, lyophilisation has become essential for preserving a wide variety of pharmaceutical products. These include anti-infectives and vaccines, encompassing chemical and biochemical entities that span small molecules, natural and plasma proteins, to recombinant biologicals. Figure 1 illustrates the range of products in common conventional presentations.

Preparing a lyophilised product for parenteral administration requires reconstituting the dried "cake" into a sterile liquid suitable for injection. This preparation step occurs in diverse settings – for example, in a hospital pharmacy, when preparing an anti-infective prior to surgery as a prophylactic treatment; in an institutional setting, such as for oncology therapy; in a clinic for vaccine administration; as part of a "crash trolley" ("crash cart") in emergencies; in the field by a healthcare professional; or even by patients themselves in at-home healthcare.

Figure 1: An array of presentations of parenteral products.

QUALITY ATTRIBUTES

The standard requirements for any parenteral product include quality, purity and efficacy. Quality ensures that the product is suitable for its intended use. A level of purity entails physical, chemical/biochemical and microbiological attributes, and it is free from any contamination. Efficacy is demonstrated in clinical studies and confirmed that there is the required potency at batch release.

Any parenteral product needs to meet the requirements as described in USP General Chapter 1, Injections.[2] Lyophilised parenterals, however, embody a unique set of attributes in addition to those required of any injectable. Critical quality attributes that define success or failure in lyophilised presentations include residual moisture, full dissolution to form a homogenous composition and acceptable reconstitution time. A "pharmaceutically elegant" cake appearance is also desirable.

"LYOPHILISED PARENTERALS, HOWEVER, EMBODY A UNIQUE SET OF ATTRIBUTES IN ADDITION TO THOSE REQUIRED OF ANY INJECTABLE."

Figure 2: Reconstituting a lyophilised product to form a homogenous solution and improper technique causing aggregation of a protein parenteral.

Lyophilised products are preserved by preventing degradation from hydrolytic reactions between the active drug substance and water. To achieve this, the residual water content must be reduced to sufficiently low levels during the lyophilisation process, and the potential for water ingress through the primary packaging during storage must be mitigated. For a conventional vial and stopper combination, the elastomeric closure must provide adequate barrier properties, and the glass vial and elastomer must achieve container closure integrity. This requirement places unique demands on cartridges and syringes, as the plunger separating the dried product from the diluent must not permit water permeation throughout the product's shelf life.

Inspection adds an additional challenge for lyophilised products. When converted from a solution to a dried solid during the lyophilisation process, only the surfaces of the finished product cake can be observed, hindering inspection of the entire contents of the vial. Lyophilised products are therefore categorised as difficult-to-inspect. The 100% physical inspection of the dried product is to be supplemented with inspection of constituted samples of the lot.[3]

Once diluent is added, the dried product must dissolve completely to form a homogeneous solution with all required parenteral quality attributes. The method of reconstitution depends on the sensitivity of the active drug substance to stresses encountered during mixing. Small molecules generally dissolve readily, however, biologics such as peptides and proteins may be sensitive to shear, turbulence and at the air-liquid interface, which can lead to aggregation (Figure 2).[4]

"THE DURATION OF DISSOLUTION IS INFLUENCED PRIMARILY BY THE PHYSICOCHEMICAL CHARACTERISTICS OF THE ACTIVE DRUG SUBSTANCE AND FORMULATION EXCIPIENTS, WITH PRODUCT VOLUME PLAYING ONLY A SECONDARY ROLE."

In conventional lyophilised preparations, such as those shown in Figure 1, reconstitution requires multiple components: the vial of lyophilised product, a container of liquid diluent, a syringe, two needles and alcohol wipes. Assembling these items is just the beginning of an 18-step process that starts with removing a protective cap on the diluent and ends with withdrawing the constituted solution for administration. For trained personnel, these steps can be completed in as little as 100 seconds; for someone unfamiliar, the process can take up to 12 minutes (unpublished data, Lyophilization Technology, Inc).

Although reconstitution time is often defined as the interval required for dissolution after diluent addition, in practice it includes the entire procedure: preparation, mixing and withdrawal of the final solution. The duration of dissolution is influenced primarily by the physicochemical characteristics of the active drug substance and formulation excipients, with product volume playing only a secondary role.

The clinical significance of reconstitution time varies by product. For Vancomycin Hydrochloride for Injection (Pfizer), an anti-infective available in a 10 g pharmacy bulk package, the time required is not critical. Reconstitution and further dilution occur in the hospital pharmacy before intravenous (IV) infusion, and delays pose little impact beyond inconvenience. Dantrolene, a component of an operating room crash trolley for malignant hyperthermia, must be prepared immediately. Up to 36 vials may be required for the patient, with two nurses often working together – one reconstituting while the other administrates the doses – to keep up with the patient's needs. Here, reconstitution time can determine survival. At the extreme, glucagon injections for the treatment of hypoglycaemia require near instantaneous dissolution. During insulin shock, each second is precious, as delays can lead to dizziness, weakness, seizures and

potentially coma. For this reason, glucagon is supplied in emergency kits where all necessary items are packaged together (Figure 3).

Figure 3: An "emergency kit" for treatment of an acute life-threating condition.

COMBINING DRUG AND DILUENT

To improve methods of reconstitution, Abbott Laboratories developed the ADD-Vantage system™ (now a Pfizer product), which introduced significant convenience for hospital pharmacies. This design allowed a lyophilised product vial to connect directly to an IV bag, with the IV solution itself serving as the diluent. The system streamlined workflow, eliminated multiple steps and enhanced sterility assurance (Figure 4). Abbott later introduced the ADD-Vantage ADDapter™ device, allowing conventional vials to connect to the specialised IV bag port. Despite its success, Pfizer has announced it is discontinuing the presentation after 2025.[5]

Further innovation came with dual-chamber devices designed to simplify reconstitution for home healthcare products, particularly those used to treat chronic conditions. These assemblies combine a vial of a lyophilised drug product and a vial of the diluent into a single device specifically configured for reconstitution. The Baxject unit (Takeda, Tokyo, Japan), for example, is used for administering antihaemophilia Factor VII (Figure 4).

Activation of the system begins by pressing on the diluent vial, which transfers the liquid into the product vial under reduced headspace pressure. This transfer is facilitated by a syringe attached to the side of the assembly via a Luer lock connection, which also serves later to withdraw the constituted solution for administration. Once the diluent has entered the bottom vial, the assembly is gently swirled to complete dissolution of the dried product to form a homogenous solution. The constituted solution can then be withdrawn into the syringe through the Luer lock connection and prepared for injection. The final preparation step involves attaching a needle to the syringe, making the dose ready for administration. Although great efforts are employed to make such delivery systems easy to use, patient compliance continues to be a significant consideration.[6]

Dual-chamber systems offer clear advantages: fewer steps, shorter preparation times, assurance of correct diluent volume, reduced contamination risk and lower needlestick potential. Reconstitution times were reported to range from 20 to 65 seconds, depending upon the age of the user.[7] In addition, there is a greater likelihood that the correct amount of diluent will be added compared with traditional vial-to-vial transfers. Because dual-chamber configurations function as a more closed system, the potential for contamination is greatly reduced, sterility assurance is higher and needle handing is only required at the point of administration, thereby decreasing the risk of needlestick injuries.

There has been an increased interest in products that can be self-administered in a home healthcare setting. As patients have grown accustomed to this convenience, demand has risen for prefilled syringe presentations for lyophilised products. Building on the success of dual-chamber devices, further development has led to single primary packaging units configured similarly to syringes that integrate both the container and delivery device into one system. These designs provide enhanced assurance of quality and purity while simultaneously improving patient compliance.

Figure 4: ADD-Vantage IV Mixture system and Baxject delivery of reconstitution protein for self-administration in home healthcare.

"BUILDING ON THE SUCCESS OF DUAL-CHAMBER DEVICES, FURTHER DEVELOPMENT HAS LED TO SINGLE PRIMARY PACKAGING UNITS CONFIGURED SIMILARLY TO SYRINGES THAT INTEGRATE BOTH THE CONTAINER AND DELIVERY DEVICE INTO ONE SYSTEM."

In these integrated systems, the dried product and diluent are contained within the same primary packaging, reconstituted directly inside the device and then delivered through the same unit. This approach minimises manipulations, reducing preparation just to steps essential for self-administration. By simplifying the process, the system decreases the risk of handling errors, limits opportunities for contamination and improves sterility assurance. One example is Abbvie Laboratories' LUPRON DEPOT® (leuprolide) used for the management of endometriosis, including pain relief and reduction of endometriotic lesions.[8] Supplied in a ready-to-administer format, it allows reconstitution and delivery in just a few simple steps, offering a patient-friendly alternative to traditional vial-and-diluent combinations.

Figure 5 shows the product in a ready-to-administer configuration that reduces the reconstitution process from the 18 steps described earlier to just three. The patient attaches the plunger rod, pushes the plunger past the bypass in the syringe barrel to allow the diluent to enter the chamber with the dried product, then gently inverts the syringe back and forth until reconstitution is complete. After these three simple steps, the product is ready to administer.

This type of presentation also reduces preparation time compared with dual-vial configurations. It ensures that the correct volume of diluent is delivered, eliminating uncertainty and further reducing user error. Because the process occurs entirely within a closed system, the potential for contamination is minimised, sterility assurance is maximised and needle handling is only required at the point of administration. This not only enhances safety but also decreases the risk of needlestick injuries.

DELIVERY DEVICES IN THE FUTURE

As new products for chronic conditions continue to be developed, the range of therapies suitable for home use has expanded. This reflects an era of unprecedented innovation in drug development. Many of these emerging therapies present delivery challenges, often requiring larger volumes, higher viscosities or novel formulations that exceed the capabilities of traditional technology.

To meet these demands, advances in delivery devices are providing solutions that enable safe self-administration while improving patient compliance. One such development is the introduction of systems that combine a reusable power unit with an interchangeable drug cassette, capable of accommodating both prefilled syringes and cartridges. These platforms offer greater flexibility in handling different drug formats, viscosities and volumes, supporting a wide variety of formulations and therapeutic regimens.

In practice, such systems are designed for ease of use – the patient simply loads a cassette, removes the protective cap and presses the device against the injection site. By reducing the number of manual steps and handling requirements, these devices make complex therapies more accessible for patients and help ensure that treatments are delivered safely and consistently in the home, achieving improved therapeutic outcomes.

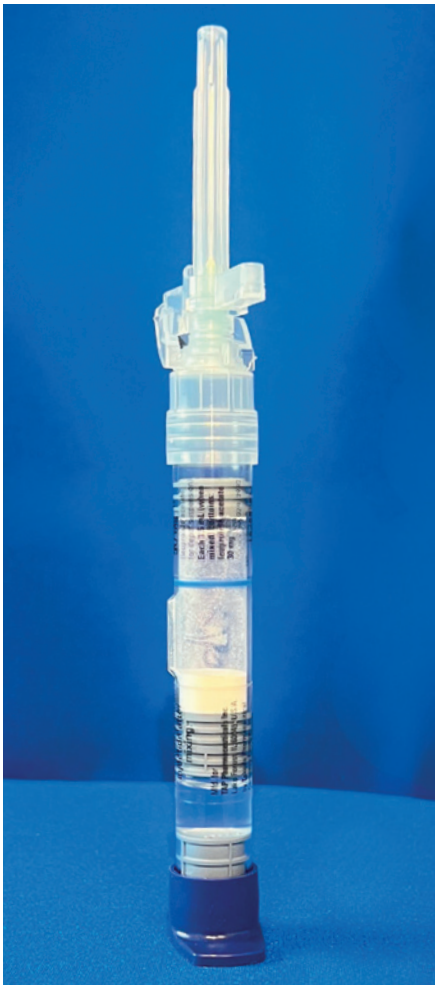

Figure 5: LUPRON DEPOT® has a ready-to-administer format.

Connectivity is also another feature, benefitting both the patients and primary care providers. A radio frequency identification (RFID) tag on the product cassette can communicate the drug information to the device, which automatically adjusts delivery parameters, such as depth and injection duration, providing improved patient compliance. This simplifies the administration process for the patient and reduces the risk of errors.

"BY REDUCING THE NUMBER OF MANUAL STEPS AND HANDLING REQUIREMENTS, THESE DEVICES MAKE COMPLEX THERAPIES MORE ACCESSIBLE FOR PATIENTS AND HELP ENSURE THAT TREATMENTS ARE DELIVERED SAFELY AND CONSISTENTLY IN THE HOME, ACHIEVING IMPROVED THERAPEUTIC OUTCOMES."

Cellular connectivity can also be integrated into the delivery device, further improving patient compliance. Control of the power unit can be automated by the RFID-enabled disposable drug cassette, ensuring that the proper delivery parameters are used without the need for user input or creating opportunities for human error. Capabilities for control of such devices by healthcare providers offer unique capabilities for patients where dosing may be variable or determined by factors expected to change over time. The flexibility to deliver multiple volumes and use a variety of primary containers allows patients to use the same power unit with multiple drug cassettes. Without requiring patient input, there is no risk of the wrong dose being delivered and the user experience is identical, if not improved.

ON THE HORIZON

In the ever-changing landscape of parenteral drug delivery, new systems must evolve to accommodate an increasingly diverse range of product formulations and presentations. As therapeutic innovation accelerates, the growing complexity of treatments introduces new challenges and unmet needs for both patients and healthcare providers. Device technologies are advancing in parallel with the development of more capable and flexible autoinjectors that improve usability and adapt to novel product requirements.

Beyond supporting approved therapies, these innovations are also valuable in drug development. Next-generation delivery platforms play a crucial role in clinical research, enabling dynamic dosing strategies, accelerating evaluation, improving adherence and de-risking development through consistent administration. Connectivity features enhance these benefits by providing real-time data availability and integrity, allowing healthcare providers and developers to monitor usage, outcomes and compliance more effectively.[9]

Taken together, these advances are redefining what is possible for drug delivery in the home healthcare setting. The shift from multistep vial-and-diluent systems to integrated, connected platforms, including dual-chamber cartridges and syringes, is not only simplifying preparation but also expanding access to complex therapies. By reducing user burden, improving sterility assurance and enabling safe self-administration, these systems are making advanced treatments more practical. As delivery devices continue to evolve, patients and providers alike will benefit from safer, smarter and more adaptable solutions that support the future of pharmaceutical innovation.

ABOUT THE COMPANY

Lyophilization Technology, Inc (LTI) is a CDMO focused exclusively on the development and clinical manufacturing of lyophilised drug products. Founded in 1992, LTI provides formulation development, product design, process engineering, technology transfer and

clinical supply manufacturing. With deep expertise in parenteral delivery systems, the company supports integration of lyophilised products into prefilled syringes and dual-chamber devices, enabling simplified reconstitution, assured sterility and patient-friendly administration. LTI's focus on freeze drying across all clinical phases helps sponsors advance stable, usable and reliable investigational therapies.

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Edward Trappler is the Founder of Lyophilization Technology, Inc, established in 1992 to provide scientific and technical services and advance the knowledge of lyophilisation across the healthcare industry. With over 45 years of experience in product development, toxicology, clinical supply manufacturing, and parenteral production, Mr Trappler has become a recognised leader in the field. He has contributed to six books, authored numerous papers and frequently presents at international conferences and courses for AAPS, ISPE and PDA. An active member of the PDA, Mr Trappler has served in leadership roles, including chairperson of the Lyophilization Interest Group, the Validation Task Force and the Education Advisory Board.

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Denise Miller has been with Lyophilization Technology, Inc since 2008 and currently serves as Associate Director, Quality Assurance. She is responsible for directing quality operations to support the preparation of toxicology and clinical trial materials, collaborating across departments to ensure compliance and guiding the Quality Assurance team. Ms Miller has published and presented on quality and technical aspects of lyophilised products and remains active in industry organisations, including the Parenteral Drug Association and the American Society for Quality. Her career began in the allied health field, where she gained valuable patient-care experience that continues to influence her patient-first approach to quality.

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Michael Thomas, Research Fellow, has been with Lyophilization Technology, Inc for over 22 years. He is involved in directing client projects, including product and process development, technical support, validation, troubleshooting and clinical manufacturing. Focused activities include product design in novel container closure delivery systems, such as dual-chamber cartridges and syringes, which he continues to present to the industry through podium discussion, posters and webinars. Mr Thomas is active on Lyophilization Technology, Inc's Scientific Advisory Board, and is a member of the PDA. His educational background consists of a BS in Biology from Arcadia University (PA, US) and a Pharmaceutics Master's degree from Temple University (PA, US).

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Bjørn Andersen and **Iain Simpson**, both at **Phillips Medisize**, explore the factors contributing to interest in lyo-liquid and liquid-liquid drug delivery, highlighting some of the current unmet needs in this space. Following this, they discuss how platform technologies, such as electromechanical drives, may help address these unmet needs and improve the stability and convenience of administering lyophilised and dual-liquid formulations from dual-chamber containers.

Many modern therapeutics – particularly biologics (such as proteins, monoclonal antibodies, peptides, vaccines and enzymes) – are inherently unstable in aqueous solutions. Lyophilisation is an established method used to address this challenge. By removing water under low temperature and vacuum, the process locks the active ingredient into a dry matrix that reduces chemical and physical degradation.

A 2023 review of approved biotherapeutics identified 89 marketed antibodies in a total of 96 presentations of which 22 (22.9%) were presented as lyophilised powders.[1] An analysis of PharmaCircle data by Phillips Medisize yielded 71 lyophilised products approved for subcutaneous delivery between 2014 and 2024 inclusive (Figure 1). Several factors seem to be involved:

- Some biologic drugs are inherently unstable. For example, messenger RNA (mRNA)-based and cell and gene therapies often require storage at ultra-low temperatures – sometimes as low as -70°C. These storage requirements can present challenges for distribution logistics. Lyophilisation may offer a way to store and transport these drugs at higher temperatures.[2]

- Lyophilisation may allow for higher concentrations of injectable drug formulations, which could support subcutaneous delivery as single injections instead of higher-volume infusions.[3]

- Compared with developing liquid-stable formulations, lyophilisation may offer a faster route to drug product development for clinical studies and initial market entry. Liquid-stable formulations typically require investigation and selection of excipients to address potential issues, such as aggregation, oxidation or hydrolysis over the product's shelf life.[4] Demonstrating adequate stability to support early clinical studies may be quicker for lyophilised formulations.

However, several challenges continue to influence the adoption of lyophilised drug formulations in commercial drug products. These include:

- Higher manufacturing costs associated with longer cycle times, capital expenditures for processing equipment and energy use during the lyophilisation process.

- Process complexity and potential scale-up challenges. Transferring lyophilisation processes from pilot to commercial scale may involve difficulties, and adjustments to the process could require additional revalidation.

- The need for reconstitution before injection places a burden on the user of the drug product. While this may be less of an issue for healthcare professional (HCP)-administered drugs, the shift towards patient and caregiver administration could increase the risk of use errors. In markets where lyophilised drugs might need to compete with liquid-stable formulations in easy-to-use devices, this factor may affect their uptake.

- Dual-chamber containers offer a good approach to reduce patient and HCP burden in preparing and administering lyophilised formulations. However, only a limited number of CMOs currently offer commercial scale filling services for dual-chamber primary containers.

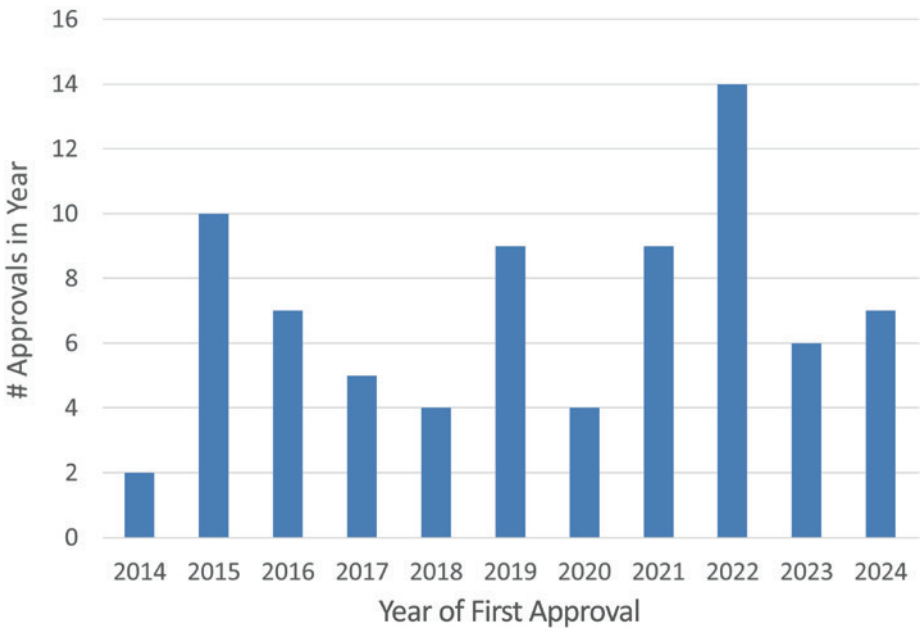

Figure 1: Marketed subcutaneously delivered lyophilised drug products by year of approval.

Combining multiple therapies into a single dose – known as fixed-dose combinations (FDCs) – is an area of focus in drug development.[5] Delivering FDCs as a single dose requires coformulation, which may pose challenges in ensuring long-term drug stability due to potential drug-drug interactions. Even when coformulation is possible, it may extend clinical development timelines. As a result, alternatives that allow administration of two separate injections while ensuring drug stability are being explored for both clinical development and commercial use.

CURRENT DELIVERY SOLUTIONS

Before injection, powder or lyophilised formulations must be reconstituted with a diluent, typically water for injection (WFI). This process requires careful handling and may increase the complexity for users, which may lead to higher risk of use errors. As self-injection becomes more common, there is a need for improved solutions that support non-HCPs in preparing and administering these formulations.

Most lyophilised drug products in the market are provided in vial formats. In the Phillips Medisize internal review mentioned above, 67 of 71 approved products are presented in a vial or similar container, requiring users to add WFI into the drug container, mix and then withdraw the combined product for injection. While vial use is common in healthcare practice, the shift towards self-administration outside the clinic transfers the preparation and delivery burden from HCPs to patients and caregivers. Without professional training, the risk of use errors may increase, and the added complexity in preparation may affect adherence.

"THE SHIFT TOWARDS SELF-ADMINISTRATION OUTSIDE THE CLINIC TRANSFERS THE PREPARATION AND DELIVERY BURDEN FROM HCPs TO PATIENTS AND CAREGIVERS."

In competitive markets, such as immunology, the availability of alternative medicines offered in more convenient forms – for example, liquid-stable injections – may impact the uptake of new lyophilised formulations, even if these provide additional clinical benefits. When considering device preference, HCPs seem to take the number of steps involved in device use into account, which may influence their prescribing decisions.[6]

Approach	Storage of Lyo Cake	Storage of Diluent	Delivery Device	Method of Use	Example
Two Vials	In a vial	In a vial	Separate syringe	Syringe is used to draw diluent from first (diluent) vial and inject into the second (lyo) vial. The mixed drug is then withdrawn from the vial by a second syringe and is ready for injection.	OMNITROPE™ 5.8 mg/vial
Two Vials and Dual-Spike Transfer Device	In a vial	In a vial	Separate syringe	Diluent and lyo drug vials are connected using the transfer set. After mixing the final drug, product can be withdrawn via injection.	Mix2Vial™ Transfer set (available as a device for use with multiple drugs)
Vial and Prefilled Syringe (PFS)	In a vial	In a PFS	Diluent PFS can be used to deliver the final product	Diluent in PFS is injected into the vial containing the drug and mixed. After mixing the drug, product is withdrawn using a second syringe and is ready for injection.	GATTEX™ (teduglutide)
PFS, Vial and Transfer Device, which has delivery needle pre-attached	In a vial	In a PFS	PFS integrated with the Mixject adapter	Prefilled diluent syringe is attached to the vial adapter. Diluent is injected into the vial via the adapter. After mixing the final drug, product is withdrawn from the vial into the diluent syringe. This is then detached from the vial and is ready for injection via the needle that was integrated into the transfer device.	BETASERON™ (interferon beta-1b)
Dual-Chamber Syringe	In the delivery device	In the delivery device	PFS used to store and prepare the injection	Drug and diluent are contained in a dual-chamber primary container. Partial movement of the plunger rod introduces the diluent into the lyo chamber via a bypass channel or valve. After mixing the final drug, product can be injected via a needle that is either attached or integrated with the syringe.	GENOTROPIN MiniQuick™
Dual-Chamber Cartridge (DCC)	In the DCC	In the DCC	DCC loaded into a delivery device such as a pen injector or autoinjector	Drug and diluent are prefilled in a dual-chamber syringe which is then loaded into the delivery device. Instructions to mix and deliver the drug are then device specific.	GENOTROPIN™ Pen SKYTROFA™ Auto-Injector NEMLUVIO™ (nemolizumab-ilto) Pen

Table 1: Commercial solutions that support patients administering injectable lyophilised formulations.

Given the complexities involved in preparing and administering lyophilised formulations, device technologies have been developed with the intention of reducing user burden and lowering the risk of use error. Table 1 summarises some of the solutions on the market that have been used to support patients administering injectable lyophilised formulations.

Unlike vials, in which the lyophilised drug and diluent are stored in separate containers, dual-chamber delivery systems house both components within a single primary container – divided into two chambers separated by a plunger stopper. The diluent is introduced into the chamber containing the lyophilised cake either through a valve, by piercing the stopper, or by moving the plunger stopper to open a bypass channel around it. From the user's perspective, this approach simplifies the reconstitution process by reducing the chance of incorrect mixing, which is instead managed by the manufacturing process. Table 2 lists approved products that use a dual-chamber primary container.

Dual-chamber syringes offer a device option that supports both reconstitution and delivery from a single device. They can include either a staked needle or a needle attached via a luer lock connection, depending on the design. While dual-chamber cartridges (DCCs) do not include a needle, they can be incorporated into a device such as pen injectors or autoinjectors. Examples of devices incorporating dual-chamber primary cartridges include Pfizer's GENOTROPIN™ pen (somatropin), Ascendis Pharma's (Hellerup, Denmark) SKYTROFA™ (lonapegsomatropin-tcgd) autoinjector and Galderma's (Zug, Switzerland) NEMLUVIO™ (nemolizumab-ilto) autoinjector.

Product or Pipeline Name	Molecule/API Name	Formulation	Indication	Owner Company	Delivery Device
Systems Containing a Dual-Chamber Cartridge					
Atropine ComboPen Autoinjector	Atropine	Powder	Intoxication/Poisoning	MMT	ComboPen
Caverject™	Alprostadil	Lyophilised Powder	Erectile Dysfunction	Pfizer Inc	Caverject Pen Injector
DuoDote™ Pen	Atropine	Powder	Intoxication/Poisoning	MMT	Binaject
Edex™ Dual-chamber Cartridge	Alprostadil	Lyophilised Powder	Erectile Dysfunction	Advanz Pharma	Reusable edex™ Injection Device
GENOTROPIN™ Cartridges	Somatropin	Lyophilised Powder	Growth Hormone (GH) Deficiency	Pfizer	GENOTROPIN Pen
GENOTROPIN GoQuick	Somatropin	Lyophilised Powder	GH Deficiency	Pfizer	Genotropin Disposable Pen
Natpara Lyophilized Powder*	Parathyroid hormone	Lyophilised Powder	Hypoparathyroidism	Shire/Takeda	Q-Cliq Reusable Injection Pen
NEMLUVIO™ Dual-Chamber Pen	Nemolizumab-ilto	Lyophilised Powder	Atopic Dermatitis	Chugai	NEMLUVIO Dual-Chamber Pen
PEG Intron Redipen**	Peginterferon alfa-2b	Lyophilised Powder	Hepatitis	Merck and Co	BD Liquid-Dry Pen Injector
SKYTROFA™ Autoinjector	Lonapegsomatropin-tcgd	Lyophilised Powder	GH Deficiency	Ascendis	SKYTROFA Electromechanical Autoinjector
Systems Containing a Dual-Chamber Syringe					
Abilify Maintena™	Aripiprazole	Lyophilised Powder	Schizophrenia/ Bipolar	Otsuka	Arte Dual-Chamber Prefillable Syringe
GENOTROPIN MiniQuick	Somatropin	Lyophilised Powder	GH Deficiency	Pfizer	MiniQuick DCS
Lupron Depot	Leuprolide acetate	Lyophilised Powder	Prostate Cancer	AbbVie	LuproLoc DCS
NEMLUVIO Prefilled DCS	Nemolizumab-ilto	Lyophilised Powder	Atopic Dermatitis	Chugai	Vetter DCS
RenehaVis	Sodium hyaluronate	Powder	Osteoarthritis	MDT Intl	RenehaVis DCS
Suprecur	Buserelin acetate	Powder	Endometriosis	Sanofi	DCS
ViATIM Injection Suspension	ViATIM	Powder	Infectious Diseases	Sanofi Pasteur	ViATIM Dual-Chamber Syringe
XYNTHA™ Solofuse	Moroctocog alfa	Lyophilised Powder	Haemophilia A	Pfizer	SoloFuse Dual-Chamber Syringe

Table 2: Approved products that use a dual-chamber primary container. *Discontinued globally 2024. **Discontinued in EU in 2021, in US in 2016.

Several studies have considered the usability and user preferences for different systems used to prepare and inject lyophilised drug formulations. Cimino *et al*[7] evaluated five device scenarios for haemophilia A treatment. Four scenarios involved vial-based systems similar to those in Table 1, while one used a prefilled dual-chamber syringe (PFDS). The majority of the study was conducted as a survey with 299 participants who were experienced with haemophilia drugs. A subset of 98

participants also performed a simulated use study with the PFDS. Among this group, 57% preferred the PFDS over their current device, 26% preferred their current device and 17% found no preference. Overall, the survey data suggested a preference for the PFDS option.

In another study exploring the burden of at-home preparation of lyophilised injectable medications, Franzese *et al* asked 14 experienced participants to perform simulated use of one of four reconstitution methods: a double-ended spike adapter, a dual-chamber syringe, a prefilled diluent syringe or large-volume pooling (where contents of several lyophilised vials are combined and transferred into a cassette for infusion).[8] Participants were distributed relatively evenly across the four approaches and performed a simulated use of the method relevant to their medication. The process was divided into three stages: assembly, reconstitution and transfer. Sessions were video recorded and analysed for deviations from protocol or potential breaches in sterility due to incorrect technique. A total of 85% of participants reported experiencing at least one preparation complication over the course of treatment with their current product.

In the simulated use study, seven out of eight instructions-for-use (excluding pooling) and all sterility breaches occurred during the reconstitution phase, indicating the importance of this step. The authors noted that all studied approaches imposed some level of burden on patients and emphasised the need for better, purpose-built reconstitution devices to help patients and caregivers prepare medication more efficiently and with steps.

The GENOTROPIN pen, NEMLUVIO autoinjector and SKYTROFA autoinjector aim to reduce patient burden and lower the risk of use errors compared with traditional vial-based and PFDS approaches. The NEMLUVIO autoinjector is a single-use disposable system delivering a fixed dose, the GENOTROPIN pen and SKYTROFA autoinjector are reusable devices supporting multiple drug presentations. SKYTROFA delivers fixed doses corresponding to the full cartridge content, whereas the GENOTROPIN pen supports variable dosing across multiple individual dual-chamber drug presentations.

Regarding patient feedback, to the best of the authors' knowledge, there is a lack of published data directly comparing the usability of these more advanced devices with traditional lyophilised drug preparation methods previously described. However, a study on SKYTROFA involving experienced and injection-naive children and caregivers (N = 120), along with 15 HCPs, showed that all participants were able to successfully prepare and complete an injection using the autoinjector.[9] The authors concluded that usability issues were low and comparable with results from other usability studies. All participants reported that they could follow the instructions as written, and 98% of participants felt that they could use the device as intended on their own or with supervision.

These examples illustrate some strategies that may be considered when selecting a device to support a dual-chamber lyophilised presentation. Increasing complexity – such as support for multiple presentations or variable dosing – may make reusable device solutions more suitable. Additional factors include safe reconstitution, where increased user burden might require greater attention to device usability support for critical user tasks.

Environmental burden is a consideration influencing interest in reusable delivery devices. In the context of lyophilised dual-chamber drug presentations – where inherent complexities exist – there is potential to combine usability and sustainability by using reusable delivery systems.

The following section explores how the use of proven and pervasive technologies and, in particular, electronic technologies can support the development of improved delivery solutions for more complex and diverse programme needs.

APPLICATION OF ELECTROMECHANICAL DELIVERY TECHNOLOGY TO DUAL-CHAMBER DRUG PRESENTATIONS

Lyophilised medicines presented in dual-chamber primary containers may offer formulation and stability benefits but require reconstitution before injection. This additional preparation step, compared with using prefilled syringes (PFSs) or autoinjectors with a liquid-stable formulation, increases scope for risks in the overall administration procedure related to the user's ability to correctly perform required manual operations during the preparation process. Examples of such risks include:

- Mixing WFI with the lyophilised cake before the needle is properly mounted could result in drug back-flush and a loss of dose due to pressure build-up in the drug chamber. Attempting to mix with the needle pointing downwards may also lead to unintended loss of dose.

- After the prescribed reconstitution period, the drug may require gentle swirling, repeated inversions or occasionally rigorous shaking to achieve sufficient homogeneity. The challenge is to ensure that users can replicate the process developed in the laboratory to support satisfactory mixing and reconstitution.

- The final step in the drug preparation process involves visual inspection to confirm the absence of particles or discolouration before injection. At this stage, priming may be performed by evacuating excess air from the front mixing chamber, while the user ensures the needle is pointing upwards.

"IN THE CONTEXT OF LYOPHILISED DUAL-CHAMBER DRUG PRESENTATIONS – WHERE INHERENT COMPLEXITIES EXIST – THERE IS POTENTIAL TO COMBINE USABILITY AND SUSTAINABILITY BY USING REUSABLE DELIVERY SYSTEMS."

In a previous article,[10] it was suggested that the dominance of mechanical disposable injection devices may face competition from reusable devices, which offer potential advantages – such as greater user support and flexibility. These reusable devices can accommodate a wider range of formulations, including high-viscosity drugs,[11] with minimal need for device modifications, unlike many spring-driven devices.

Given the complexities involved in preparing and delivering lyophilised drugs, electromechanical reusable autoinjector devices may offer a way to provide a user experience similar to that of a PFS autoinjector system.

In another article,[12] Phillips Medisize explored how electromechanical autoinjector systems could assist in the preparation and injection of lyophilised drugs in DCCs. The SKYTROFA autoinjector serves as an example of this approach. Even without fully automating every process step, electromechanical autoinjectors can offer additional support to users, which may help reduce the likelihood of use errors. These devices may incorporate sensors that detect correct cartridge and needle mounting, as well as device orientation during manual handling. Combining these inputs with the device's internal status – such as plunger position and timers – may allow the device to control the process sequence and communicate real-time guidance to the user. Graphical user interfaces, enhanced with animations and combined with focused acoustic and tactile signals, may further aid users throughout the process.

The development of electromechanical devices that can address some of the usability and patient burden challenges highlighted before provides a good example of how a company, like Phillips Medisize, with the right technical capabilities, can use its platform technologies in a flexible and versatile way to meet different sets of product requirements. This approach enables new developments, where possible, to use proven technologies from earlier developments to help reduce technical risk, time and cost.

For example, in the case of dual-chamber autoinjector development, subsystems such as the electromechanical drivetrain, electronic hardware and firmware, graphical user interface screen technology, sensors to monitor device orientation and passive needle shielding via a movable sleeve that also acts as a skin-contact can be used. This approach can lower technical risk compared with starting entirely new developments with untested technologies.

"USING PLATFORM TECHNOLOGIES MAY HELP ENABLE A MORE ROBUST SUPPLY CHAIN TO BE PUT IN PLACE AND DRIVE ECONOMIES OF SCALE IF COMPONENTS CAN BE USED ACROSS MULTIPLE PROGRAMMES."

Moreover, the flexibility of electronics and electromechanical systems can allow changes to be made later in the development process with less impact on time and cost. The approach may also simplify reconfiguring the device technology for future drug programmes with different delivery requirements. Finally, using platform technologies may help enable a more robust supply chain to be put in place and drive economies of scale if components can be used across multiple programmes.

Although this article has focused on the complexities of preparing and delivering lyophilised formulations, DCCs can also be used to mix and deliver two liquids stored separately until the time of use. In many cases, the mixing process may be less complex. However, electromechanical delivery systems may still provide benefits in terms of usability and potentially support faster development timelines, particularly during clinical stages, and the use of electromechanical drive technology may make it easier to work with a wider range of viscosities for the two drug components.

CONCLUSIONS

Two-step mechanical autoinjectors for delivering liquid-stable drugs from PFSs have become a common approach for self-injection of biologic drugs, setting a benchmark for usability and patient convenience. While this approach generally balances usability, cost and device complexity, it does not address formulation challenges posed by some drugs that lack sufficient stability in aqueous solutions. Lyophilisation and the co-administration of separate drugs have long been options to address stability issues, but current device technologies face limitations in offering a user experience and use burden comparable with autoinjectors designed for liquid-stable formulations.

With emphasis on patient centricity and self-administration, the need to improve usability in preparing and delivering more complex formulations will only intensify. This article has highlighted how electromechanical delivery technologies have the potential to enhance the user experience in the preparation and delivery of lyophilised and liquid-liquid drugs from DCCs. Such technologies may also contribute to environmental stewardship (through device reusability), while offering user confidence by providing controlled processes and real-time feedback. Furthermore, the ability to incorporate technology that has already been proven on previous developments can facilitate a more modular approach to future developments, potentially reducing technical and timeline risks compared with a completely new approach starting from a "blank sheet of paper".

Advances in delivery technology, combined with innovations in formulation and filling of dual-chamber containers, may expand options beyond traditional liquid-stable formulations. These developments may support accelerated time-to-market and enable delivery of new drugs that present stability challenges or require additional processing to remain stable in liquid form. By addressing these challenges and offering flexibility around different delivery needs, electromechanical delivery systems could play a role in shaping the future of self-administered drug therapies.

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Early Insight

RETHINKING DUAL-CHAMBER SYRINGES: A LATERAL APPROACH TO FASTER, SAFER RECONSTITUTION

Eric Sugalski of **Ampulis** examines the limitations of current concentric dual-chamber syringe designs and explores a novel, lateral-chamber approach from Ampulis – the Ampulis Reconstitution Syringe.

Reconstituted drugs hold enormous promise – from improving stability and extending shelf life to enabling life-saving therapies. But delivering these therapies to patients efficiently, accurately and safely is far from straightforward. Dual-chamber syringes (DCSs) have emerged as a seemingly elegant solution – a single device that stores lyophilised drug and diluent separately, then enables quick reconstitution at the point of use. On paper, DCS technology offers convenience, faster preparation and reduced risk of contamination.

In practice, however, the story is more complicated. Despite years of availability, DCS devices have yet to see broad market adoption. Beneath the surface lie persistent usability, manufacturing and cost challenges that limit their real-world uptake. Variability in activation forces, awkward plunger strokes, intricate tooling requirements and complex fill-finish processes all combine to create friction – both literal and figurative – in their path to widespread use.

By rethinking the basic geometry and using simpler, more reliable manufacturing methods, Ampulis's novel lateral-chamber approach, the Ampulis Reconstitution Syringe (ARS), holds promise to solve the very problems that have long hindered DCS adoption – and to open the door for faster, safer and more user-friendly reconstitution both in clinical and at-home settings.

THE DCS DILEMMA

While the concept of DCS technology is sound, the execution, particularly with today's dominant concentric designs, has exposed practical and economic hurdles, which are difficult to overcome. What appears at first glance to be a simple adaptation of a standard prefilled syringe actually introduces a cascade of engineering, usability and manufacturing complexities. These challenges do not just impact the user experience; they ripple through the entire product lifecycle, from device design and production to fill-finish operations and final market viability.

Understanding why adoption has stalled requires a closer look at the most common pain points with current DCS systems, and why these issues matter for both patient safety and commercial success.

There are numerous factors involved, but we will consider some of the known challenges with existing DCS devices that may be limiting market uptake.

Variable Activation Forces

Most DCS devices are designed in concentric form, wherein the lyophilised formulation (lyo) and diluent chambers are coaxial. While this design appears simple and familiar to existing prefilled syringes, some significant differences and challenges require consideration. One of these challenges relates to the difference in frictional resistance during the displacement of multiple stoppers within the DCS. If a user applies a constant force at the end of the plunger rod, the displacement velocity will vary depending on the position of the stoppers and the pressurisation of air pockets within the two chambers. The velocity will also differ significantly between break-loose, diluent transfer and the extrusion stages. This rapid change in frictional resistance not only creates confusion and fatigue for users but can also result in incomplete diluent transfer that affects dose accuracy.

Long Plunger Stroke

Another usability challenge associated with the concentric DCS configuration is the necessity for the lyo compartment to accommodate the full volume of diluent. Additionally, both lyo and diluent chambers require air pockets to facilitate diluent transfer. These air pockets significantly increase the travel required of the plunger rod, as the stroke needs to accommodate not only the dispensing of the reconstituted formulation but also the transfer of the diluent into the lyo compartment and the compression of multiple air pockets. For many users, this requires a two-handed operation, which is much less controlled than a precision grip with a single hand. Compounded with the variable activation force issue already mentioned, this presents further human factors and dose-accuracy challenges.

Complex and Costly Manufacturing

Existing DCS devices require bypasses and/or valves to transfer diluent into lyophilised formulation chambers. These intricate features require complex and expensive tooling with tightly controlled processing requirements to produce reliable components. These manufacturing complexities translate into high non-recurring engineering and unit costs for DCS devices.

A NEW TWIST ON DCSs

Rather than a concentric configuration, consider one where the chambers are positioned laterally to one another. This is the basis for the ARS. In between these two lateral chambers is a small passage that is used for diluent transfer. Additionally, a simple one-way valve is used to prevent backflow. Figure 1 illustrates two versions of ARS.

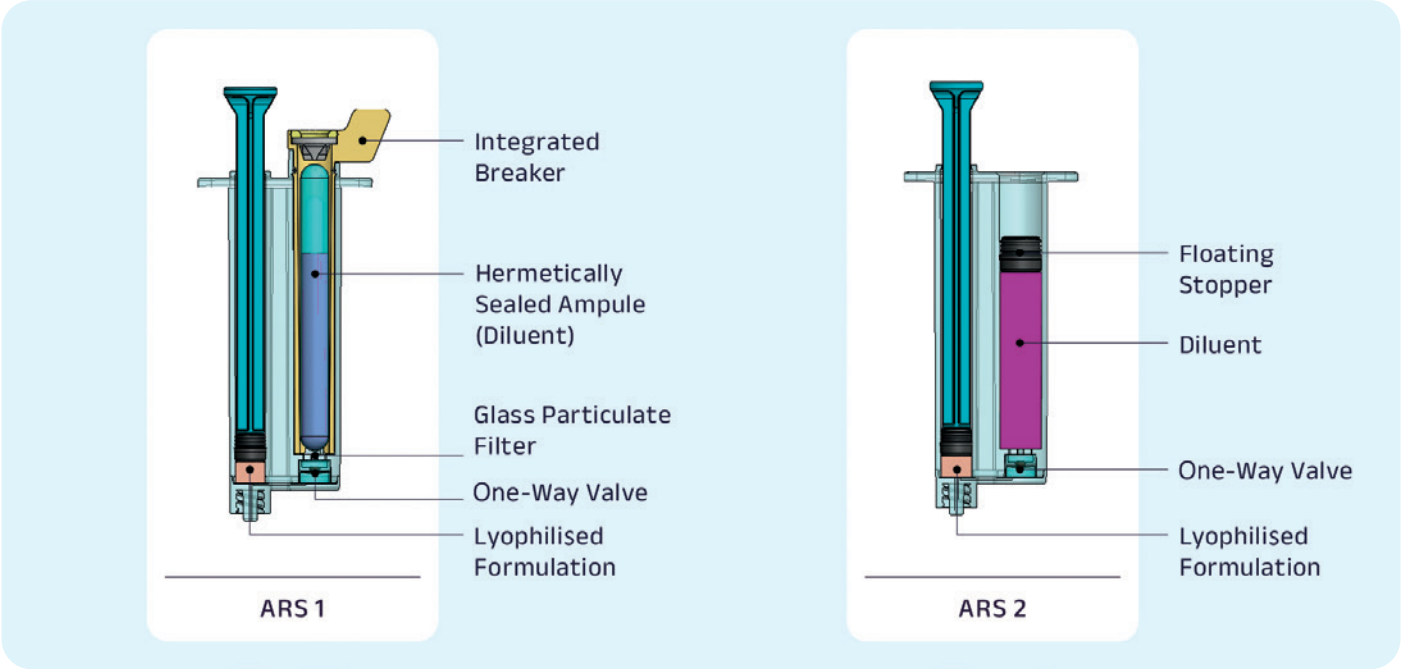

Figure 1: Ampulis ARS1 and ARS2 platforms.

In both configurations, the DCS problems previously mentioned are resolved.

- Following stopper break-loose, the glide force is constant. Unlike existing DCS devices, there are no bypass sections, momentarily actuated valves or multistopper displacements that cause glide force variability. The lateral configuration of ARS minimises frictional variation, improves usability and increases dose reliability.
- Plunger height is near-standard and stored in its collapsed position. The ARS design avoids the air pockets in existing DCS devices that are required for diluent transfer. As a result, the plunger stroke is nearly identical to that of standard prefilled syringes, even for larger fluid volumes. Furthermore, since the plunger rod is stored in its collapsed state, the packaged product height is considerably shorter than concentric DCS devices, which can present advantages for shipping and inventory management.
- ARSs use conventional drug-compliant materials and manufacturing processes. They do not need the intricate valves, cannulas and bypass features that require complex tooling and tightly toleranced components.

ARS1 – DILUENT IN AMPOULE

This first configuration of ARSs aims to simplify the fill-finish process by eliminating the subsequent filling steps following lyophilisation. With the ARS assembly in final form, the lyophilisation process can occur, immediately followed by packaging.

"THE LATERAL CONFIGURATION OF ARS MINIMISES FRICTIONAL VARIATION, IMPROVES USABILITY AND INCREASES DOSE RELIABILITY."

Additionally, the ARS1 configuration ensures that there is no possibility for premature mixing of diluent and lyophilised formulation. Some of the key features of the ARS1 configuration include:

Hermetically Sealed Ampoule

The diluent is stored within a hermetically sealed ampoule. This provides intrinsic container closure integrity and minimises risks related to extractables and leachables due to the all-glass contact surface with the diluent. Furthermore, this ampoule ensures that there is no possibility for premature mixing of lyophilised formulation and diluent.

Integrated Breaker

A simple rotating component is integrated into the device to easily fracture the ampoule, which releases the diluent into the ampoule chamber. This integrated breaker is an injection moulded component that creates a force concentration on the ampoule at a specific location for reliable fracturing.

Embedded Glass Particulate Filter and Valve

A filter is integrated into ARS1 to eliminate all-glass particulate while transferring the diluent into the lyophilised chamber. Additionally, a one-way valve is embedded to prevent backflow of reconstituted drug into the ampoule chamber after the diluent has been transferred.

ARS2 – NO AMPOULE

The second configuration of ARS excludes the ampoule and the integrated breaker. This ARS2 configuration can accommodate larger drug volumes and has similar manufacturing and fill-finish processes to ARS1. Some of the unique aspects of ARS2 include:

Floating Stopper

On the diluent side of the ARS2 is a cartridge-style stopper that sustains the the hydrostatic pressure maintained between the lyo and diluent chambers. As the user displaces the plunger rod, this pressure is translated through the passage and into the diluent chamber, resulting in consistent and accurate displacement of the floating stopper.

Embedded One-Way Valve

Similar to ARS1, ARS2 also includes a one-way valve that prevents backflow of the reconstituted formulation into the diluent chamber. However, ARS2 does not require the embedded glass particulate filter because it does not contain a glass ampoule.

Autoinjector Applications

This version of ARS2 is well-suited to autoinjector applications, which are currently under development at Ampulis.

STEPS OF OPERATION

The steps involved in operating the ARS have been designed with the user in mind. Each of these steps are familiar actuations that are common in standard drug delivery processes. Figures 2–4 illustrate the primary steps involved in operating ARS1.

Step 1: Rotate Breaker

As illustrated in Figure 2, the first user step is to rotate a tab at the top of the device, which causes pressure to be applied at the lower end of the ampoule, resulting in the ampoule fracturing and releasing the diluent into the ampoule chamber (for ARS2, this step is avoided, as there is no ampoule).

Step 2: Draw Syringe Upwards

As shown in Figure 3, the user then draws the syringe upwards. This causes the diluent to flow from the ampoule chamber into the lyo chamber. This transfer process forces the diluent through the embedded filter, which eliminates any glass particulate. The diluent proceeds through a one-way valve, which prevents it from backflowing into the ampoule chamber (this user step is identical for ARS2).

Step 3: Prime and Inject

As illustrated in Figure 4, the last step in operating ARS1 is to prime the reconstituted therapeutic and inject – an identical step to that used in a standard prefilled syringe (this step is identical for ARS2).

CONFIGURATION OPTIONS

While ARS configurations are already optimised for usability, there are often unique elements of therapeutics and use cases that must be considered. For these unique applications, ARSs can be customised across several parameters. Some of these opportunities for customisation include:

Multiple Dose Volumes

ARSs can be produced in various dose volumes. Graduations and dose marks can also be customised

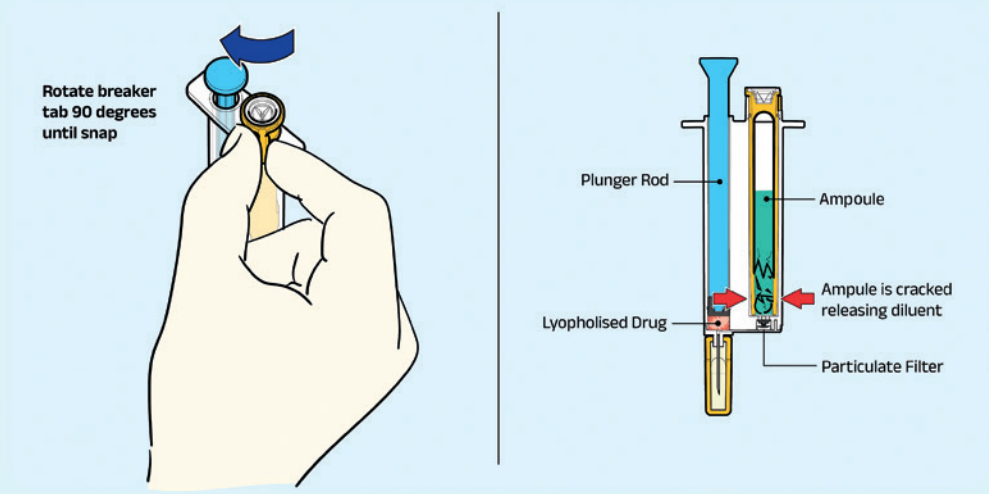

Figure 2: Rotate breaker tab to access diluent.

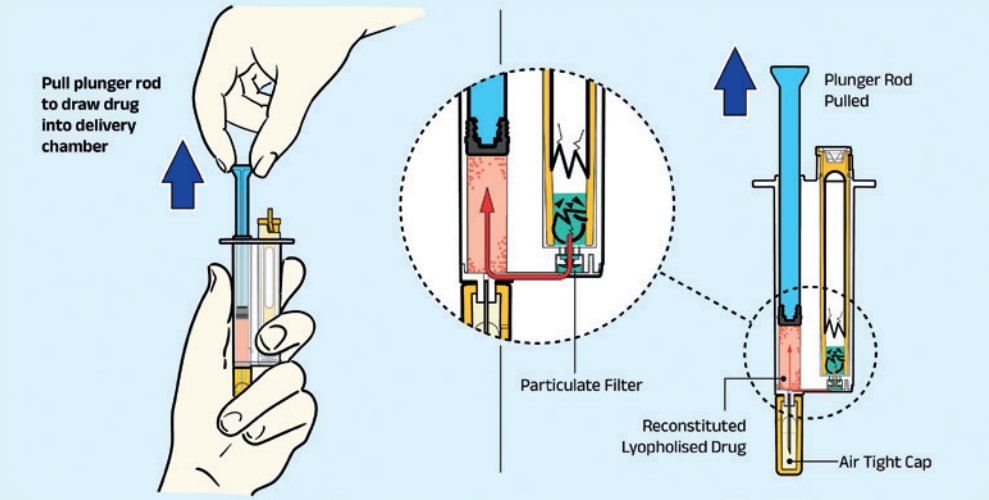

Figure 3: Pull plunger to combine diluent with lyophilised therapeutic.

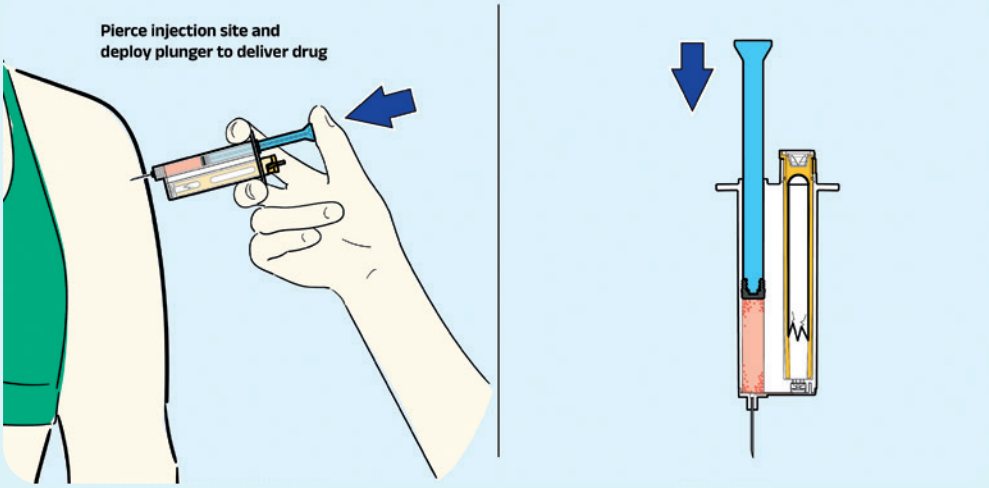

Figure 4: Prime and inject therapeutic.

Figure 5: ARS 1.0 mL (left), ARS 2.25 mL (centre), ARS 3.0 mL (right).

to specific formulation requirements. Figure 5 illustrates three potential dose volume options for ARS1. ARS2 can achieve larger volumes (up to 20 mL).

Needle Options

ARSs can be produced with staked needles in various gauges and depths for subcutaneous and intramuscular administration modes. Additionally, ARSs can be produced with a luer connection for intravenous administration or to accommodate user-applied needle subassemblies.

Safety Cover Options

In addition to the needle options, ARSs can be configured with an integrated safety cover to accommodate OSHA requirements.

Branding and Labelling Options

Colours, logos and other labelling can be customised to meet the customer's brand requirements while providing users with sufficient information for safe and effective use.

COLLABORATING FOR USABILITY, COST SAVINGS AND FASTER MARKET ENTRY

For years, DCSs have promised to streamline reconstitution for lyophilised drugs, offering faster preparation, reduced contamination risk and a simpler patient experience. Yet widespread adoption stalled, primarily due to the limitations of concentric DCS designs. These devices often suffer from inconsistent activation forces, long and awkward plunger strokes, intricate manufacturing requirements, and expensive, highly specialised fill-finish processes. The result: higher per-unit costs, complex supply chains and usability challenges that can affect both patient safety and market acceptance.

The ARS rethinks the DCS from the ground up with a lateral-chamber design that eliminates bypasses, multistopper displacement and air pockets. This results in constant glide force, standard plunger stroke, and simpler, more reliable manufacturing and fill-finish process, reducing capital investment and unit cost. For pharmaceutical partners, ARS offers not only significant cost savings and manufacturing efficiency but also improved usability, fewer human factors risks and a streamlined regulatory pathway. In short, ARS makes the commercial case for reconstituted therapies stronger than ever, accelerating development, lowering risk and improving patient outcomes.

ABOUT THE COMPANY

Ampulis designs and develops drug delivery devices that enhance usability, ensure drug stability and streamline manufacturing. Partnering with pharmaceutical companies, Ampulis customises platforms to meet the specific needs of each therapeutic. Founded in 2024, the company is headquartered in West Chester, PA, US.

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2. *Werk T et al, "Technology, Applications, and Process Challenges of Dual Chamber Systems". J Pharm Sci, 2016, Vol 105 (1), pp 4–9.*

Eric Sugalski

Eric Sugalski is the Founder and CEO of Ampulis, leading the development of next-generation medical devices and combination products that improve safety, usability and manufacturability. With over two decades of experience spanning engineering, human factors, quality management and regulatory affairs, he has guided cross-functional teams in bringing complex drug delivery solutions to market. Before founding Ampulis, Mr Sugalski served as Founder and CEO of Archimedic for 16 years, partnering with global pharma and medtech leaders to deliver breakthrough innovations. He holds a BS in Mechanical Engineering from the University of Colorado Boulder (CO, US) and an MBA from the Massachusetts Institute of Technology (Cambridge, MA, US).

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Credence MedSystems solves challenges in parenteral drug delivery. Its philosophy of Innovation Without Change preserves existing processes and primary package components. Companion includes needle-retraction, reuse prevention and usability features. The Dual Chamber platform simplifies delivery requiring reconstitution or sequential delivery. The Metered Dosing lineup enables precise microdosing in ophthalmics and aesthetics.

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KEY SPONSOR

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

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Windgap Medical, Inc. develops next-generation autoinjector platforms that simplify, automate and accelerate the delivery of complex injectables. By overcoming the constraints of traditional dual-chamber systems, Windgap helps biopharma teams shorten development timelines, streamline manufacturing and deploy scalable, user-friendly devices. The platform is protected by over 100 issued patents and is engaged in programmes with eight of the world's top 25 pharmaceutical companies.

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As a partner of choice for pharmaceutical and biotech companies across the globe, **BD Medical – Pharmaceutical Systems** provides a broad range of parenteral drug delivery systems including prefillable syringes, safety and shielding systems as well as advanced drug delivery solutions that help ensure pharma meets its drug delivery goals while considering drug complexity, viscosity and dosing volume.

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Contexo is a family-run mechanical engineering company based in Germany that specialises in building high-performance assembly machines. Most of Contexo´s machines process plastic parts with sizes of up to 500 cm³ and can handle over 80 production processes. In the medical device sector, Contexo focuses on primary packaging and diagnostic products, as well as contract manufacturing services.

To learn more, see **Page 50**

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Grand River Aseptic Manufacturing (GRAM) is a pharmaceutical contract development and manufacturing organisation providing fill-finish services for liquid and lyophilised vials, syringes and cartridges. GRAM's syringe and cartridge technology and drug delivery partnerships place it at the forefront of client value delivery and pharmaceutical manufacturing services.

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Lyophilization Technology, Inc (LTI) is a CDMO focused exclusively on the development and clinical manufacturing of lyophilised drug products. LTI provides formulation development, product design, process engineering, technology transfer and clinical supply manufacturing. LTI's focus on freeze drying across all clinical phases helps sponsors advance stable, usable and reliable investigational therapies.

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Owen Mumford is a medical device manufacturer that develops products for its own brand and custom device solutions for pharmaceutical and diagnostic companies. Owen Mumford provides research, design and manufacturing capabilities for device production.

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Phillips Medisize, a Molex company, collaborates with leading medical technology, pharmaceutical and *in vitro* diagnostic companies to design, engineer and manufacture lifesaving innovations. As a CDMO, the company leverages 60 years of expertise and capabilities and a global presence to help millions live healthier, more productive lives.

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Vetter is a CDMO with headquarters in Ravensburg, Germany and production facilities in Germany, Austria and the US. With decades of experience in the manufacturing of prefilled injection systems, Vetter provides support from drug product development through clinical and commercial filling to assembly and packaging for vials, syringes and cartridges.

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GRAND RIVER
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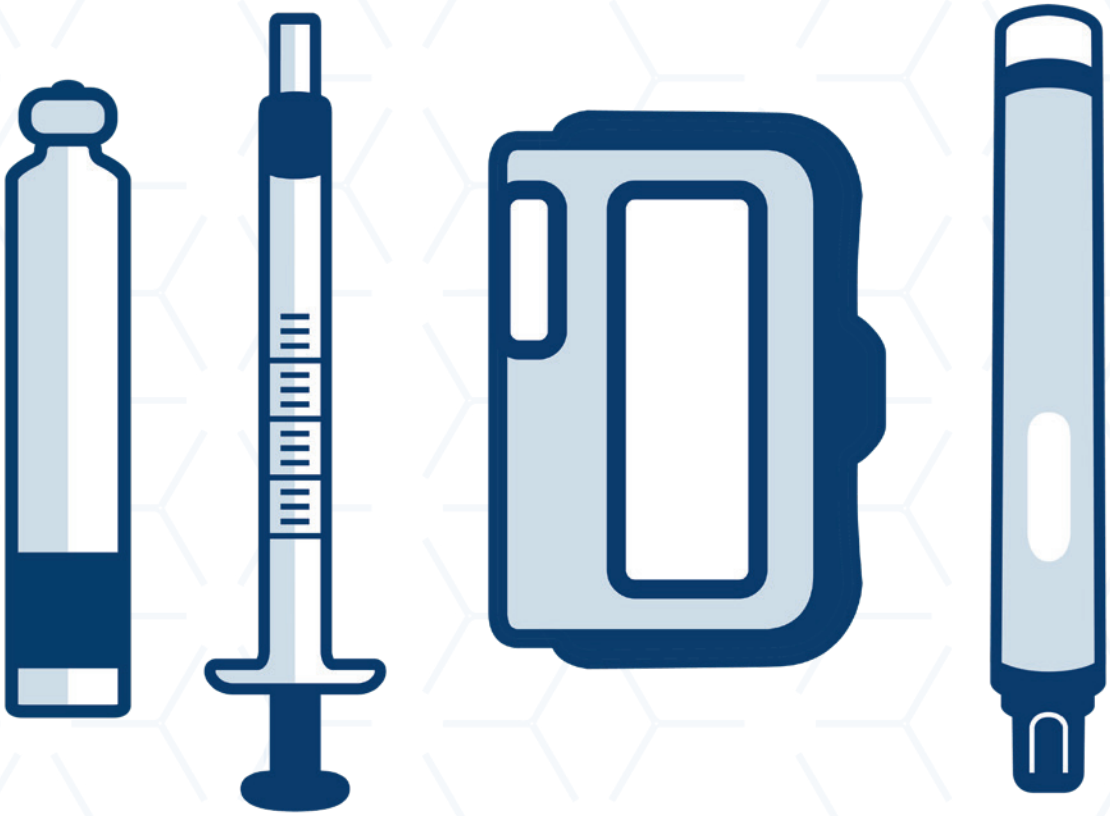

Fill-finish CDMO dedicated to supporting advancements in patient care

Grand River Aseptic Manufacturing provides sterile filling and finishing for **syringes, cartridges, and vials** used in drug delivery devices. We are committed to working closely with our customers to develop solutions that meet the evolving needs of patients. We invite conversations on how we can best support your product requirements.

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