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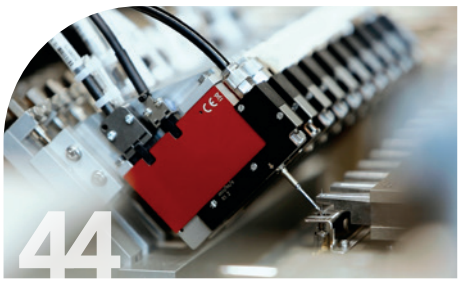

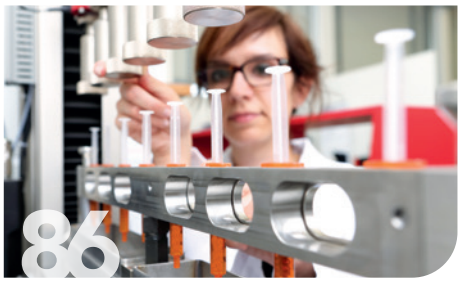

PREFILLED SYRINGES & INJECTION DEVICES

ONdrugDelivery Issue N° 168, January 20th, 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.

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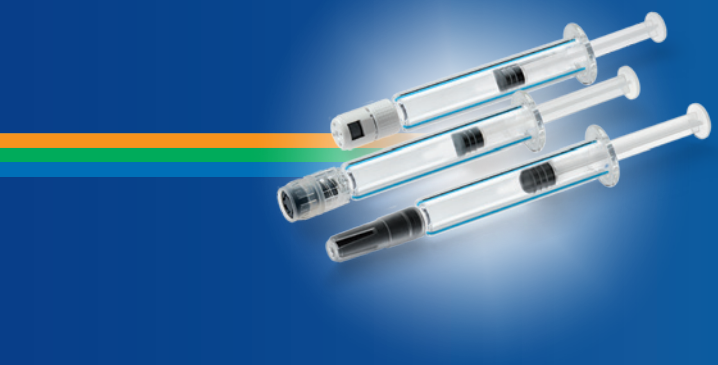

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A New Look for a Milestone Year

As we celebrate ONdrugDelivery's 20th Anniversary, we kick off this milestone year with a fresh new look for the magazine, and this bumper issue focused entirely on the topic "Prefilled Syringes & Injection Devices". This was the topic of Issue 1, which was published back in January 2005. The articles in this January 2025 issue cover the full sweep of injectable product development, from components to production, from devices to partnering.

The issue opens with our Outstanding Sponsor **Ypsomed**, providing an overview of a recent review of clinical-stage and approved biopharmaceuticals that investigates the progress on the industry's move from intravenous to subcutaneous delivery for this key category of drug, and how Ypsomed's device portfolio is well situated to meet the challenges posed by subcutaneous delivery of these crucial therapeutics (see Page 10).

An Expert View from **Springboard**'s Tom Oakley (Page 18) covers the trends to look out for in the sector for 2025. And our Key Sponsors **Stevanato** and **Terumo** discuss two critical components of prefilled syringes. Stevanato provided insights into primary drug containers (Page 22) and Terumo discusses the development of needles for highly sensitive applications, such as intravitreal injection (Page 26).

We hear from a range of companies on advanced devices to tackle unmet needs in injectable drug delivery, including **Haselmeier**'s PicoJect (Page 50), **Altek**'s Alcee platform (Page 60) and **Congruence Medical**'s Microlitre Dosing System (Page 120). In the field of wearable technology, **Eitan Medical** discusses infusion technology (Page 124), **MicroMED** highlights a novel approach to large-volume on-body injectors (Page 77), and **Cirtec** explores implantable devices (Page 103).

Digging deeper into the subject, **Phillips Medisize** (Page 90), **Cambridge Design Partnership** (Page 116) and **Cambridge Consultants** (Page 32) offer insights on a number of the challenges facing advanced autoinjector development, and offer potential solutions.

This issue also prominently features several excellent contributions on industrialisation, which tackle this topic from different angles. **ZwickRoell** covers automated testing (Page 86), **BAUMANN MEDICAL** highlights springs and stampings (Page 106), **STÜKEN MEDICAL** offers insights on deep-drawn metal components (Page 100), **teamtechnik** details bonding technologies (Page 44), **Fischer Söhne** engages with nest and tub packaging (Page 112), and **Syntegon,** and **InnoMedica** in a Pharmapack Start-Up Spotlight, explore the challenges of small-batch production (Pages 97 and 38).

Rounding out the issue, we feature articles from **ten23 health** on how CDMOs can offer expertise to help drug developers pair their drug with the right device in the right dose (Page 66), and from **Team Consulting** on how to get the most out of digital support for patients (Page 56), as well as an interview with **Aptar Pharma** on their sustainability progress, including how this critical subject factors into the design of their new manufacturing site (Page 72).

We're grateful for the strong support and truly excellent contributions to this very special issue, and proud of our brand-new 20th Anniversary look. We hope you're as excited to read the insights the issue brings as we are to share them with you, and we look forward to many more issues of ONdrugDelivery, and many more decades serving the drug delivery industry.

I will be attending Pharmapack in Paris on January 22-23, 2025, along with other members of the ONdrugDelivery team. It's always a pleasure to meet our readers. Please do come and see us in the Media Hub (**Stand MH3**)!

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THE RISE OF LARGE-VOLUME SUBCUTANEOUS ADMINISTRATION OF BIOPHARMACEUTICALS AND DELIVERY IMPLICATIONS

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Andreas Schneider and **Jakob Lange** of **Ypsomed** consider the subcutaneous administration of larger volumes of biopharmaceuticals in the pharmaceutical industry and summarise a recent study that reviews clinical-stage and approved intravenous and subcutaneous biopharmaceuticals to provide valuable guidance for new product development, as well as for marketing and commercialisation strategies in the rapidly evolving large-volume subcutaneous landscape.

The evolution of biopharmaceuticals has profoundly impacted healthcare, offering innovative treatments that address previously unmet medical needs. Advances in monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, oligonucleotides and other protein-based therapeutics have led to greater specificity and efficacy in targeting complex diseases. These innovations, coupled with the high approval rates and commercial success of antibody-based drugs, have underscored the potential of biopharmaceuticals to transform patient outcomes across oncology, autoimmune disorders and other chronic conditions.

Traditional delivery methods, however, often present barriers to optimal patient care. Intravenous (IV) infusions – a dominant delivery route for biopharmaceuticals – are typically administered in acute-care settings due to safety concerns and dosing requirements that exceed the capacity for subcutaneous (SC) injection. These IV regimens often demand extended administration times – sometimes exceeding several hours – and impose significant logistical and resource burdens on healthcare systems and patients alike.

To alleviate these challenges, SC drug delivery has emerged as a practical, patient-friendly alternative. By enabling care to shift from hospital settings to outpatient clinics, or even home environments, SC administration offers notable advantages, including shorter injection times and reduced healthcare costs. A prominent

"BY ENABLING CARE TO SHIFT FROM HOSPITAL SETTINGS TO OUTPATIENT CLINICS, OR EVEN HOME ENVIRONMENTS, SC ADMINISTRATION OFFERS NOTABLE ADVANTAGES, INCLUDING SHORTER INJECTION TIMES AND REDUCED HEALTHCARE COSTS."

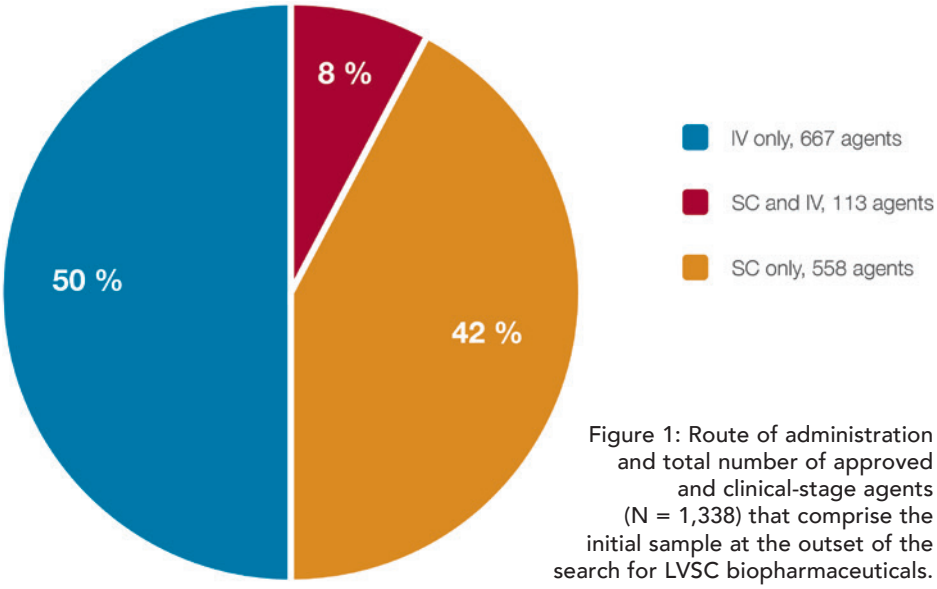

Figure 1: Route of administration and total number of approved and clinical-stage agents (N = 1,338) that comprise the initial sample at the outset of the search for LVSC biopharmaceuticals.

example of this transition is DARZALEX FASPRO® (daratumumab, Janssen), which replaced its IV formulation requiring hours-long infusions with a SC injection that can be completed in under five minutes. This transition not only improved the efficiency of care delivery but also demonstrated the broader viability of SC delivery for biopharmaceuticals.

Industry efforts to expand SC delivery have prioritised the development of large-volume dosing options that accommodate growing therapeutic payloads without compromising the patient experience. While handheld autoinjectors currently support volumes of up to 2 mL with administration times of less than 15 seconds, ongoing research aims to push these limits further. Innovations such as permeation enhancers (e.g. hyaluronidase) and high-concentration formulations are paving the way for SC injections that exceed traditional volume thresholds. In tandem, devices such as on-body injectors (OBIs) and tethered syringe pump drivers are gaining traction for larger doses ranging from 2 to >30 mL, enabling patients to manage treatments independently.

Despite these advances, critical gaps remain in understanding the optimal volume and frequency parameters for large-volume SC (LVSC) biopharmaceuticals. Addressing these gaps is essential for developing next-generation delivery systems and ensuring the seamless integration of LVSC therapeutics into clinical practice. This article explores the trends, challenges and opportunities shaping the future of LVSC biopharmaceuticals, drawing on insights from the study, "Navigating Large-Volume Subcutaneous Injections of Biopharmaceuticals: A Systematic Review of Clinical Pipelines and Approved Products".[1]

STUDY OVERVIEW: TRENDS AND INSIGHTS

The study employed a four-step review process to identify approved and clinical-stage biopharmaceuticals requiring LVSC (>2.0 mL) maintenance doses and their expected dosing intervals. The research analysed 1,338 approved and clinical-stage SC and IV biopharmaceuticals to identify LVSC agents (Figure 1).

The study identified 182 LVSCs – predominantly monoclonal or bispecific antibodies – representing approximately 15% of all IV and SC biopharmaceuticals. These agents target both cancer and a range of chronic non-cancer conditions, including autoimmune, neurological and cardiovascular diseases. Figure 2 illustrates the distribution of these LVSCs by therapeutic category.

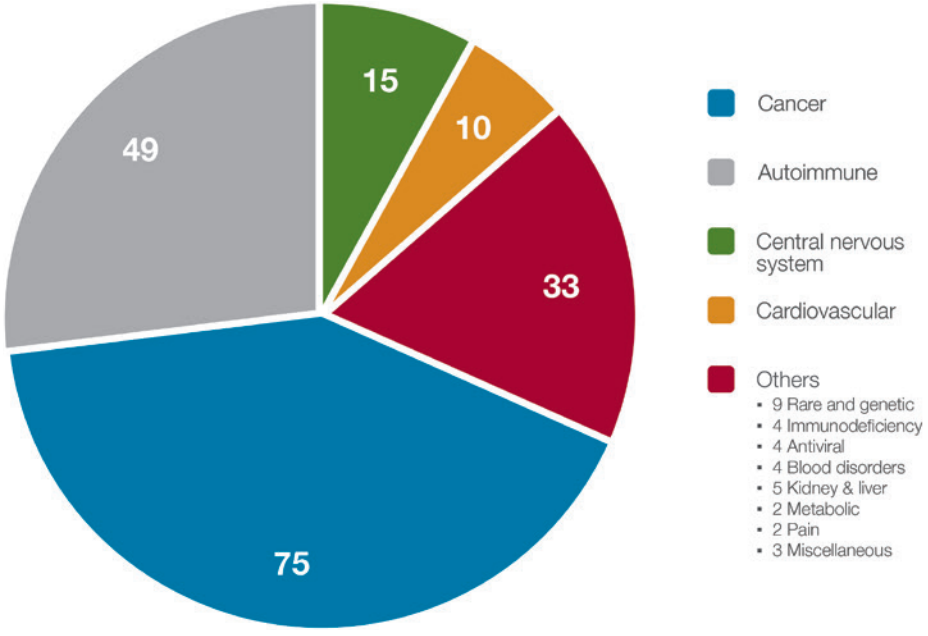

Figure 2: Therapeutic areas for approved and clinical-stage anti-cancer and non-cancer LVSCs (N = 182).

When analysing the dose-volume ranges of these LVSCs, the distribution highlights distinct trends by clinical development stage. Figure 3 shows the distribution of these LVSCs by dose volume and therapeutic category, with a notable concentration in oncology and autoimmune diseases. Clinical-stage LVSCs tend to have lower dose volumes, with 63% of clinical-stage agents falling into the 2–5 mL range compared with 48% of approved LVSCs in the same range. Conversely, IV-to-SC candidates often require higher volumes, with 76% of these agents requiring doses >5 mL. Figure 4 depicts dose-volume ranges across clinical development stages.

The study also discusses LVSC dose-volume ranges by clinical development stage, LVSC modality types, biological targets, therapeutic areas and dosing intervals, providing a comprehensive overview of the LVSC landscape. These insights form the basis for designing future delivery systems tailored to the diverse needs of new and existing biopharmaceuticals.

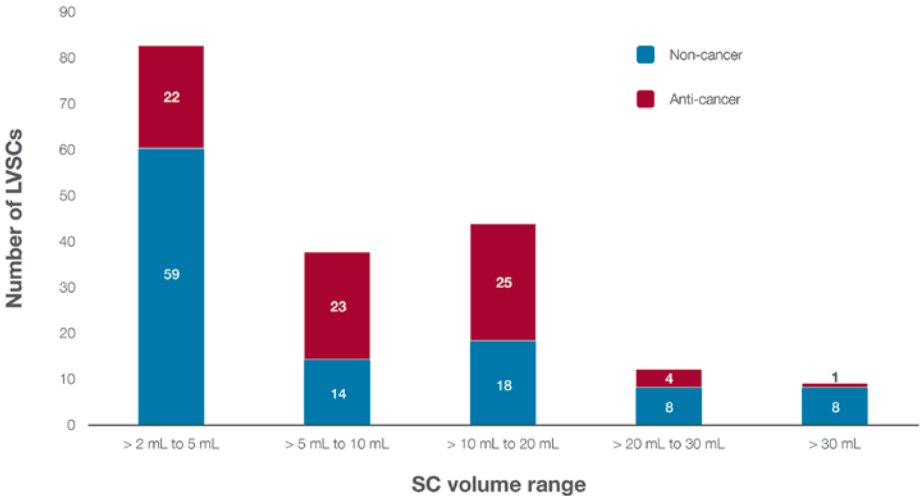

Figure 3: Distribution of LVSCs (N = 182) by dose-volume range and therapeutic category (anti-cancer versus non-cancer).

CHALLENGES AND OPPORTUNITIES FOR LVSC DEVICE DELIVERY

LVSCs span all SC injection volume tiers, with most therapies falling within the 2–20 mL range. The most common tier is 2–5 mL, with 68 out of 81 LVSCs in this category being ≤4 mL. Handheld injections of 2 mL are widely accepted, and evidence suggests that handheld devices for doses well above 2 mL are possible. However, one of the big questions currently under investigation is whether rapid handheld SC injections can be extended to volumes as high as 5 mL, if not 10 mL. This extension would significantly expand the scope of handheld autoinjectors in the market, enabling broader self-administration options.

For the self-administration of volumes between 4 and 10 mL, manual injection remains a key delivery method, particularly when combined with permeation enhancers. This approach temporarily modifies the extracellular matrix, facilitating the injection of larger SC volumes. Such manual injections, typically performed by healthcare providers (HCPs) for up to 10 minutes, are already used for many large-volume agents. However, efforts are underway to shorten administration times and explore automation through

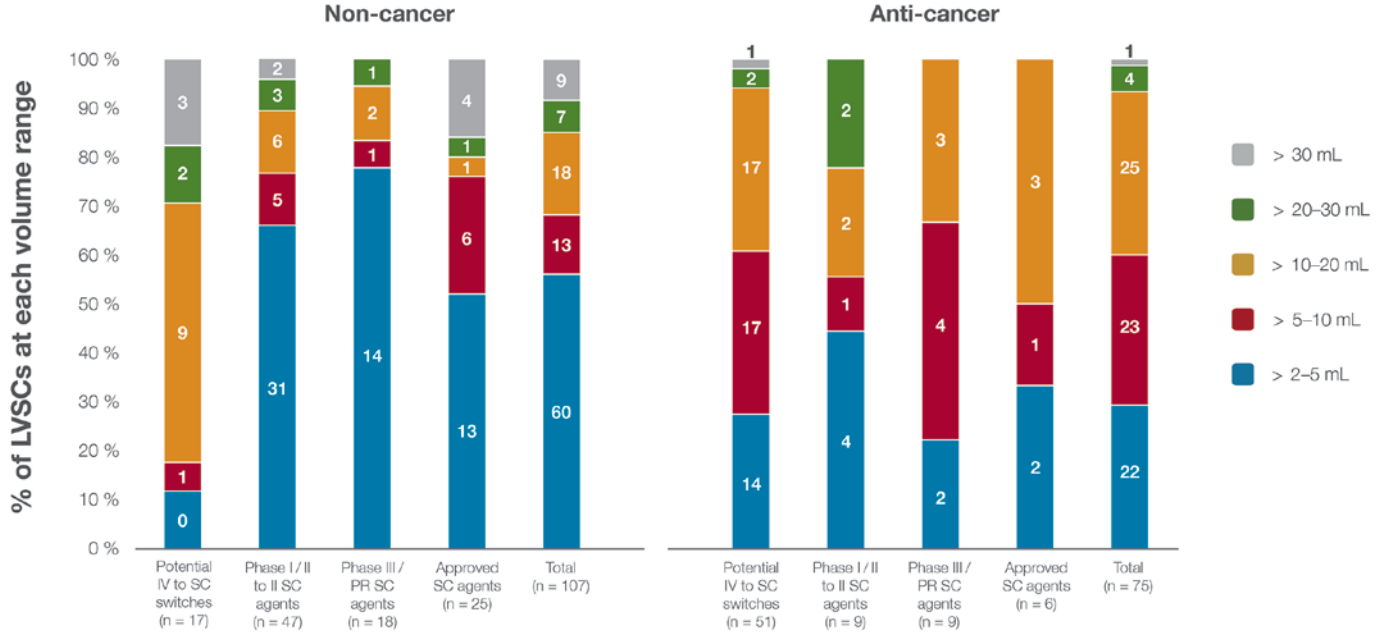

Figure 4: Dose-volume ranges for all IV-to-SC switching candidates, SC clinical-stage assets and approved LVSCs (N = 182) for non-cancer and anti-cancer indications across various stages of clinical testing. The number of LVSCs in each volume range is indicated on the bar chart.

handheld autoinjectors, which would enable patients to self-inject, even at these larger dose volumes.

For volumes exceeding 10 mL, alternative delivery methods, such as OBIs and syringe pumps, become more important. OBIs, which are wearable injection devices, can facilitate SC administration of larger doses either in a clinical setting or at home, offering significant convenience for patients requiring regular treatments. These devices are particularly suited for chronic conditions requiring consistent administration rates, such as autoimmune disorders. Syringe pumps are practical for patients with limited IV access and can deliver consistent doses over extended periods. At volumes exceeding 30 mL, manual injections and multiple OBIs may become impractical, making tethered SC infusion pumps a viable alternative. These pumps are already established in the market for therapies such as SC immunoglobulins, which often require high-volume administration.

Another strategy to manage the challenges of large-volume SC delivery is to reduce the physical volume of injections by increasing drug concentration. High-concentration formulations (>200 mg/mL) enable smaller injection volumes, but these often lead to higher viscosities, which present additional challenges for device design. For such formulations, devices must employ advanced technologies, such as shorter and wider needles to reduce injection force or high-force autoinjectors capable of delivering viscous solutions without compromising user comfort.

"ANOTHER STRATEGY TO MANAGE THE CHALLENGES OF LARGE-VOLUME SC DELIVERY IS TO REDUCE THE PHYSICAL VOLUME OF INJECTIONS BY INCREASING DRUG CONCENTRATION."

The distinction between non-cancer and cancer LVSCs further highlights unique challenges and opportunities. Non-cancer LVSCs, such as those targeting asthma, inflammatory bowel disease and migraine, typically fall into the 2–5 mL range, making them well-suited for handheld autoinjectors designed for at-home self administration. However, some clinical-stage non-cancer LVSCs require volumes exceeding 5 mL, necessitating OBIs or tethered pumps for home or outpatient use. For conditions such as Alzheimer's disease, which involve significant unmet medical needs, the development of convenient SC delivery systems would not only enhance access to therapies but also improve overall patient care.

In contrast, most cancer LVSCs fall within the 5–20 mL range, with many requiring administration in a hospital setting by an HCP. These injections are typically delivered over 2–7 minutes, often in combination with hyaluronidase. While this approach is effective, there is a growing interest in shifting some cancer LVSC treatments to outpatient clinics, or even home settings. This transition will require more user-friendly delivery technologies capable of handling larger volumes without compromising efficacy or patient safety. Devices such as OBIs, syringe pumps and even advanced handheld autoinjectors are expected to play a crucial role in facilitating this transition.

However, several barriers remain for home-based self-injection of cancer LVSCs. For instance, patients undergoing combination therapy with IV chemotherapy or radiotherapy often visit infusion centres, limiting the added value of at-home SC

administration. Despite this, there is potential for certain cancer patients to self-administer their treatments at home, either independently or with assistance from caregivers or HCPs. Clinical studies are currently investigating the feasibility of at-home administration for various anti-cancer agents and new delivery technologies are being designed to address these scenarios.

Another critical factor in LVSC delivery is dosing frequency. There has been a notable shift towards less frequent, more patient-friendly dosing intervals, such as every four weeks. This trend is particularly prominent in non-cancer LVSCs, where extended dosing intervals are associated with improved adherence and patient satisfaction. For cancer LVSCs, dosing schedules often align with IV chemotherapy or radiotherapy regimens, typically every three weeks. However, some therapies are moving towards longer intervals, such as every four or six weeks. These extended intervals necessitate larger SC doses, creating additional challenges for device design.

Recent advancements in drug development are also driving the growth of LVSC biopharmaceuticals. Anti-cancer agents, for example, often require high systemic doses (>300 mg) to offset reduced SC bioavailability or to effectively target difficult-to-reach tumour sites. Similarly, autoimmune and neurological conditions frequently demand large SC doses due to high circulating levels of endogenous targets or rapid protein turnover. In these cases, innovative delivery solutions that accommodate large volumes, high viscosities and frequent dosing schedules will be critical to meeting patient needs.

"INNOVATIVE DELIVERY SOLUTIONS THAT ACCOMMODATE LARGE VOLUMES, HIGH VISCOSITIES AND FREQUENT DOSING SCHEDULES WILL BE CRITICAL TO MEETING PATIENT NEEDS."

POTENTIAL FOR IV-TO-SC TRANSITION AND IMPLICATIONS FOR DEVICE DESIGN

Ypsomed is addressing the growing demand for SC injections of high-dose therapeutics – the YpsoMate 2.25 and YpsoMate 2.25 Pro offer a reliable platform for <2 mL SC injections, featuring a simple two-step automatic process. To accommodate higher-viscosity formulations, the YpsoMate product platform range can be configured with an 8 mm needle, which reduces injection force through a thinner wall for rapid yet comfortable delivery.

Expanding this platform, the YpsoMate 5.5 supports volumes of 2–5.5 mL. Based on the proven YpsoMate 2.25 Pro technology, it employs a constant force drive mechanism to reproducibly inject viscous, large-volume formulations – essential for many high-dose therapies that conventional compression springs cannot handle.

For larger doses, the YpsoDose patch injector manages payloads <1,000 mg in 5–10 mL volumes. This modular, customisable platform uses Ypsomed's expertise in prefilled pen injectors and autoinjectors, accelerating time to clinic while minimising pharma partners' upfront risks. It provides an effective solution for delivering high-dose medications requiring larger volumes or higher viscosities. Figures 5 and 6 illustrate Ypsomed's portfolio of device solutions for LVSC administration and their relationship to the viscosities and volumes supported.

THE FUTURE OF LARGE-VOLUME SC BIOPHARMACEUTICALS

The study highlights key trends in LVSC biopharmaceuticals, including the increasing focus on SC delivery for both cancer and chronic diseases, the shift towards patient-friendly dosing intervals and the evolving need for innovative delivery devices. These insights underscore the growing demand for technologies capable of managing high-dose therapies, including high viscosities, large volumes and diverse drug formulations for different therapeutic needs.

Together, Ypsomed's comprehensive portfolio of innovative device solutions addresses the full spectrum of

Figure 5: Ypsomed solutions for large volumes and high viscosities. Pictured from left to right: YpsoMate 2.25 with 8 mm needle configuration, YpsoMate 2.25 Pro with 8 mm needle configuration, YpsoMate 5.5 and YpsoDose.

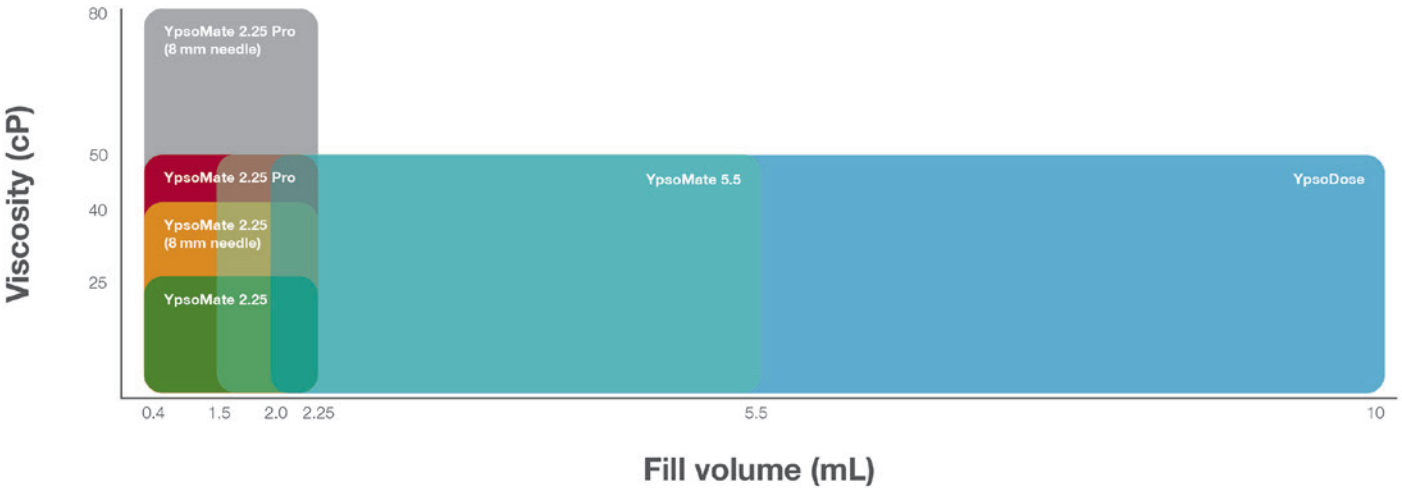

Figure 6: Viscosity (cP) versus volume (mL) for YpsoMate (YM) 2.25 autoinjectors, including models with the 8 mm needle configuration, YpsoMate 5.5 and YpsoDose.

large-volume and high-viscosity SC delivery needs. With platforms designed to streamline the delivery of high-dose therapies, Ypsomed's self-injection devices ensure scalability, patient comfort and ease of use. Designed for fast time-to-market and global success, these solutions support the transition from IV to SC administration, making self-injection accessible to a wide range of patient populations and therapeutic applications. As the field of LVSC biopharmaceuticals continues to expand, Ypsomed remains committed to partnering with pharmaceutical innovators to drive the future of high-dose biopharmaceutical delivery.

REFERENCE

1. *Green P, Schneider A, Lange J, "Navigating large-volume subcutaneous injections of biopharmaceuticals: a systematic review of clinical pipelines and approved products". MABS, 2024, Vol 16(1), 2402713, pp 1–19.*

Dr Andreas Schneider

Andreas Schneider, PhD, is Head of Innovation at Ypsomed. He leads a group that drives innovation end to end, from insights to ideas to prototypes to proof-of-concept. The team's responsibilities range from market and technology intelligence to strategy and business development, engineering and technology, and digital innovation. Dr Schneider has published and presented extensively in the areas of innovation management and drug delivery. He holds a PhD in Innovation Management from ETH Zurich (Switzerland).

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Dr Lange holds an MSc in Chemical Engineering from the Royal Institute of Technology in Stockholm, Sweden, and a PhD in Polymer Science from the Swiss Federal Institute of Technology in Lausanne, Switzerland. He has written and published more than 40 peer-reviewed papers on medical devices, packaging materials and polymers.

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Expert View

DRUG DELIVERY TRENDS FOR 2025

Tom Oakley and **Alex Vasiev** of Springboard look back at how the trends anticipated for 2024 played out in reality and look forward to four major trends expected to influence the drug delivery industry in 2025.

"EMERGENCY DEVICES ARE TYPICALLY SINGLE USE, SO A SIX-FIGURE NUMBER OF TESTS IS COMMERCIALLY IMPRACTICAL. THEREFORE, ADVANCED DEVICE DEVELOPMENT AND STATISTICAL EXPERTISE ARE NEEDED TO JUSTIFY CONFIDENCE TO THE 5 NINES LEVEL."

2024 TRENDS IN REVIEW

At the start of 2025, the drug delivery device industry is larger and more innovative than ever. In the "Drug Delivery Trends for 2024" article in ONdrugDelivery's January 2024 issue,[1] we identified five key trends for the past year:

- The booming market for weight-management drugs
- Closed-loop insulin systems (artificial pancreases)
- Large-volume injection
- Ophthalmic injections
- New development budgets for 2024.

Sales of weight management drugs, led by glucagon-like peptide-1s (GLP-1s) such as Wegovy (semaglutide, Novo Nordisk) and Zepbound (tirzepatide, Eli Lilly), have indeed increased substantially from around US$40 billion (£31.8 billion) in 2023 to around $53 billion in 2024. Growth is expected to continue in the region of 16% to 18% annually.[2] The $16.5 billion acquisition of Catalent by Novo Holdings (Dartford, UK) in February 2024 caused shockwaves through the drug delivery industry as fill-finish and injection device manufacturing capacity became saturated.[3] This trend shows no signs of slowing but will change significantly as semaglutide's core patents expire in various countries in 2026.

Closed-loop insulin systems continue to innovate, with the Omnipod 5 (Insulet, Acton, MA, US) pump able to integrate with the FreeStyle Libre 2 (Abbott Diabetes Care, Chicago, IL, US) or Dexcom G6 (DexCom, San Diego, CA, US) continuous glucose sensors[4] and the t:slim X2 (Tandem Diabetes, San Diego, CA, US) integrating with the FreeStyle Libre 2.[5]

Meanwhile, new options for large-volume injections continue to emerge, such as 5 mL autoinjectors. Additional ophthalmic injector development demand continues to be high, but the innovative projects in this area remain confidential.

Finally, anecdotal evidence suggests that new development budgets increased substantially in 2024. As predicted, many major pharmaceutical and medical device companies emerged from their corrections after the significant investments made in the industry during the covid-19 pandemic, multinational supply chains adjusted to new geopolitical realities and interest rates reduced throughout the year, thus freeing up capital for investment.

2025 TREND 1: EMERGENCY COMBINATION PRODUCTS

Many people think of EpiPen from Viatris when emergency medication is mentioned. EpiPen contains adrenaline (epinephrine) to treat anaphylaxis, which can be life threatening. However, some patients and caregivers delay or do not administer treatment in an emergency due to fear of the needle, lack of portability or, for untrained users, fear of giving an injection, among other reasons.[6] The first nasal adrenaline for anaphylaxis was approved in Europe in June 2024, and the US in August 2024.[7] The product is called EUR*neffy* in Europe and *neffy* in the US (ARS Pharmaceuticals, San Diego, CA, US). We look forward to other emergency drugs being delivered through new administration routes or using new and improved delivery devices.

Regulatory guidance for emergency combination products is evolving. In April 2020, the US FDA released draft guidance on "Technical Considerations for Demonstrating Reliability of Emergency-

Use Injectors Submitted under a BLA, NDA or ANDA". This draft guidance is being used for developing devices that are injectors or use different routes of administration.

The draft guidance contains the "5 Nines" rule, wherein it "recommends that emergency-use injectors include design control specifications for successful injection reliability of 99.999% with a 95% level of confidence." If taken literally, this would mean that a development programme would have to test nearly 300,000 devices with zero failures. Emergency devices are typically single use, so a six-figure number of tests is commercially impractical. Therefore, advanced device development and statistical expertise are needed to justify confidence to the 5 Nines level.

2025 TREND 2: REUSABLE DRUG DELIVERY DEVICES

Many drug delivery devices can be developed as either disposable or part-reusable (Figure 1). In our "Drug Delivery Device Trends for 2022" article,[8] we identified a trend whereby pioneering devices tend to be partly reusable, and then wholly disposable versions appear and take some of the market. Many of the devices in development indicate that there is renewed interest in reusable devices. Drivers for this trend are likely to include the following:

- Patients and other stakeholders are becoming increasingly sensitive to the environmental impact, especially from plastic waste, of fully disposable devices.
- The current generation of devices tends to be more complicated and costly than the previous generation. For example, on-body injectors are likely to have more components and mechanisms, and therefore have a higher built-in cost than prefilled syringes, safety systems and autoinjectors. The economics of fully disposable devices sets an upper limit on their cost.
- Many new devices have a "connectivity" aspect. The electronics and batteries that are typically involved in these features lend themselves to reusable modules.

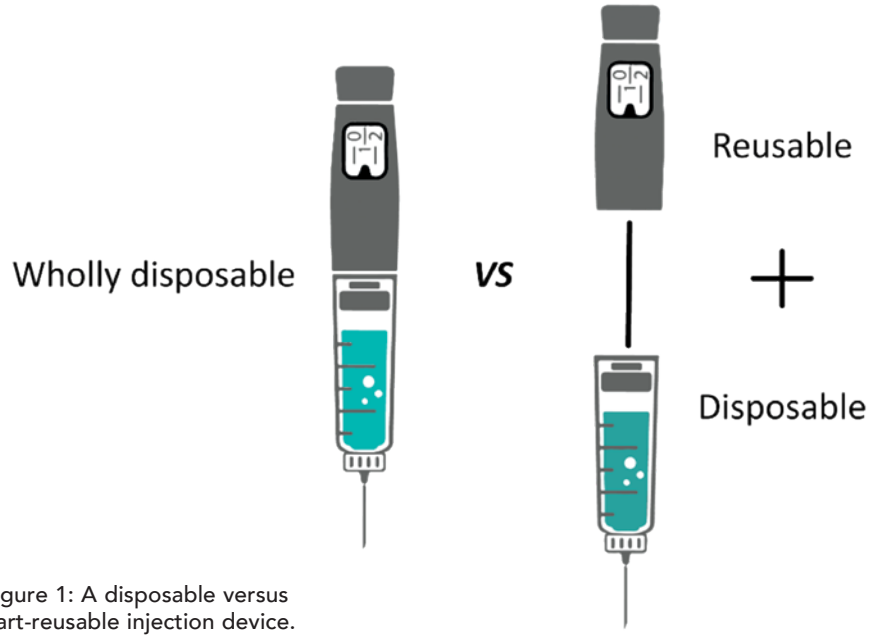

Figure 1: A disposable versus part-reusable injection device.

Example reusable autoinjectors that have been announced recently include:

- The Elexy reusable autoinjector from SHL Medical (Zug, Switzerland)
- The Aria reusable autoinjector from Philips Medisize (Hudson, WI, US)
- AstraZeneca's reusable autoinjector.

Reusable injection devices from earlier years include easypod/RebiSmart from Merck Group, AutoTouch from Amgen, and ava from UCB Biopharma (Brussels, Belgium).

2025 TREND 3: RENEWED INTEREST IN GAS-POWERED INJECTORS

Development of new biologics, particularly monoclonal antibodies, is leading to demand for injection devices capable of handling increased volumes and viscosities. Most commercial autoinjectors are driven by a mechanical (typically stainless steel) spring. However, compressed or liquefied gas canisters can provide higher energy densities than springs. As such, several companies have developed gas-powered autoinjectors, with current examples including:

- The Aerio range from Kaléo (Richmond, VA, US)
- ZENEO from CrossJect (Dijon, France)
- LVDC from Windgap Medical (Watertown, MA, US)
- AltaVISC from Altaviz (Irvine, CA, US)
- The Congruence Autoinjector from Congruence Medical (Baltimore, MD, US)
- Bios from SMC (Somerset, WI, US).

This is not an exhaustive list of the gas-powered injectors in development, and several have ceased development, such as Syrina by Bespak (Crewe, UK). The clear trend is that many device companies are betting on gas power as their future platform for high-viscosity and/or high-volume injections.

2025 TREND 4: REDUCED INJECTION SITE PAIN

Patient adherence remains a critical challenge in the management of chronic conditions, with injection site pain (ISP) playing a significant role in non-compliance.[9] ISP is a multifaceted issue influenced by environmental factors,[10] patient physiology, and the characteristics of formulations and delivery devices. Formulations often include excipients – such as buffering agents, tonicity adjusters, bulking agents, surfactants and preservatives – essential for maintaining the stability of complex and fragile therapeutics. However, these excipients may inadvertently contribute to ISP. Similarly, device characteristics, including needle geometry and delivery rate, significantly impact the level of pain perceived by patients during administration. Addressing these factors is critical for improving patient experience and adherence.

The introduction of innovative adjuvants, such as hyaluronidase, represents a breakthrough in reducing ISP, particularly for larger-volume formulations. These adjuvants facilitate more tolerable delivery and their adoption has gained momentum, including the FDA's recent approval of VYVGART Hytrulo by Argenx (Boston, MA, US) in 2024. This development sets the stage for broader use of adjuvants in 2025 and beyond.[11]

"ADVANCES IN INJECTION TECHNOLOGIES, FROM INNOVATIVE ADJUVANTS TO CUTTING-EDGE DEVICE DESIGNS, CAN REDUCE ISP AND THEREBY REDUCE ONE OF THE KEY BARRIERS TO HIGHER PATIENT ADHERENCE."

Autoinjectors, such as the YpsoMate 2.25 (Ypsomed, Burgdorf, Switzerland), will use syringes featuring short, ultra-thin needles specifically designed for high-viscosity formulations,[12] with the announcement of a collaboration with BD on integration of the Neopak™ XtraFlow™ system.[13] This trend is expected to expand into broader applications and other primary packaging systems intended for subcutaneous delivery.

There has also been a sustained adoption of on-body devices that, among other things, achieve slow injections, which inherently limits ISP:

1. The UDENCYA ONBODY™ Injector by Coherus BioSciences (Redwood City, CA, US) was approved by the FDA in December 2024.[14] This device delivers a pegfilgrastim biosimilar for treating neutropenia competing with Amgen's Neulasta Onpro.
2. The enFuse onbody injector from Enable Injections (Cincinnati, OH, US) has been approved for Apellis Pharmaceuticals' (MA, US) EMPAVELI (pegcetacoplan), providing a self-administration option for patients needing high-volume subcutaneous injections. Development agreements between Enable Injections and companies such as Sobi (Waltham, MA, US) may lead to more of these devices reaching the market.[15]

Advances in injection technologies, from innovative adjuvants to cutting-edge device designs, can reduce ISP and thereby reduce one of the key barriers to higher patient adherence. We expect an increased adoption of new technologies through 2025 across a broader range of formulations and therapeutic areas.

SUMMARY

The weight-management drug market continues to boom and new closed-loop insulin systems continue to come to market. There has also been progress in large-volume injectors and ophthalmic injectors. There are signals that the development budgets for drug delivery devices increased in 2024 over 2023 as predicted.

Those trends are likely to continue and, to those, we have added the following predictions for 2025:

- Increased interest and use of new emergency combination products
- Increasing development of reusable drug delivery devices
- Renewed interest in gas-powered injectors
- Developments in low pain drug delivery.

ABOUT THE COMPANY

Springboard, part of Sanner Group since 2024, is an engineering company that specialises in the design and development of new products and technologies in the field of medtech and drug delivery devices, resolving technical challenges and decreasing time to market.

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Tom Oakley

Tom Oakley, Vice-President Design and Development at Springboard, leads engineering and scientific teams developing new injection devices, pumps and inhalers. He has been the named inventor on dozens of patents throughout his 25 years' experience in the drug delivery industry. His most recent work focuses on developing robust device strategies and plans for a wide range of clients from the largest multinationals to the most dynamic start-ups. Mr Oakley is a regular speaker at various international conferences on innovation and medical device development. He read Engineering at Cambridge University (UK) before becoming the Choate Fellow in Human Physiology and Pathology at Harvard University (MA, US).

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Alex Vasiev, PhD, Head of Biointerface at Springboard, a multidisciplinary engineer with extensive R&D experience in both academia and consultancy. His primary focus is on the intersection of engineering, physics and biological systems. Before joining Springboard, Dr Vasiev managed front-end design and development at Oval (now SMC). In the field of drug delivery, Dr Vasiev has developed a range of innovations, including smart hydrogel microcarriers, patch pumps, soft-mist inhalers and several high-viscosity autoinjectors. He holds an MEng in Mechanical Engineering with Aeronautics and a PhD in Biomedical Engineering from the University of Glasgow (UK).

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CONTAINER SELECTION FOR A HIGHLY SENSITIVE DRUG PRODUCT: A SUCCESS STORY

Stevanato Group

Enrico Barichello of **Stevanato Group** discusses the organisation's collaboration with a leading pharmaceutical company to identify a suitable container for a high-concentration monoclonal antibody. The partnership addressed key challenges and contributed to maintaining the drug's stability and integrity throughout its lifecycle.

In the pharmaceutical industry, the selection of primary containers for new drug products is a critical step that can significantly impact the drug's stability, efficacy and patient safety. The process involves a complex analysis of various factors, including the interaction between the drug and the container, the performance of the container under different conditions and the integration of the container into a drug delivery device such as an autoinjector.

These devices are designed to simplify self-administration of injectable therapies, giving patients greater autonomy in managing chronic conditions while reducing reliance on healthcare professionals and clinical visits. Despite their ergonomic exterior, autoinjectors are the result of a sophisticated design and manufacturing process.

A key element of these systems is the glass primary container, often in the form of a prefilled syringe (PFS). The syringe plays a critical role in maintaining the drug's efficacy and safety until

"INTEGRATING GLASS SYRINGES WITH DRUG DELIVERY DEVICES PRESENTS SEVERAL CRITICAL CHALLENGES THAT CAN IMPACT BOTH PRODUCT PERFORMANCE AND PATIENT SAFETY."

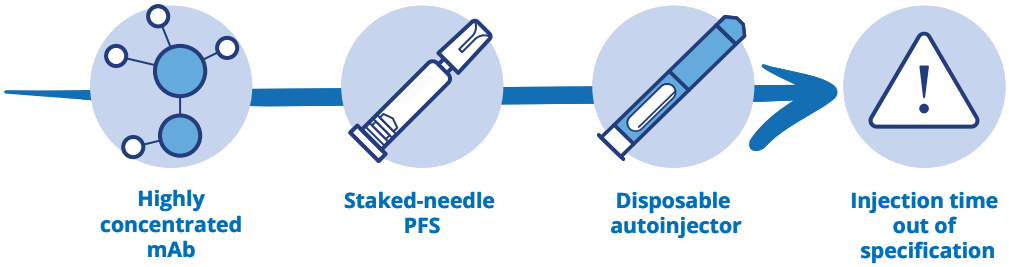

Figure 1: Initial challenges of the case study.

administration. When the device is activated, the syringe must withstand mechanical stress and handle the viscosity of the drug formulation. Failures, such as syringe breakage, can harm patients and disrupt manufacturing, especially when defects are worsened by high-viscosity or large-volume drugs.

THE CHALLENGES OF INTEGRATING GLASS SYRINGES WITH DRUG DELIVERY DEVICES

Integrating glass syringes with drug delivery devices presents several critical challenges that can impact both product performance and patient safety. One of the primary concerns is dimensional accuracy, which includes specific design features such as the syringe's length, the rigid needle shield and the needle's position and angle. Variations in these dimensions can lead to inconsistent injection depths, affecting the delivery efficacy and potentially resulting in missed doses.

Another significant challenge is functionality, which encompasses factors such as activation force, injection time and the break-loose and glide force of the syringe. If the required activation force is too high, the injection may not start, causing a missed dose. Similarly, if the injection time is too slow, patients might remove the device prematurely, leading to underdosing. Additionally, while the plunger must move during device use, unintended displacement during handling and shipping can compromise product integrity and sterility, posing risks to patient safety. This highlights the importance of an optimised design and a robust validation strategy.

Drug stability is also a critical parameter, particularly concerning the use of silicone oil, as well as the materials that come into contact with the drug. Excess silicone particles can lead to protein aggregation, resulting in a loss of drug efficacy or even immunogenicity. Moreover, additional materials in contact with the drug can increase the levels of extractable and leachable compounds, which may degrade the drug over time.

Lastly, the physical quality of the syringe is crucial, including its cosmetic appearance and resistance to breakage. Accumulation of physical defects can increase the risk of breakage, which not only poses a safety hazard but also increases the potential for missed doses.

Addressing these challenges requires a comprehensive and collaborative approach, leveraging advanced technologies and rigorous testing to ensure the optimal performance of the drug delivery system.

A SUCCESS STORY: STEVANATO GROUP TACKLING THE MOST COMPLEX CHALLENGES

A leading pharmaceutical company approached Stevanato Group with a specific challenge: it needed a new staked-needle PFS to be used in a disposable autoinjector for its high-concentration monoclonal antibody (mAb) product. mAbs are among the most sensitive drugs on the market, requiring advanced containment solutions and delivery systems. These drugs are particularly sensitive to interactions with the container and silicone particles, which can jeopardise drug stability and integrity.

During a benchmarking and stability study, the client had encountered out-of-specification injection times with other syringes in the market, a critical parameter that directly affects both the patient experience and drug delivery system efficacy. If not addressed, these out-of-specification results could lead to serious consequences, including project delays and potentially the need to change the primary container. This would not only delay commercialisation but also pose safety risks to patients.

APPROACH AND KEY OUTCOMES: A COMPREHENSIVE ANALYSIS FOR CONTAINER SELECTION

To address the challenges (Figure 1) posed by high-concentration mAbs, Stevanato Group leveraged the capabilities of its Technology Excellence Centers (TECs). The TEC team conducted a thorough analysis to identify the most suitable primary container. The first step in this process, supported by the company's analytical services, was to gain a deep understanding of all the components involved in the container closure system. This included examining the materials used in the syringe, the specific silicone used for lubrication and the design of the needle and plunger. Each of these elements can interact with the drug product in unique ways, potentially affecting its stability and efficacy.

A key part of this analysis was assessing the interactions between the drug and the container components using both the drug product and a placebo. By simulating the conditions under which the drug would be stored and used, the TEC team observed how the drug interacted with the container components. This step was essential in identifying potential issues, such as changes in drug stability or the formation of silicone particles. The investigation revealed that the thickness of the silicone layer inside the syringe was a contributing factor. It was found that the silicone layer depleted

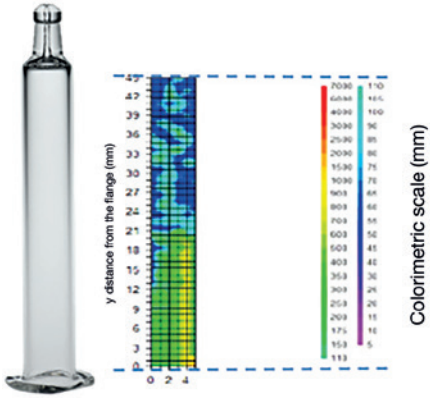

Figure 2: Example silicone layer (tested with Bouncer) showing depletion when in contact with the drug product.

or thinned when in contact with the drug, due to the wettability effect, particularly with the use of standard sprayed-on silicone oil. Traditional siliconised syringes, for example, were found to have higher levels of silicone particles, which could interact with the drug and compromise its stability (Figure 2).

To solve this problem, the client decided to restart the packaging selection process. This time, they included the use of Alba® syringes, which have a cross-linked silicone coating (Figure 3).

The new syringes were filled with the drug product and stored at 40°C under accelerated ageing conditions for 1.5 months and three months to simulate one year and two years of shelf life at 5°C. The tests conducted included silicone thickness and distribution, glide forces, injection time and particle analysis. The results showed that the cross-linked silicone coating used in Alba® syringes significantly reduced silicone migration, providing a more consistent and durable performance. This helped minimise the depletion of the silicone layer (Figure 4).

In addition to reducing silicone particle levels, Alba® syringes also demonstrated consistent and predictable glide force over time, compared with the standard sprayed silicone oil category. This was shown through a boxplot analysis of extrusion force, which revealed stable performance over an accelerated ageing period of three months at 40°C/75% RH (Figure 5).

Another crucial part of the analysis involved investigating the integration of the syringe with the drug delivery device. This required evaluating how the container would perform when assembled into the autoinjector and whether it would meet the necessary specifications for injection force and time. Because Alba® syringes demonstrated a stable, predictable glide force, they also successfully met the injection time requirements – in this case, less than

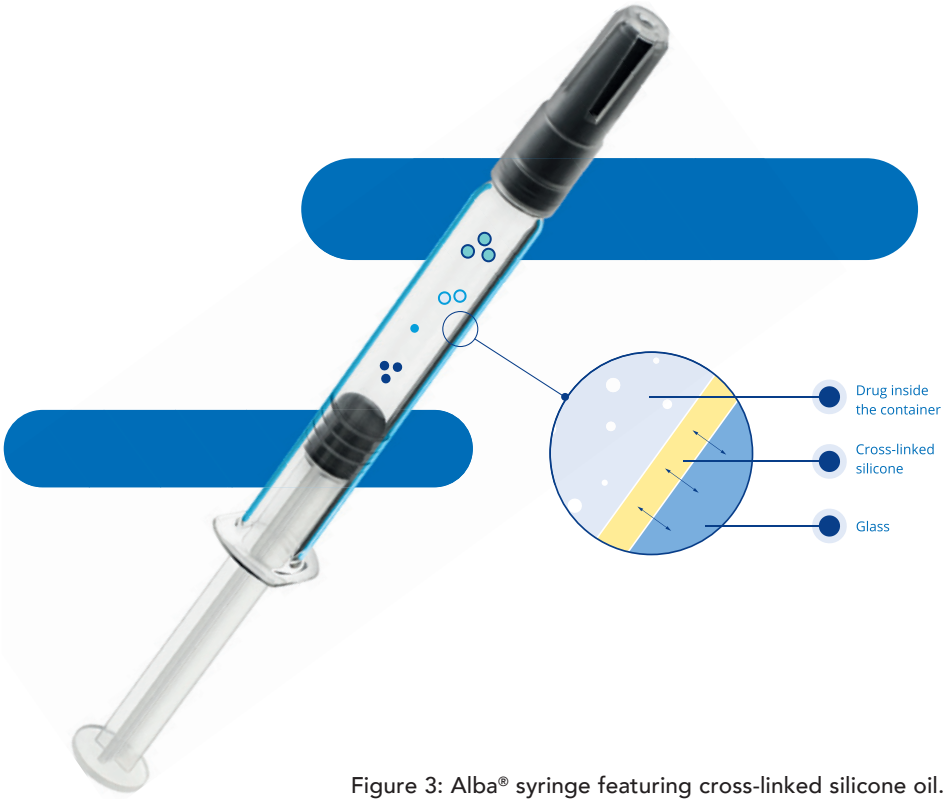

Figure 3: Alba® syringe featuring cross-linked silicone oil.

"THE RESULTS SHOWED THAT THE CROSS-LINKED SILICONE COATING USED IN ALBA® SYRINGES SIGNIFICANTLY REDUCED SILICONE MIGRATION, PROVIDING A MORE CONSISTENT AND DURABLE PERFORMANCE."

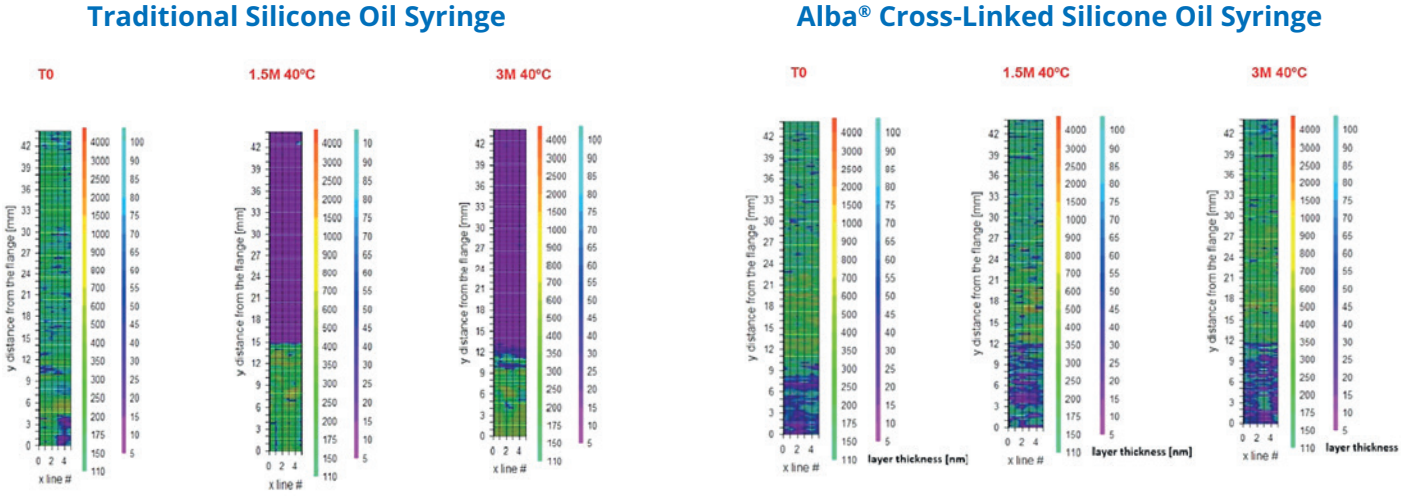

Figure 4: Higher stability of Alba® syringe compared with traditional silicone oil syringe.

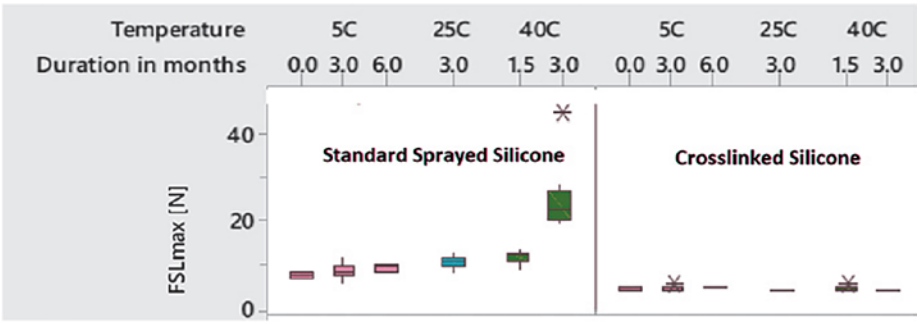

Figure 5: Lower extrusion forces over time and temperature ranges tested.

15 seconds – over time. This consistency ensured that the syringes adhered to the specified injection times, addressing the client's primary concern (Figure 6).

KEY BENEFITS OF ALBA® SYRINGES AS DEMONSTRATED BY TECs' ANALYTICAL CAPABILITIES

The comprehensive analysis revealed that Stevanato Group's Alba® syringes were the optimal solution for the client's high-concentration mAb formulation. Alba® syringes are designed with advanced technology that improves upon standard silicone by cross-linking it for exceptional stability and resistance to breakdown. This innovative approach provides multiple key benefits:

1. **Consistent Extrusion Force:** The cross-linked silicone coating ensures a consistent and predictable glide force for the syringe, which is critical for the performance of autoinjectors. This consistency helps to maintain the specified injection time, addressing the client's primary concern.
2. **Reduced Silicone Migration:** The cross-linked silicone oil layer on the inside of the syringe barrel significantly reduces silicone migration. This minimises the risk of drug-container interactions and the formation of silicone particles, which can compromise drug stability.

COLLABORATION AND DATA-DRIVEN SUPPORT

Stevanato Group's success in this project was not only due to its advanced technology but also its collaborative approach. From the early stages of the project, the company worked closely with the client to understand their specific needs and challenges. This collaboration involved regular face-to-face visits, which allowed Stevanato Group to strengthen the relationship with the client and gain a deep understanding of their requirements.

Stevanato Group's TECs provided comprehensive data-driven analysis to support the client's decision-making process. This included detailed performance data and insights into how the drug interacted with the container components. This is particularly important for the integration of the syringe in delivery devices such as autoinjectors. Stevanato Group's TECs can help clients decide on the appropriate tests and take care of the development, optimisation and validation of the method, based on their specific drug product requirements.

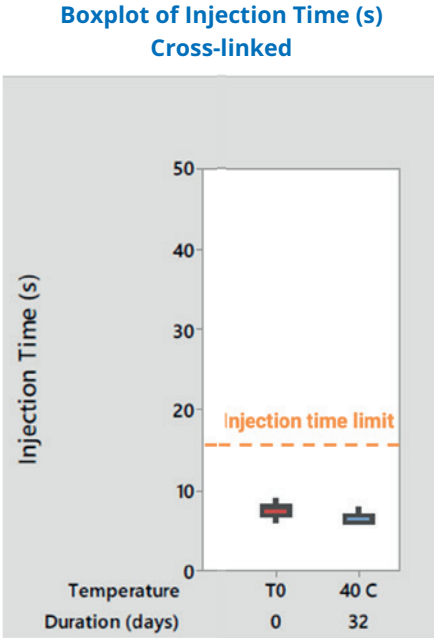

Figure 6: Injection time within specification.

The success of this leading pharmaceutical company highlights the importance of collaborating as early as possible with container suppliers that have strong analytical capabilities in the development of new drug products.

Enrico Barichello

Enrico Barichello, Product Manager, Syringe Platform, at Stevanato Group, has a background in industrial engineering and a master's degree in Management from the University of Padua (Italy), giving him a broad spectrum of skills in technical concepts and complex processes. Mr Barichello joined Stevanato Group in 2017 as a Product Management Specialist for the syringe platform. He has defined and co-ordinated the activities required to bring the company's products to market, bridging gaps between different company functions and aligning the involved teams. Mr Barichello was responsible for the roadmap and execution of the Alba® platform and since 2023 he has been Product Manager for the glass syringe platform.

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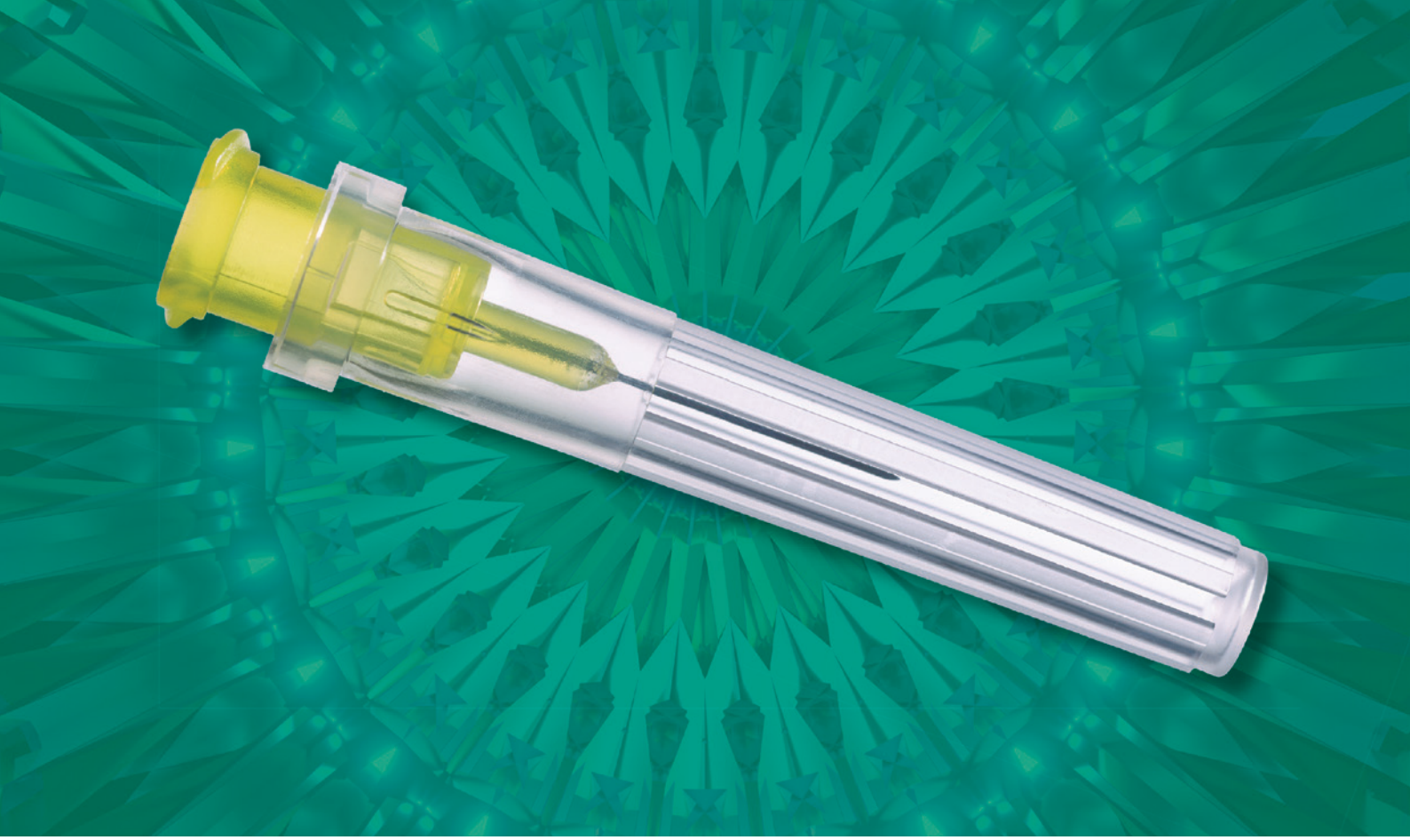

INTRODUCING THE TERUMO INJECTION FILTER NEEDLE – A FIRST STEP OF THE INFINO™ DEVELOPMENT PROGRAMME

TERUMO
MEDICAL CARE SOLUTIONS

Thomas Isaac at **Terumo Pharmaceutical Solutions** considers the issues associated with injection to highly sensitive areas, such as the vitreous body, and the potential to optimise needle design and features to address these issues, discussing the key features of Terumo's Injection Filter Needle, indicated for hypodermic and intravitreal injections within this context.

Successful drug delivery by injection relies on the selection of a needle well-matched to the application's requirements, with some therapeutic regimes being more exacting than others. Sensitivity to foreign particulates may be particularly acute in some instances, while higher potential for discomfort and tissue damage is also influential. Improved needle designs and features can offer safer treatment and a better patient experience.

These challenges are exemplified by injection into the vitreous body (eye) for the treatment of increasingly prevalent diseases such as neovascular age-related macular degeneration, diabetic macular oedema, diabetic retinopathy and retinal vein inclusion.[1] Estimates suggest that over 7 million intravitreal injections are delivered annually in the US alone.[2] The scarcity of regulated needles for this application presents an obstacle to market access and means that many of these injections may be performed with disposable needles neither developed nor validated for ophthalmic use, as evidenced from several recent field safety notices warning against off-label use.

REDUCING RISK FOR HIGH-SENSITIVITY INJECTION

Parenteral drug delivery is routine for the treatment of diseases ranging from diabetes to rheumatoid arthritis with daily injection a reality for many. Needle selection plays an important role in defining the patient experience, not only

at the point of administration but also with respect to subsequent and long-term complications. The prevention of particulate matter transfer and the need for precise and aseptic delivery are focus points within device development.

The level of visible and sub-visible particles in injectable formulations is a critical quality attribute because, other than the geometry of the needle and the device, there is usually no barrier to prevent their administration to the patient. The associated clinical risks are difficult to fully assess given the range of possible particulates and the difficulty of carrying out robust studies. However, cited complications include phlebitis, granuloma and the obstruction of pulmonary capillaries, the smallest of which are in the region of just 7 µm in diameter.[3] For intramuscular and subcutaneous delivery to healthy adult patients, the risks associated with particulate injection are considered to be relatively low but, for immune-compromised patients, those suffering from diseases of the major organs, and neonates and infants, concerns may be considerably higher.[3,4] Particulate injection into confined volumes – the eye, a joint or the spine – is also potentially more problematic.[3]

The drive to minimise the negative clinical impact of injected therapeutics makes particulate contamination an important focus for regulators.[5] Standards and test methods for detection are defined in US Pharmacopoeia (USP) <787>, <788> and <789>, but particulate control is challenging. Despite considerable effort, it is likely that millions of particles are injected or infused into patients every day, possibly exacerbating illness and health outcomes.[4] Terumo's literature research shows that the use of filters at the point of delivery may be effective in preventing injected-particulate-related complications, but hypodermic needles with embedded filters are far from common, as noted in USP <789>.

When it comes to other aspects of the injection process, the industry's understanding of how to improve both safety and the patient experience continues to evolve. For example, the needles used for insulin injection have become progressively shorter and finer – shorter needles help to prevent unintentional intramuscular, as opposed to subcutaneous, injection – while thinner needles are associated with less discomfort, within the constraint of necessarily using larger bores for higher dosage.[6,7] Together, the bore and length of the cannula, along with formulation viscosity (given same syringe specification), determine the extrusion force required, with wider bores and shorter cannulas associated with lower injection force.[8]

> "REDUCING DISCOMFORT IS HELPFUL, NOT JUST FROM THE PERSPECTIVE OF PATIENT EXPERIENCE BUT ALSO WITH RESPECT TO SUDDEN EYE MOVEMENT DURING THE PROCEDURE AND LONG-TERM COMPLIANCE."

Know Your Particulates

Particulate contamination is typically classified as either intrinsic, which means that it arises from a material relating to the formulation, its packaging or the manufacturing/assembly process, or extrinsic, which means that it is foreign and unexpected. Glass lamellae resulting from interactions between the formulation and primary packaging are a good example of intrinsic particles; for biologics, there is also the possibility of unexpectedly high levels of protein aggregates. Extrinsic particles might include hair, clothing fibres and paint and are effectively "unknowns". These, therefore, tend to present the higher risk, especially for aseptic drug delivery.

FOCUSING ON INTRAVITREAL INJECTION

Injection into the vitreous body provides a very specific example of the challenges that can face physician and patient alike with respect to minimising complications, discomfort and tissue damage.

Common issues associated with intravitreal injection include discomfort during the procedure, subconjunctival haemorrhage (a broken blood vessel in the eye), vitreous reflux (the leakage of vitreous humour and drug product) and transiently elevated intraocular pressure.[9] In addition, the injection of particulates into the vitreous body, including silicone oil droplets, has been specifically linked with floaters (spots that impair vision), sustained increases in intraocular pressure and endophthalmitis, a rare but severe ocular inflammation that can lead to loss of sight.[10] The fact that patients typically require regularly repeated injections to maintain vision increases the likelihood of long-term damage from such complications, focusing attention on equipment and practices that can mitigate risk.

There are frequent references in the literature to the suitability of a 30G needle (or thinner) for intravitreal injection.[6,11,12] Wider outer diameter 26G and 27G needles (given the same wall type) have been shown to increase vitreous reflux compared with 29G and 30G needles, as well as being associated with higher levels of discomfort.[6] Reducing discomfort is helpful, not just from the perspective of the patient experience but also with respect to sudden eye movement during the procedure and long-term compliance. Both larger and smaller bore cannulas have been linked with lower intraocular pressure, though comparative studies are complicated by the physical properties of the formulation being tested and the dose delivered.[13,14]

With respect to cannula length, longer needles increase the risk of retinal injury,[8,9] as well as the injection and insertion forces required, making them less conducive to gentle, controlled administration. Needles ranging from 8 to 12 mm are routinely referenced, with an upper limit of 18 mm indicated for safe administration.[6,8,9]

Although prefilled syringes are available for some therapeutics, the process of intravitreal injection typically involves the physician drawing up or transferring the formulation from a vial using a relatively wide bore needle before switching to a finer disposable one for administration. In the absence of needles validated for intravitreal use, standard hypodermic needles are routinely used off-label.[15] Ensuring aseptic delivery, protection from the ingress of particulates and precise dosing can therefore be challenging.

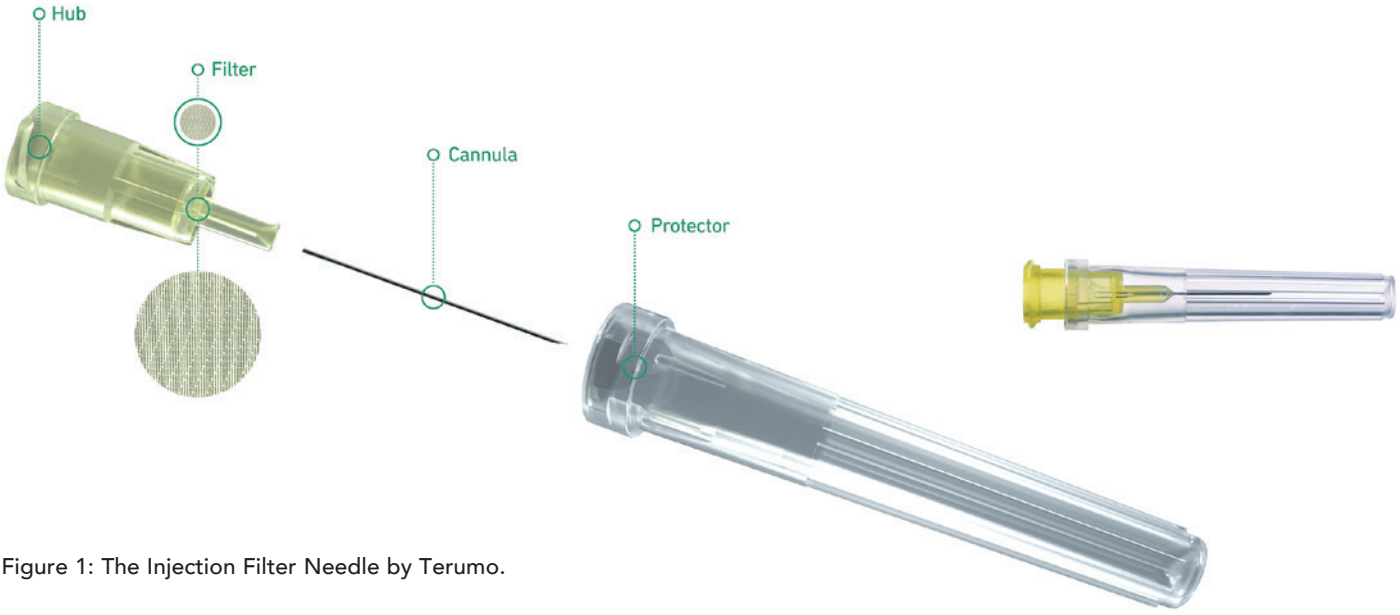

Figure 1: The Injection Filter Needle by Terumo.

INTRODUCING THE INJECTION FILTER NEEDLE BY TERUMO

Terumo has set the specifications of its Injection Filter Needle in collaboration with a leading pharmaceutical company, drawing on extensive in-house experience from past developments (Figure 1). Key features include:

- A needle hub with an embedded polyamide 5 µm mesh filter designed to retain particles in the fluid delivery path
- A 30G 12 mm extra-thin wall cannula (compliant with ISO 15510 and EN 10088-1) – used for Terumo's K-Pack II needles – that offers a higher flow rate compared with regular wall needles at equivalent injection pressure
- Soft blister packaging to support aseptic presentation and the packaging of drugs in prefilled syringes
- Polymethylmethacrylate (PMMA) hub with threaded flanges – compatible with syringes compliant with ISO 80369-7
- No components made from natural latex.

These features may help healthcare providers to more effectively protect patients from injected particulates, reduce tissue damage at the injection site, avoid interruptions to the injection process, ensure adequate priming and safeguard aseptic processes. Importantly, Terumo has carried out the necessary verification and validation processes to support a complete solution for intravitreal injection when combined with a similarly validated syringe.

"TERUMO HAS CARRIED OUT THE NECESSARY VERIFICATION AND VALIDATION PROCESSES TO SUPPORT A COMPLETE SOLUTION FOR INTRAVITREAL INJECTION WHEN COMBINED WITH A SIMILARLY VALIDATED SYRINGE."

CONCLUSION

Innovations in hypodermic needle design have an important role to play in meeting evolving requirements for drug delivery by injection. With its embedded filter, 30G extra-thin-wall cannula, threaded high transparency hub and blister packaging, the Terumo Injection Filter Needle is an important advancement within this context. Indication for intravitreal injection is particularly valuable given the scarcity of options for this application and growing clinical need. By working with Terumo to robustly assess the capabilities of the Injection Filter Needle within the context of a target application, product developers and healthcare practitioners can quantify safety and efficacy in use and capitalise on the potential benefits of this new solution.

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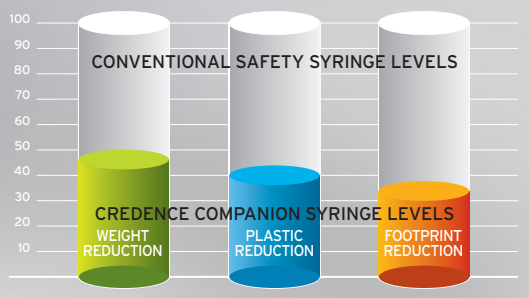

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Expert View

NEXT-GENERATION AUTOINJECTORS: BALANCING PATIENTS, PHARMA, PAYERS AND PLANET

David Latham, **Matthew Allen** and **Charlie Dean** of Cambridge Consultants use a case study of a reusable electromechanical autoinjector to outline the novel product development approach needed to achieve better outcomes for patients, pharma, payers and the planet.

"THE PREVALENCE OF BIOLOGICS TO TREAT CHRONIC DISEASES MEANS THAT THE NUMBER OF PATIENTS INJECTING THEMSELVES AT HOME HAS GROWN SIGNIFICANTLY OVER THE PAST FEW DECADES."

The stakeholder needs in drug delivery device development are continually evolving, resulting in an increasing breadth of variables at play and the number of tools required. Having a clear product development roadmap created with iterative design inputs from multiple disciplines is key to determining the optimal path to satisfy these conflicting requirements. This succeeds by elevating conventional product development with the integration of business strategy, product cost, environmental product stewardship and patient-centric design. To unlock this potential, a culture of smart risk-taking is also necessary. Discovering dead ends early on and tackling the highest risk areas first gives the best development value to investment ratio.

"RECENT DEVELOPMENTS HAVE SEEN REUSABLE DEVICES THAT SHOW POTENTIAL TO REDUCE THERAPY COST AND ENVIRONMENTAL BURDEN BUT HAVE DRAWBACKS THAT LIMIT THEIR WIDESPREAD ADOPTION."

WHAT IS MISSING WITH CURRENT AUTOINJECTOR PLATFORMS?

The introduction of autoinjector drug delivery systems in the 1970s significantly improved the standards of care by removing the need for multiple healthcare professional (HCP) consultations and allowing patients to treat themselves. The prevalence of biologics to treat chronic diseases means that the number of patients injecting themselves at home has grown significantly over the past few decades.

Evolution of the core drug delivery technology has, however, been limited. The most common devices are single-use, disposable mechanical systems with a prefilled syringe (PFS) and staked needle. Device activation is either two-step contact-activated or three-step button-activated systems. Sharps injury protection features appeared around the turn of the millennium and have become an expected, if not required, feature. The product portfolio has extended beyond 1 mL PFS platforms, to 2.25 mL, and is now pushing towards the 5 mL mark, where higher-viscosity formulations and higher-gauge needles require greater spring force. However, features such as variable injection depth setting, variable injection speed control and connectivity have remained niche improvements.

Recent developments have seen reusable devices that show potential to reduce therapy cost and environmental burden but have drawbacks that limit their widespread adoption. Sharp injury protection is either omitted or achieved using a cassette sub-assembly attached to the PFS by the manufacturer or by the use of a PFS with passive needle retraction at the end of dose. Mechanical, spring-driven systems that are manually reset by the patient introduce usability and plunger force challenges.

Patients	Availability, ease of use, safety and reliability, convenience, minimal pain.
Pharma	Grow sales and profit in both the short and long term. Minimise capital expenditure and internal investment. • Fit with a heavily invested installed base of infrastructure and a supply chain dominated by single-use autoinjectors incorporating PFS technology • Low competencies in electromechanical device development compared with mechanical device development in many cases • Fit with drug portfolio forecast, potentially increasing dose volumes and viscosities.
Payers	Minimising cost burden of treatment. Affordable co-pay in applicable markets. Stay within agreed budgets, often for fixed accounting periods (e.g. annual).
Planet	Reducing emissions and waste associated with therapy. Maximising resource efficiency and moving towards the circular economy.

Table 1: Summary of needs for the 4Ps.

Electromechanical devices have had limited appeal largely due to their high unit costs of incorporating electronic elements and the temptation to make feature-rich concepts where the business case does not justify the extra feature(s) inclusion.

Looking into the broader needs and desires of patients, pharma, payers and the planet (the 4Ps), there are conflicting requirements (Table 1).[1] Pharma and medical device organisations need to innovate to redress the 4Ps imbalance.

There is a need for new autoinjector technology that is based on PFS primary packaging, which allows users to self-administer with the same or improved level of safety and efficacy while making trade-offs in other areas to achieve economic and environmental goals. A development environment is needed to enable product development teams to look again at the real challenges and develop new devices that are unconstrained by current technology.

CALL TO ACTION

The mission was to demonstrate how a new autoinjector design might answer the aforementioned challenges:

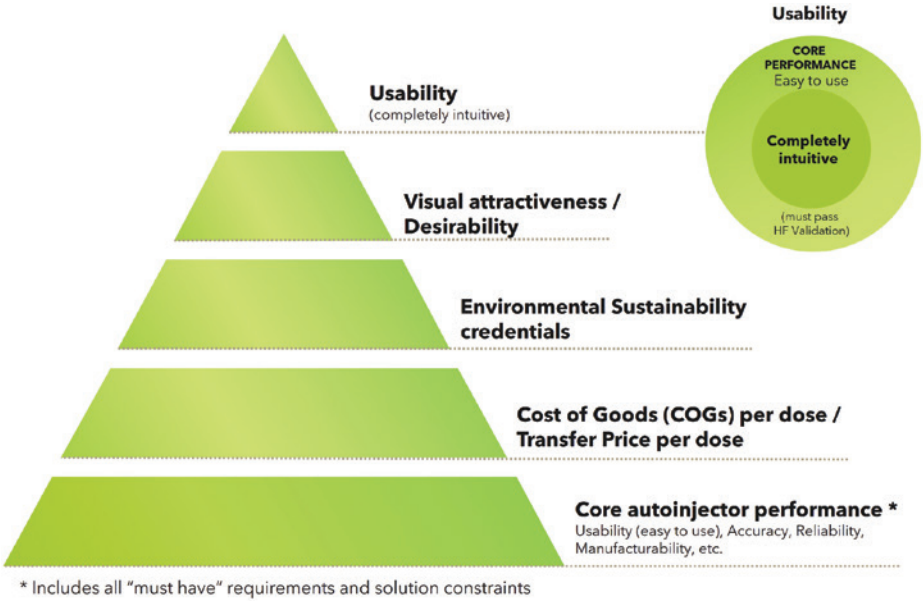


Figure 1: Hierarchy of optimisation.

maintaining the levels of safety and efficacy provided by current disposable mechanical autoinjectors while reducing both financial and environmental costs. The requirements are:

- Must use ISO-standard PFS containers currently used on validated filling lines
  - Avoiding any new investment in filling systems and use economies of scale of existing PFS components
  - Including 1 and 2.25 mL sizes, with scalability to 5 mL and beyond, both cut flange and small round flange
- Must support a range of fill volumes and a range of viscosities greater than those commonly seen today in autoinjectors.

The design vision was controlled by a simple hierarchy of optimisation (Figure 1). Working on the same principle as Maslow's hierarchy of needs, the base layer was satisfying all **core autoinjector functionality** and being able to **pass verification and validation**. The core functions were based on current disposable mechanical device core features, with the option to add or remove technology-dependent features later if relevant. Once this layer was satisfied, the second layer of cost reduction was targeted.

Cost was second because a compelling business case to stakeholders must be demonstrated. Cost optimisation also has synergies with the third layer of **environmental sustainability** and could be reversed in some cases.

The fourth layer was **desirability**. Its inclusion was a clear acknowledgement of the importance of good design to multiple stakeholders, not least the commercial marketing teams.

The fifth and final layer was enhanced **usability**, providing an emphasis to seize any remaining opportunities to go beyond easy to use and move towards completely intuitive to use.

"THE DESIGN VISION WAS CONTROLLED BY A SIMPLE HIERARCHY OF OPTIMISATION."

Figure 2: Bamboo variant 1, three-step, contact-activated electromechanical reusable autoinjector.

Figure 3: Bamboo variant 2, four-step, button-activated electromechanical reusable autoinjector.

A VISION OF WHAT IS POSSIBLE

What resulted from this project were two reusable electromechanical autoinjector variants (Figures 2 and 3). In both variants, the only disposable part is the naked PFS components with no add-on cassette. The reusable device provides sharps injury prevention, needle hiding and usability through mechatronics, which include automatic removal and replacement of the needle cap and the detection of premature lift. The impact of including limited electronics in the reusable unit was more than outweighed by the savings brought by not having a cassette on the disposable part, even before considering savings in shipping and storage costs.

While purely mechanical concepts that achieved the same functionality were investigated, it became apparent that they would be unlikely to fulfil the "easy to use" requirement. This type of system would also introduce significant mechanism complexity overall and greatly limit the potential plunger force, thus reducing the suitability for high-volume and/or high-viscosity drug products. On the commercial side, removing the need for a cassette also keeps the business model simple – avoiding proprietary "printer cartridge style" models that can lead to higher lifetime costs as the single-use element is sold at a higher mark-up to discount the price of the reusable device.

The other key factor for reducing costs and increasing sustainability was identifying the relative contributing factors in the device. Motors are by far the single biggest financial cost contributor to the bill of materials, while printed circuit boards and motors have the largest impact by mass on environmental sustainability. Therefore, given that the device essentially has three groups of automated mechanical functions – needle cap removal and replacement, needle insertion and retraction, and dose delivery – the key was using either one or two motors to deliver these functions. The architecture devised only required a single motor and minimal printed circuit board size to deliver all the automated mechanical functions. In parallel, high-quality non-medical-grade motors were identified and it was confirmed that they delivered the required performance when combined with low-cost controls – all at a fraction of the cost of traditional medical-grade motors.

Combining the automatic uncapping and recapping of the needle shield with an architecture that has a single motor performing multiple automated functions leads to the financial and environmental cost per dose figures shown in Figure 4 (excluding the impact of drug product and filling but including other PFS components), which have been benchmarked against

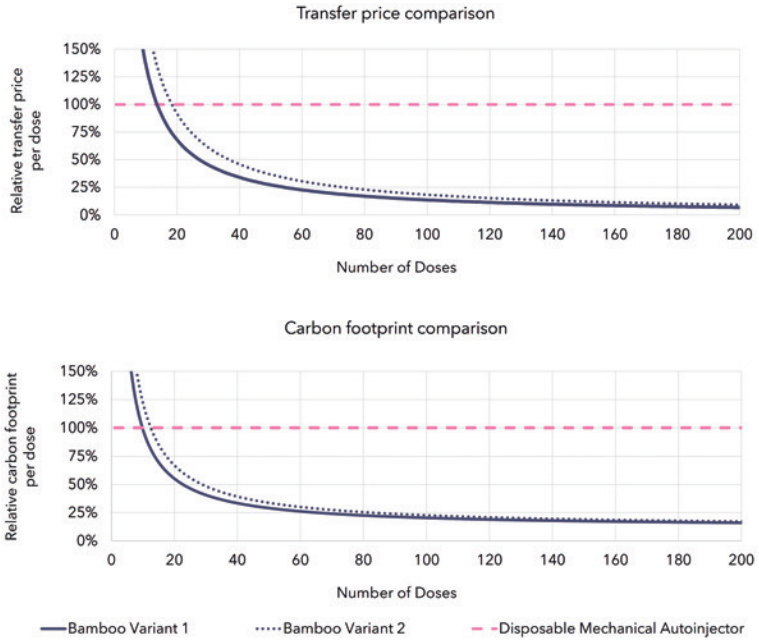


Figure 4: Transfer price (top) and carbon footprint (bottom) comparison of autoinjector technologies.

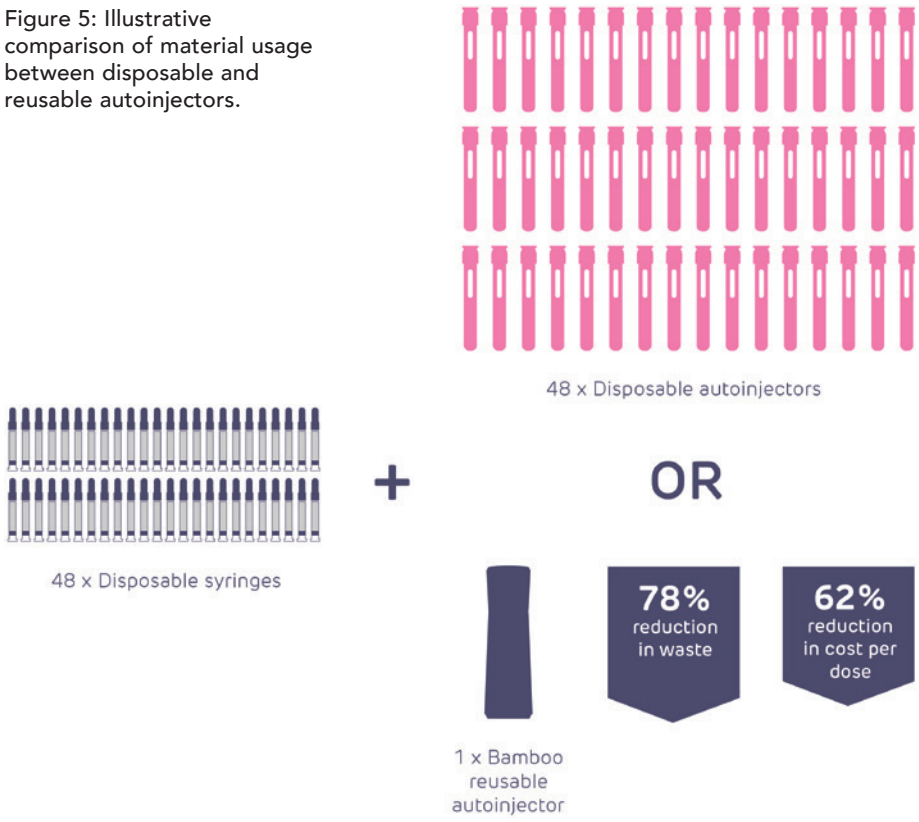
a current industry standard disposable mechanical autoinjector assessed using the same methodologies.

The figures show the impact per dose asymptote to the impact of the PFS components for both reusable electromechanical autoinjector variants. More importantly, they show the financial cost break-even point with mechanical disposable products for cost occurring after just 14–18 doses even when ignoring the extra savings associated with shipping and storage. For carbon footprint, the break-even point comes sooner at 10–13 doses. These figures make a compelling case for the reusable autoinjectors' viability for PFS-based products that have dosing frequencies down to once monthly or less frequently, with the business case looking even more attractive as the dosing frequency increases.

By applying the methodologies and capabilities that are needed to address the challenges listed at the start of this article, it can be seen that there is enormous scope to improve the current state of the art even without any quantum leaps in technology (Figure 5).

The electromechanical architecture has allowed advances in usability and desirability:[2] true end-of-dose user feedback or "safe to lift from injection site" feedback to reduce the risk of wet injections; consistent injection time; the absence of stored mechanical energy at the end of injection; and avoidance of loud or irregular noises during use. In addition, they enable delivery of drug viscosities far outside the

Figure 5: Illustrative comparison of material usage between disposable and reusable autoinjectors.



"BY APPLYING THE METHODOLOGIES AND CAPABILITIES THAT ARE NEEDED TO ADDRESS THE CHALLENGES LISTED AT THE START OF THIS ARTICLE, WE CAN SEE THERE IS ENORMOUS SCOPE TO IMPROVE THE CURRENT STATE OF THE ART EVEN WITHOUT ANY QUANTUM LEAPS IN TECHNOLOGY."

range of standard mechanical autoinjectors – and delivery of standard viscosities through smaller diameter needles – due to the significantly higher plunger rod stall forces (170 N in the autoinjector example).

In conclusion, current disposable mechanical autoinjectors have served the market extremely well over the past few decades and will continue to play a role going forwards. However, for the current and future needs of the 4Ps in treating chronic diseases safely and effectively at home, autoinjector technology needs to evolve to reduce both the financial and environmental burden on healthcare systems and the planet. Fortunately, this case study has demonstrated that there is ample scope to dramatically improve both. This can be achieved without compromising the current levels of clinical safety and efficacy (and possibly improving it in some respects), with the proviso that compromises on other elements, such as convenience, are accepted. Whether this is compelling enough to effect change among key decision makers remains to be seen; to make the leap of faith in pursuing a fresh paradigm of home-use parenteral drug delivery over the "faster horse" option of selecting established autoinjector types.

David Latham

David Latham is Associate Director – Healthcare Programme Management at Cambridge Consultants and has worked in healthcare product development since 2007. He is a Chartered Mechanical Engineer by background, having graduated from the University of Oxford (UK) with a master's degree in Engineering Science. He has led a broad range of drug delivery projects, including autoinjectors, pen injectors, ophthalmic syringes, on-body pumps, special-purpose delivery systems and more. He is passionate about developing next-generation products that meet unmet needs and are holistically viable from all aspects.

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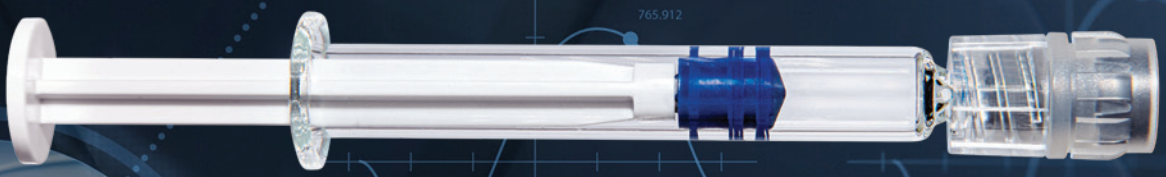

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Interview

Pharmapack Start-up Spotlight: InnoMedica Accelerating Trials with Novel Nanoparticle Filling

At **Pharmapack Europe 2025** (January 22/23, 2025), an expected 5,700 attendees will meet and connect with 364 exhibitors and learn about the latest drug discovery and packaging insights from more than 70 dedicated content sessions. In this interview, **Pascal Halbherr**, Manufacturing Manager at **InnoMedica**, discusses the company's innovative nanocarrier filling technology platform, its impact on biotech and drug delivery, and the company's bold vision for the future.

InnoMedica, a Swiss biotech, is one of the 28 early-stage companies presenting cutting-edge innovations in Pharmapack Europe 2025's Start-up Market. Pharmapack provides an invaluable platform for start-up innovators to engage with larger drug-device companies and big pharma partners. Many breakthrough technologies in device design and sustainable packaging have gained their first industry recognition at Pharmapack, making it an unmissable event for any executive looking to explore tomorrow's biggest innovations in drug delivery and packaging.

PHARMAPACK By CPHI

Q Tell us about your innovation and what brings you to Pharmapack for the first time?

A We're a small company based in Switzerland, working with nanoparticles, with two products currently in clinical trials – one for oncology and one for Parkinson's disease. We faced a big challenge when it came to filling our nanoparticles in vials for clinical samples, as we initially outsourced the fill-finish of our products. However, the long wait times and high costs at contract development and manufacturing organisations were a major challenge and we simply didn't have the resources or time to wait. The wait times to find a slot were often six months or more, and the requirement to fill large volumes didn't align with our step-by-step approach to clinical trials. So, with those costs being extremely high, we decided to develop our own semi- and fully automated system within the same budget to better meet our needs.

Figure 1: InnoMedica's innovative closed-vial filling system for clinical and early-market scale production.

Our platform allows us to fill closed, sterile vials with nanoparticles in a single step (Figure 1). We use a specially designed needle that pierces the vial's septum without compromising its integrity, eliminating the need for laser sealing or additional sealing steps. This has streamlined the traditional process, where you would normally have to open, fill and reseal the vial, making our approach much faster, safer and more cost efficient. The vials stay closed throughout the

"THE VIALS STAY CLOSED THROUGHOUT THE PROCESS, ESSENTIALLY ACTING AS AN ISOLATOR WITHIN ANOTHER ISOLATOR, WHICH ENSURES THAT NOTHING FROM THE ENVIRONMENT CAN CONTAMINATE THE VIAL, SIGNIFICANTLY IMPROVING STERILITY AND SAFETY."

Pascal Halbherr
Head of Manufacturing

Pascal Halbherr, Head of Manufacturing, joined InnoMedica in the autumn of 2012. His interest in current research in biochemistry and his willingness to engage with novel concepts led to the launch of his collaboration with Dr Noboru Yamazaki and formed the starting point for the company's cancer drug project. Together with Stéphane Gumy, Mr Halbherr set up a GMP production facility at the Marly Innovation Center (Fribourg, Switzerland) and adapted the company's production processes from research to industrial scale. He holds an MSc in Biochemistry from the University of Bern (Switzerland).

process, essentially acting as an isolator within another isolator, which ensures that nothing from the environment can contaminate the vial, significantly improving sterility and safety.

To support this technology, we've developed two robots – one semi-automated and one fully automated – that can automatically process vials without interruption. While these systems were initially designed for nanoparticle formulations, they've proven versatile enough for other liquid pharmaceutical applications as well.

Although the platform is especially beneficial for nanoparticles due to their delicate nature, it can be used for any liquid filling. Crucially, we realised that other biotechs must face similar challenges, and we are ideally placed to help with small and medium batch sizes. That's why we're attending Pharmapack – our goal is to help others expedite their new products through clinical trials.

Q How do events like Pharmapack benefit start-ups like InnoMedica?

A Pharmapack provides an excellent platform for showcasing innovations to a targeted audience of industry leaders, potential partners and investors. For us, this is the first time we're introducing our filling technology to the broader market. It's an invaluable opportunity to gather feedback, gauge interest and identify potential collaborators. Events like these also foster connections and collaborations within the biotech ecosystem, which is vital for scaling and bringing innovations to market.

Our primary goal with Pharmapack is also to look for buyers for our machines. We developed the technology ourselves because we couldn't find anything similar in the market that suited our needs. Now that we've seen them in action, they are very efficient, fast and compact, which we believe could be of interest to other companies.

Q How do you maintain vial integrity during and after filling and what are the advantages over traditional methods of filling?

A The key lies in the special needles we developed. These needles are thin enough – less than 0.8 mm in diameter – to pierce the septum without compromising its integrity. We've conducted rigorous integrity testing, which Swissmedic has approved (Figure 2). This design ensures that the vial remains intact and sterile even after multiple piercings. The entire process is done with filling robots, so is

Figure 2: The closed vial filling system can pierce a vial's septum without compromising container integrity.

very quick. Our machine can be operational within 30 minutes, making it incredibly time-efficient for smaller clinical batches compared with traditional systems, which often require lengthy set-up times and are optimised for massive production.

The main advantage is that the single-step closed-vial filling ensures that the vial's integrity remains intact while preventing any risk of contamination. The machine's footprint is also notably smaller, which is crucial, since isolator surfaces are among the most expensive in pharmaceutical manufacturing. Additionally, the isolator we use – made from cost-efficient Bioquell plastic instead of the standard stainless steel – further reduces costs. As a result, the platform is a compact, highly efficient solution that's ideal for small-to-medium batch production in Phase I or II clinical trials.

Q Given the novelty of this method, how do you see regulatory agencies reacting to it and what is the long-term potential of this platform? Could it be scaled for larger production runs or commercial use?

A Closed vial filling is significantly safer than open vial systems but, because it's relatively new, regulators might need time to adapt their frameworks. Our process is designed to meet existing regulatory standards, but we believe it could eventually pave the way for a shift in how regulators approach filling technologies.

Currently, we're focused on clinical trials, but the technology has the potential for scaling. For example, we currently handle 20 L batches with ease, and scaling to 50 L batches for market production would be no issue for our fully automated machine. Extremely large batches – such as 200 or 500 L – would require further developments, such as larger isolators or additional filling pathways. Most nanoparticle-based products don't require massive batch sizes, so our system is well-suited for both clinical and early-market applications.

Q What are your goals for next year and hopes for the drug delivery and device industry moving forward into 2025 and beyond?

A In 2025, we're aiming to scale our technology to meet growing demand for efficient, cost-effective filling solutions, moving beyond clinical trials to early-market production. Securing patents for our needle and process is a key goal, as is forming partnerships to help bring therapies to market faster and more affordably. Our pipeline, of course, remains a priority, with our oncology and Parkinson's products advancing to pivotal studies.

I'd love to see the industry shift towards more meaningful innovation in drug delivery and manufacturing, with a focus on patient outcomes. Right now, there's a lot of focus on incremental improvements for patent extensions, but there's so much untapped potential in repurposing and improving existing drugs – especially those with safety concerns, like cardiac toxicity. Our liposomal doxorubicin, for example, significantly reduces cardiac toxicity, which could have a big impact, particularly for children

We're also excited to see the continued interest in RNA-based nanoparticle formulations, especially post pandemic. But to really make these therapies successful, we'll need to address their side effects.

"RIGHT NOW, THERE'S A LOT OF FOCUS ON INCREMENTAL IMPROVEMENTS FOR PATENT EXTENSIONS, BUT THERE'S SO MUCH UNTAPPED POTENTIAL IN REPURPOSING AND IMPROVING EXISTING DRUGS – ESPECIALLY THOSE WITH SAFETY CONCERNS, LIKE CARDIAC TOXICITY."

Pharmapack 2025 will take place at Paris Expo, Paris, France from January 22 to 23, 2025. For more information, visit: www.pharmapackeurope.com

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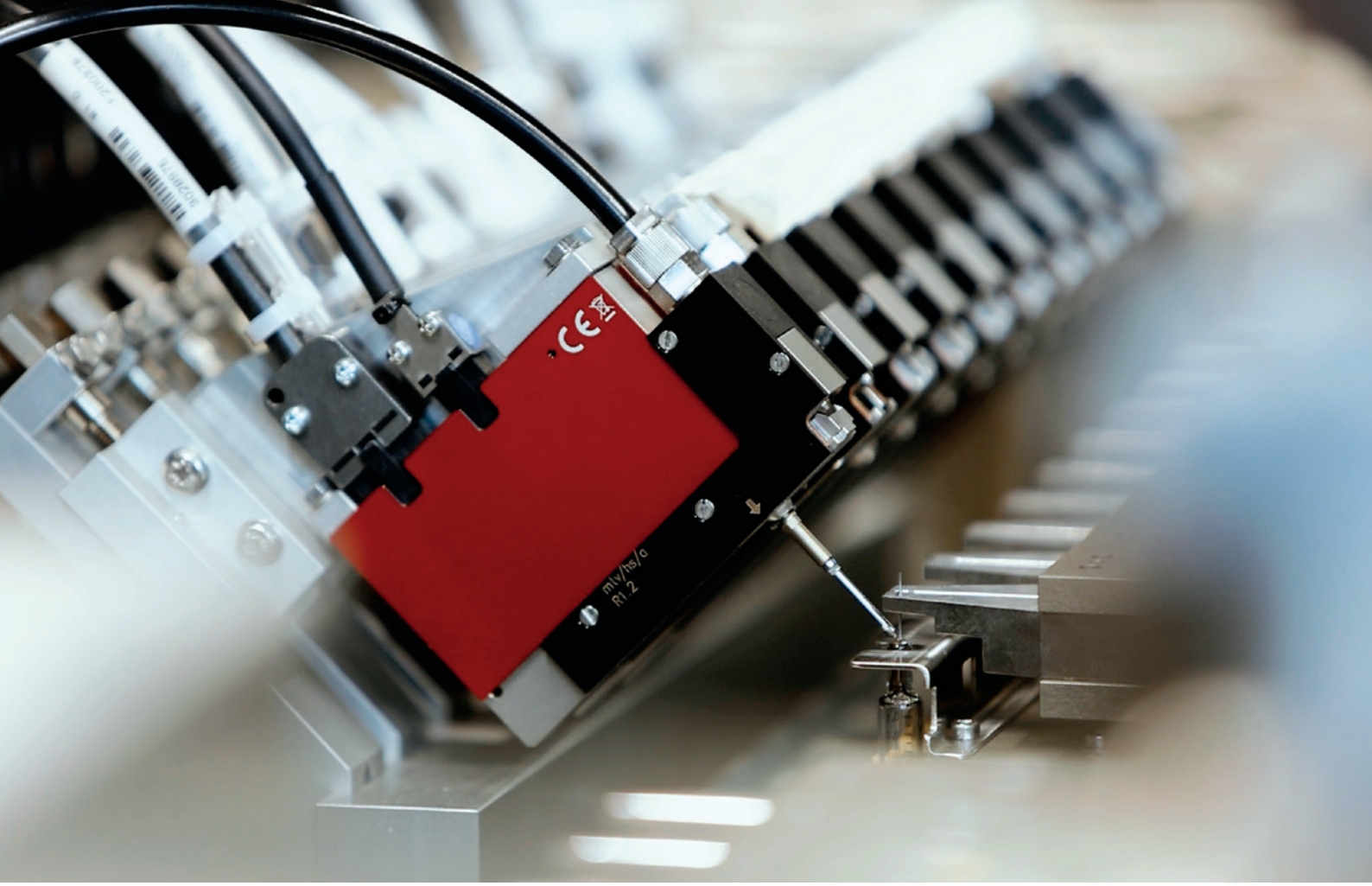
- NEEDLE GUARD LOCKOUT

Developed in close partnership with pharmaceutical companies, Instron's Autoinjector Testing System is designed to evaluate essential drug delivery outputs of devices in a single test sequence, eliminating the need for multiple devices and producing significant time savings. The system balances flexibility and reliability, allowing it to support device R&D functions and testing in production environments.



BONDING TECHNOLOGIES FOR INJECTION DEVICES – A QUICK OVERVIEW

team technik
PRODUCTION TECHNOLOGY
RENAMED BBS AUTOMATION JUNE 2025

Hisham Jamal and **Carsten Köhler** of **teamtechnik** discuss some of the bonding technologies used for medical devices – highlighting their unique strengths, limitations and suitability.

Almost every medical device has some form of bonding involved in its assembling process – where two or more parts are joined together securely by means of adhesive, heat, mechanical or chemical bonds. The bonding process used must uphold the integrity of the device through all the stages that it goes through from manufacturing to end use and function, thereby ensuring patient safety and treatment efficacy.

Over the years, teamtechnik, BBS Automation, Kahle Automation and Hekuma (all companies part of Dürr Group and soon to be renamed as BBS Automation) have assembled billions of different medical devices on their assembly systems. And almost all of the devices have undergone some form of bonding in the assembly process – giving the team a detailed insight into the commonly used bonding technologies, their advantages and challenges in high-volume production automation.

This article takes a look at some of the bonding technologies – namely, adhesive-based overmoulding and solvent-based bonding – that teamtechnik has used extensively on its assembly machines, highlighting their unique strengths, limitations and suitability. The objective is to provide a comprehensive overview on the application of these bonding technologies, paving the way for future innovation and efficiency in the production of life-saving medical devices (Figure 1).

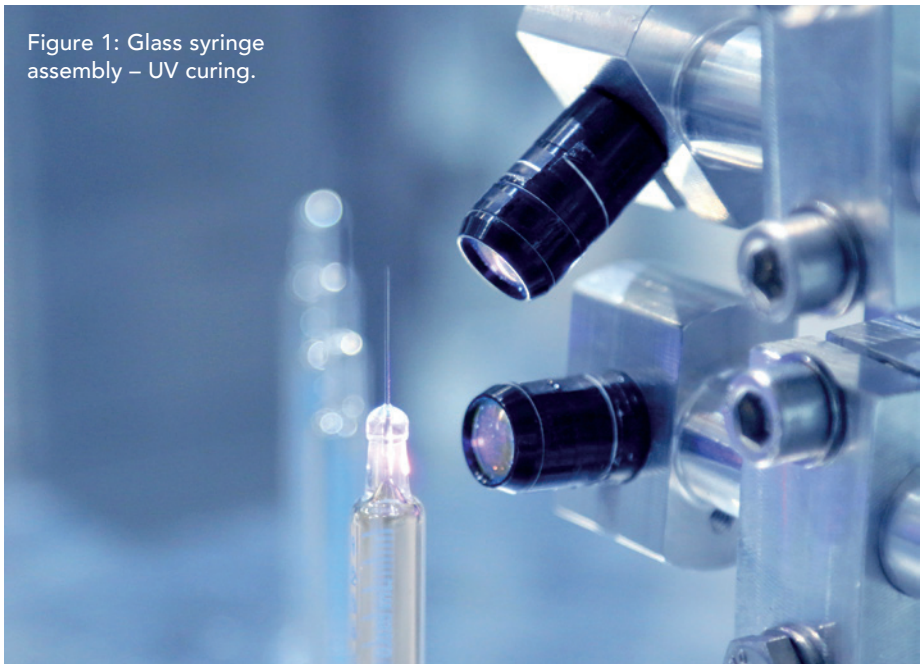


Figure 1: Glass syringe assembly – UV curing.

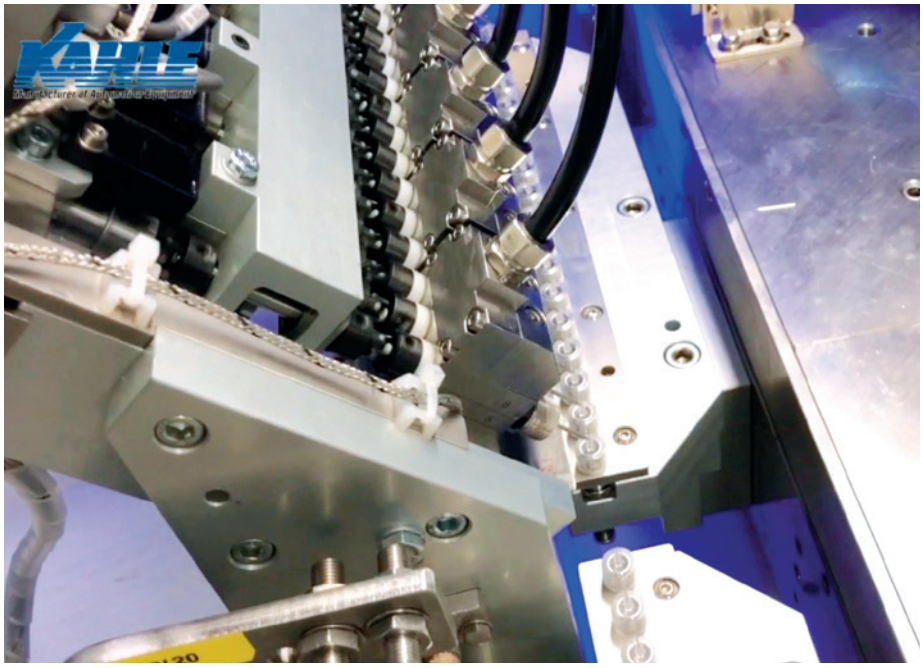


Figure 2: High-volume assembly line with adhesive dispensing.

ADHESIVE BONDING

Adhesives are increasingly being used in medical device assembly to join similar or dissimilar materials together in a functional manner. This is particularly advantageous for needle bonding where a metal needle and a plastic housing are to be bonded together. Minimal or easy pre-treatment to prepare the surface for bonding, a cleaner manufacturing environment from lack of particles generated, and easy to automate by controlled dispensing, the process has made this bonding technology a preferred option in high-volume medical device assembly (Figure 2). The adhesives also act as a conductor, insulator, seal or tolerance bridge between the materials they are bonding, while maintaining property integrity of the materials. However, they are also subject to additional regulations when used in medical devices.

"IN MEDICAL DEVICE ASSEMBLY, ADHESIVES ARE GOVERNED BY VERY STRINGENT REGULATIONS TO ENSURE THEIR SAFETY AND EFFICACY."

In medical device assembly, adhesives are governed by very stringent regulations to ensure their safety and efficacy. The US FDA regulates medical device adhesive under the Federal Food, Drug and Cosmetics Act, while the Medical Device Regulation (MDR) mandates the medical device adhesives to meet specific safety and performance criteria. For biocompatibility of the adhesive, both the MDR and FDA refer to the assessments outlined in ISO 10993.

At teamtechnik and Kahle, numerous assembly machines have been built for the manufacture of medical devices, such as cannulas, intravenous tube sets and glass syringes, among others, implementing adhesive bonding technologies. The following sections cover some specific cases.

EPOXY BONDING

Small, smooth and cylindrical joining interfaces between needles and hubs pose a complicated challenge in needle and syringe assemblies. This is where epoxy bonding has been extensively used over the years. Apart from effectively bonding cannulas to hubs, it also acts as a seal and prevents fluids, such as blood or medicine, leaking.

Its low (per-volume) cost, high toughness post curing, and best thermal and chemical resistance has made epoxy curing a prominent bonding option in needle and syringe assembly. The higher flow (dwell) time of the epoxy adhesive, owing to its high-viscosity rates, does, however, pose a challenge for high-speed and high-volume production, as it can take quite some time for the epoxy adhesive to achieve full coverage of the joint. To overcome this, pre-assembly dispensing is often implemented, where the epoxy adhesive is dispensed on the cannula before it is set in its final position in the hub.

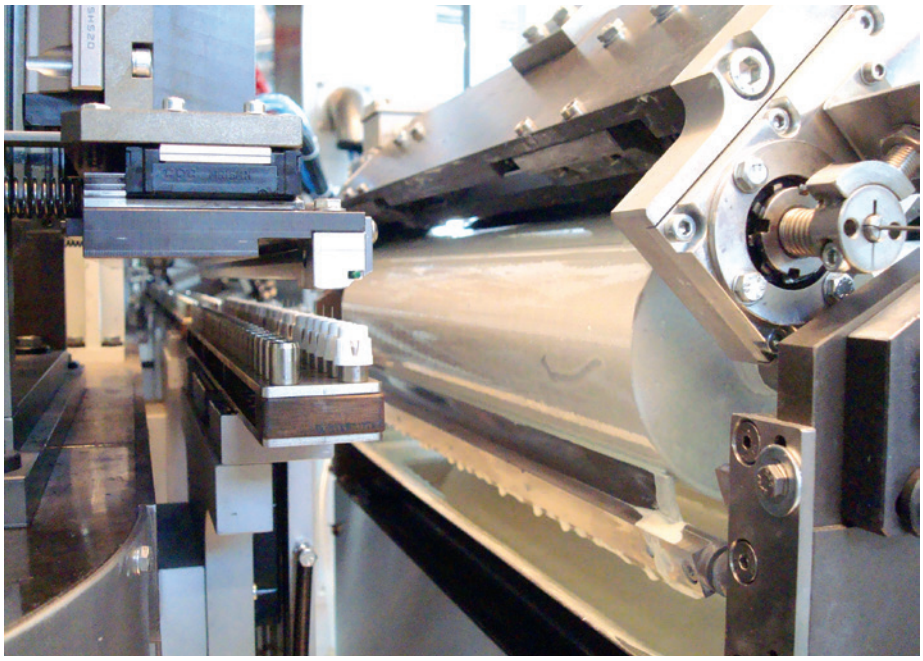


Figure 3: Epoxy glue dispensing.

Another challenge that epoxy adhesives (Figure 3) pose to high-speed and high-volume production is their curing time, which can be up to 45 minutes, depending on the curing temperature. As epoxy adhesives are heat cured, setting up a high-temperature curing oven in clean rooms also poses another challenge for manufacturers when it comes to high-volume production. Finding a balance between the dispensing method, curing temperature and curing duration is essential in order to achieve an optimised production system.

ACRYLICS

With lower viscosity and faster curing time, acrylic adhesives are increasingly being used in the assembly of medical devices, even replacing epoxy bonding at times.

"WITH LOWER VISCOSITY AND FASTER CURING TIME, ACRYLIC ADHESIVES ARE INCREASINGLY BEING USED IN THE ASSEMBLY OF MEDICAL DEVICES."

At teamtechnik, various assembly machines have been built for drug delivery systems and diagnostic devices where acrylic adhesives are used. These are adhesives where a photoinitiator is present, which, upon exposure to light of a certain intensity and spectral output, will initiate a photochemical reaction that cures or hardens the adhesive.

With a rapid curing time of less than 10 seconds in the right curing environment, combined with the generally low viscosity levels, acrylic adhesives are an ideal bonding solution for high-speed and high-volume production automation for medical devices. The challenges here, however, lie in:

1. Setting up the ambient environment for the curing process, as the presence of oxygen or humidity can inhibit surface cure, resulting in a somewhat sticky surface
2. Using UV light sources with the right spectral output depending on the required cure depth, material opaqueness, etc.

Numerous assembly lines have been built by teamtechnick implementing UV-based glue technology for medical devices such as needles and syringes, pen needles, glass syringes (Figure 4), catheters, tubes and connectors, among others. After applying the adhesive on the bonding area and assembling the components, the device is then exposed to UV light. Depending on factors, such as material properties, opacity, depth of curing and others, UVA and/or UVC wavelength ranges are often used. While UVA ranging from 315 to 400 nm are typically used for most applications, the relatively new UVC LED technology is rapidly improving and gaining popularity in certain applications.

The UVA with its higher wavelength helps to penetrate deeper, making it an ideal option for thicker curing or for applications on more opaque materials. The UVC on

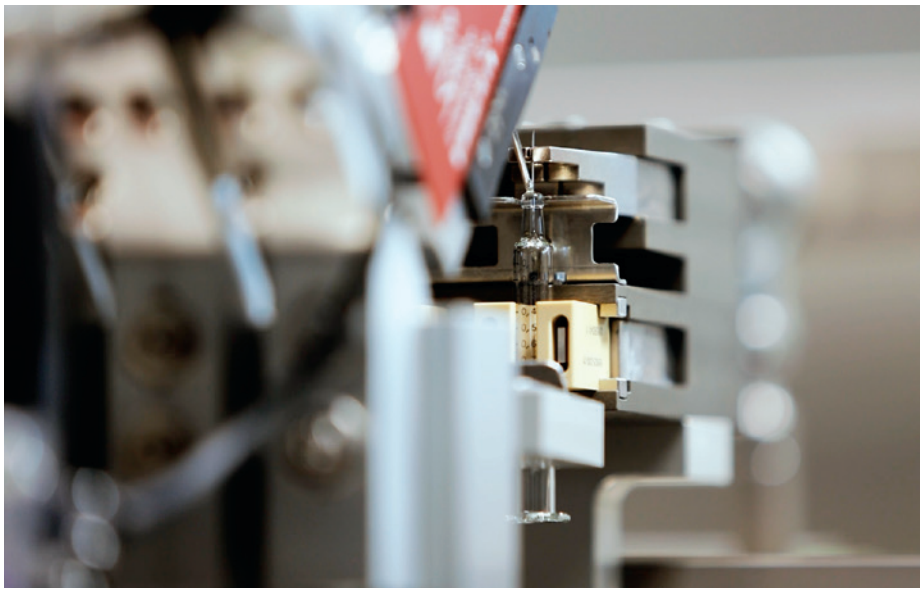


Figure 4: UV glue dispensing – glass syringe assembly.

the other hand, with its lower wavelength and higher energy levels, is more effective for surface curing. In the applications that teamtechnick has implemented on its assembly machines, it uses either or a mix of both UV ranges to ensure effective curing with the desired surface finish.

INSERT MOULDING FOR POLYMER SYRINGES

In recent years, polymer syringes – particularly cyclic olefin polymer (COP) – have been gaining popularity due to their high break resistance, glass-like transparency and inertness levels. This has made COP syringes a good alternative to glass syringes in many cases. COP syringes have also found their way into autoinjectors, replacing the traditional glass prefilled syringe.

Compared with glass syringes or other cannula and hub assembly methods where an adhesive is normally used, polymer syringes have a completely different approach to manufacturing where it is overmoulded. Overmoulding is a technique where the needle and syringe barrel are combined into a single integrated component. Here, a plastic syringe barrel is injection moulded around a pre-inserted needle, creating an integrated design that simplifies the assembly process, while enhancing reliability and ensuring a leak-proof seal (Figure 5).

The key to a successful COP overmoulding process lies in being able to handle the injection-moulding parameters (such as mould design, tooling and pressure) just as well as preparation of the cannula (such as cannula handling and surface treatment). A strong understanding of this process, combined with state-of-the-art robotic technology for injection-moulding handling systems, has helped Hekuma develop multiple high-volume COP syringe manufacturing lines for customers.

SOLVENT BONDING

Solvent bonding is another technique used to bond needles and hubs together, particularly in the context of soft hubs. Here, a solvent is applied on the hub surface that temporarily softens or dissolves the surface of the material. A needle is then inserted into the hub.

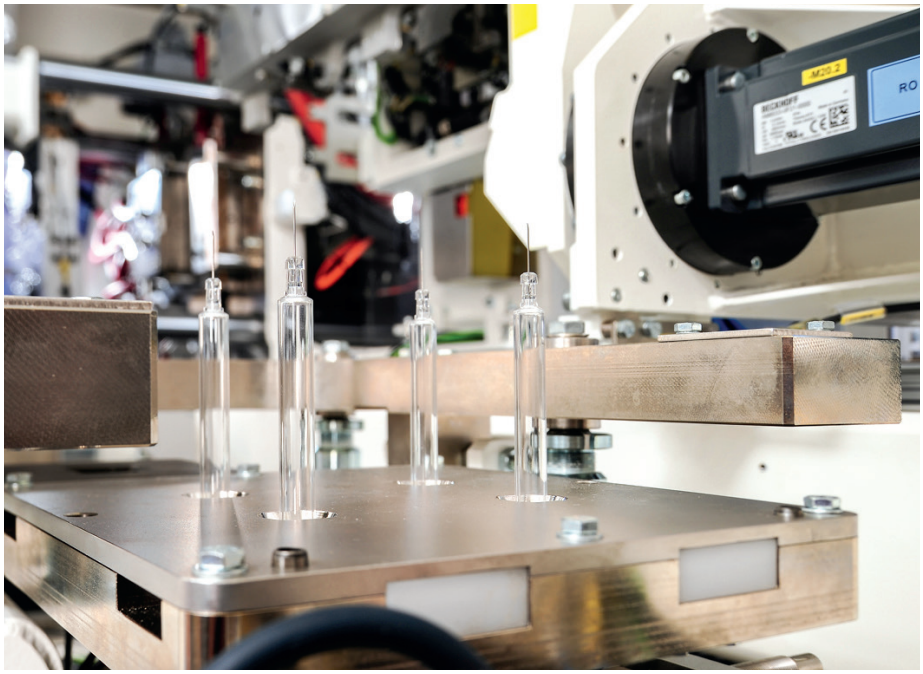


Figure 5: COP-syringe assembly line.

"THE KEY TO A SUCCESSFUL COP OVERMOULDING PROCESS LIES IN BEING ABLE TO HANDLE THE INJECTION-MOULDING PARAMETERS (SUCH AS MOULD DESIGN, TOOLING AND PRESSURE) JUST AS WELL AS PREPARATION OF THE CANNULA."

Figure 6: Glass syringe assembly line.

As the solvent evaporates, materials fuse together, creating a strong and seamless bond. The soft hubs are often made of flexible thermoplastics compatible with solvent bonding, and the needle, typically made from stainless steel, serves as the rigid component in the assembly onto which the soft hub is bonded.

The evaporation of the solvent also typically occurs quickly in the right environment, leading to rapid bonding and very fast curing times. This makes this technology a preferred choice in high-volume-production processes where speed is of paramount importance (Figure 6). A point to consider here is the need for a good ventilation/exhaust system where the solvents are used.

CONCLUSION

As the medical device industry continues to evolve, the need for innovation and adaptive assembly solutions becomes increasingly crucial. Adhesive-based, overmoulding and solvent-based bonding technologies have been in use for many years now, and they continue to innovate and offer unique advantages to enhance the high-volume production of medical devices while improving their efficiency, reliability and safety. Table 1 summarises the features of the different bonding technologies discussed in this article.

By carefully considering the strengths, limitations and specific requirements of each technique, manufacturers can select the most appropriate bonding methods for their specific needs. And with its expertise in implementing these technologies on billions of devices, teamtechnik continues to support manufacturers to enable the development and production of high-quality and reliable medical devices that meet the demanding requirements of the healthcare industry, thereby improving patient outcomes and enhancing lives.

Bonding Technology	Curing Medium	Curing Time	Products Commonly Used
Epoxy	Heat	10–20 mins	Needles & Syringes
Acrylics	UV Light, Heat (depending on initiator)	<10 seconds	Needles & Syringes, Catheters, Tubes & Connectors
Insert Moulding	Air Cooling	< 1 minute	Needles & Syringes
Solvent Bonding	Air	<5 seconds	Catheters, Tubes & Connectors

Table 1: Summary of bonding technologies discussed.

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PICCOJECT – ADVANCING SELF-INJECTION OF HIGH-VISCOSITY FORMULATIONS

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Thomas Thueer, **Chris Muenzer** and **Stefanie Manger** of **Haselmeier** discuss the challenges posed to drug delivery device designers by the needs of biologic therapies. In response, the company has developed the PiccoJect autoinjector, which has a novel parallel spring layout that enables a newfound flexibility in design, ideally positioning it to rise to the challenges of delivering high-viscosity biologics.

THE CONTINUED NEED FOR SELF-INJECTION

Since the early 2000s, the injectable route has been one of the most exciting and fastest-growing areas in drug delivery. Even with the recent interest in obesity medications, the rising number of complex therapies making their way through pharmaceutical pipelines over the last 20 years has been a primary driver of increasing interest in injectable therapies. In addition, there has also been a significant push towards administering therapies in patients' homes rather than in clinical environments when possible. Doing so has numerous benefits, from increased convenience for patients to a reduced burden on healthcare systems and lower environmental impact from the need for patients to travel to and from a clinic.

Reflecting this interest, the global self-injection devices market was valued at US$22.8 billion (£17.9 billion) in a report by Grand View Research, with a projected compound annual growth rate of 10.3% from 2025–2030.[1] With this growth in the market, it will be critical for the drug delivery industry to continue to innovate, making more patient-friendly devices and accommodating a wider array of therapies to meet demand.

However, delivering these molecules via injection, often in large volumes or highly viscous formulations, is not without its own set of challenges. This has led to a steady stream of innovation in the development of injection devices to facilitate the delivery of biologics and other novel therapeutics. Specialist drug delivery device developers have worked to find ways to

effectively deliver increasingly difficult molecules, pushing injectable drug delivery in new directions, such as high-viscosity autoinjectors and wearable devices.

DELIVERING BIOLOGICS

The Challenges

Biologics are a notoriously difficult category of therapeutic to deliver. The molecules are large, often fragile and prone to agglomerate or denature under unfavourable conditions, drastically reducing their therapeutic effect. Challenges with delivery via the oral route, where the gastrointestinal tract presents a near-insurmountable barrier to the fragile molecules, have led drug developers to see injection as the natural home for biologics.

Additionally, new targets and newer technologies with lower bioavailability have resulted in an increase in dose size. This, in turn, has resulted in therapies that require the delivery of either high volumes or high viscosities.

High-viscosity drugs are particularly challenging to deliver. In order to minimise pain, and the knock-on effects to adherence, device designers tend to prefer to keep needle gauges as narrow as possible, which means much higher injection forces are required for delivery. Higher forces in turn require more power, such as larger, heavier springs or an alternative power source, all of which must fit in a compact device format. In the case of larger springs, these also place more strain on the device housing during storage, necessitating more robust construction and materials.

Not only is designing for high viscosity a technical challenge in and of itself, but it must also be done in the context of patient-centric design. Ultimately, the purpose of any drug delivery device is to administer the contained therapeutic to a patient and so must be designed with that patient in mind – especially in the case of at-home administration. If the medicine is to be self-administered successfully, the device must be approachable and intuitive, as well as convenient, for the patient to understand and use, often on a regular basis. If the device is unacceptable in some way, such as being too difficult to use or causing too much pain, patients may make errors during delivery or be inclined to discontinue their therapy, resulting in failed treatment and disease exacerbations that lead to patients needing hospital treatment and increased strain on healthcare systems.

Therefore, any new entrants into the self-injection market must meet the exacting demands of the biologics they aim to inject and offer patients an appealing user experience. As such, device designers have attempted a variety of approaches to achieve these twin objectives, continually innovating and improving on what is available with devices capable of delivering ever-higher volumes and viscosities to enable formulators to bring increasingly challenging therapeutics to market.

Current Approaches

Wearable injectors are a more recent addition to the drug delivery device landscape. On paper, the idea is straightforward – formulation viscosity can be reduced to more manageable levels by increasing formulation volume beyond that which autoinjectors can handle. Wearable injectors, which are usually attached to the body via an adhesive patch, can deliver their sizeable payloads over an extended period of time, circumventing some of the design challenges presented by high viscosity. While many of these devices have been developed, there have been limited commercial successes, which is likely due to many devices being incompatible with established filling equipment and the requirement that patients have to wear them for extended periods, meaning that they must be both comfortable and discrete to be acceptable compared with a regular injection. Furthermore, these devices present significant technical challenges to developers due to their inherent complexity, which also leads to an increase in cost.

On the other hand, high-viscosity autoinjectors are an iteration on existing, well-established and accepted technology. The first high-viscosity autoinjectors were, in essence, scaled-up versions of existing autoinjectors, with larger springs and more advanced drive systems, such as lead screw mechanisms, to increase their output force. Since the initial launch of these devices, high-viscosity autoinjectors based on electromechanical drive systems have been developed as an alternative. In both cases, the high-viscosity versions use a specialised drive system, which is more complex, meaning pharmaceutical companies with varied portfolios must use a different device for their high-viscosity and low-viscosity formulations. Additionally, it is important to bear in mind that increasing the complexity of the drive system leads to a higher cost for the final device.

These current approaches leave space in the market for a more elegant solution to the challenges posed by delivering biologics. A device that is capable of delivering a wide range of viscosities would provide pharmaceutical companies with an ideal solution and, by employing a parallel spring layout, Haselmeier's PiccoJect autoinjector is able to provide exactly that (Figure 1).

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

PICCOJECT – AN INNOVATIVE PARALLEL SPRING LAYOUT

PiccoJect™ is a novel autoinjector capable of delivering both high- and low-viscosity formulations from a single device. To achieve this, Haselmeier has taken a new approach to the layout of the drive mechanism within the device – by placing the spring parallel to the syringe rather, than in sequence behind the plunger, PiccoJect unlocks unprecedented flexibility in its design. This parallel layout enables the delivery force to be fine-tuned to suit any given formulation by varying the spring to provide the required force. The critical advantage of PiccoJect's parallel spring layout is that it enables greater variation in the diameter of the spring by moving it out of line with the syringe (Figure 2).

When designing springs, a critical parameter to be aware of is the "spring index" – the ratio between the coil diameter and the wire diameter of the spring. This relationship provides valuable information about the stress and manufacturability of a spring. By not being constrained by the diameter of the syringe, PiccoJect's layout enables the use of springs with larger diameters compared with what is possible with a traditional autoinjector. In turn, this allows the use of larger diameter spring wire while maintaining an optimal spring index. As such, PiccoJect can deliver a high dispense force with reduced material stress, manufacturing complexity and cost.

Naturally, PiccoJect's parallel spring layout has a significant impact on the device's shape. PiccoJect is shorter than traditional autoinjectors, with a wide cross-section rather than the narrow cylindrical one usually seen with co-axial layouts. Extensive human factors testing by Haselmeier has demonstrated that users show a preference for PiccoJect's shape, which they have described as more comfortable. This alternative form factor also enables PiccoJect to have a larger, wraparound drug window for patients to track injection progress and perform visual drug inspection, which has also received high approval rates from users in Haselmeier's human factors testing.[2]

Along with its patient-centric format and features, PiccoJect has been designed with the needs of pharmaceutical manufacturing in mind. PiccoJect's parallel spring layout has been designed to be compatible with any standard 1 mL long or 2.25 mL prefilled syringe. The device itself is comprised of only eight parts, which can be manufactured using unfilled polymers, despite the large spring forces, making the device more sustainable.[3]

Figure 2: PiccoJect's innovative parallel spring layout enables significant design flexibility, accommodating both low- and high-viscosity formulations within a single device.

"HASELMEIER HAS TAKEN A NEW APPROACH TO THE LAYOUT OF THE DRIVE MECHANISM WITHIN THE DEVICE – BY PLACING THE SPRING PARALLEL TO THE SYRINGE, RATHER THAN IN SEQUENCE BEHIND THE PLUNGER, PICCOJECT UNLOCKS UNPRECEDENTED FLEXIBILITY IN ITS DESIGN."

CONCLUSION

Today, self-injection devices are a critical component of the current drug delivery landscape. A combined need for patient-centric devices and the delivery of high-viscosity formulations has fuelled innovation in the sector, as device

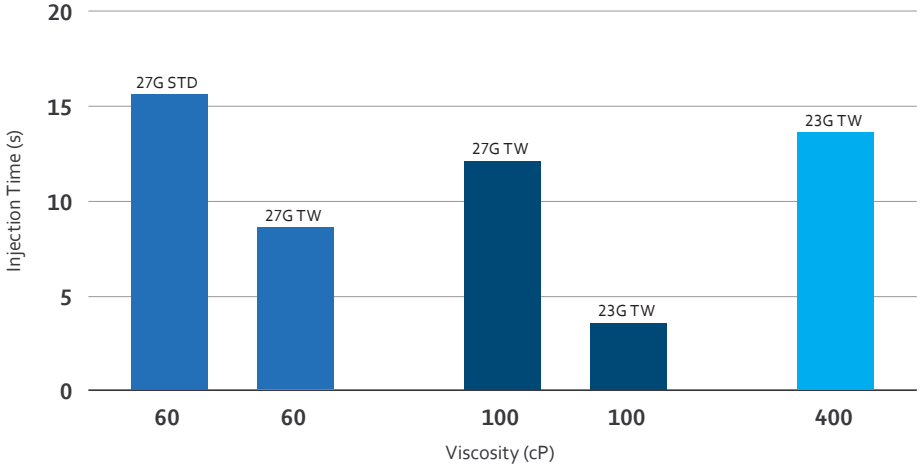

Figure 3: Test results from in-device testing of PiccoJect 100 with prefilled syringes containing 1 mL of highly viscous glycerol-based solutions (60, 100 and 400 cP) using various needle gauges.

designers innovate to fulfil the unmet needs of patients and the industry.

Haselmeier has provided the next step in the pursuit of patient-friendly delivery of high-viscosity biologics. The PiccoJect autoinjector employs a novel parallel spring layout to offer numerous benefits to patients and pharmaceutical companies alike. For users, the parallel spring layout provides a shorter, wider form factor that human factors studies have shown is preferable for a wide array of users, as well as other patient-centric features such as the large, wraparound dose window. For pharmaceutical companies, PiccoJect's parallel spring layout enables the drive mechanism to be tuned to the needs of a given formulation, making it suitable for both high and low viscosities (Figure 3).

The innovative layout of PiccoJect is a significant step forward in autoinjector design. Capable of handling a wide range of viscosities with the same drive mechanism, PiccoJect can offer pharmaceutical companies a single platform device for a vast range of biologic formulations. Comprising only eight parts, PiccoJect is simple, effective and reliable. The advantages unlocked by the parallel spring layout and patient-centric design are able to provide the foundation for the next generation of biologic drug delivery.

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MAY Delivering Injectables: Devices & Formulations DEADLINE: **Apr 3, 2025**	**MAY/JUN** Oral Drug Delivery DEADLINE: **Apr 17, 2025**	**JUN** Connectivity in Drug Delivery DEADLINE: **May 1, 2025**
JUL Industrialising Drug Delivery DEADLINE: **May 15, 2025**	**SEP** Wearable Injectors DEADLINE: **Aug 7, 2025**	**SEP/OCT** **NEW ISSUE TOPIC** Dual Chamber Delivery Systems DEADLINE: **Aug 14, 2025**
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DEC **NEW ISSUE TOPIC** Delivering Gene & Cell Therapeutics DEADLINE: **Nov 6, 2025**	**JAN 2026** Prefilled Syringes & Injection Devices DEADLINE: **Dec 4, 2025**	**FEB** Skin Drug Delivery: Dermal, Transdermal & Microneedles DEADLINE: **Jan 8, 2026**

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ELEVATING DIGITAL PATIENT SUPPORT: NOTHING MATTERS UNLESS IT CHANGES BEHAVIOUR

Ben Cox, **Thomas Grant** and **Lara Zaki** of Team Consulting discuss the role of behaviour design in onboarding for self-injection devices and how a robust and balanced framework can enhance the patient experience, reduce injection errors and promote safe and effective use.

Patient-use disposable autoinjectors are widely used for convenient drug delivery. Moreover, smart injection devices and their surrounding digital health applications can be effective tools to enhance patient engagement and adherence to treatment regimens, ultimately ensuring the best health outcomes. Most recently, the rapid rise of GLP-1 receptor agonists, originally developed for diabetes and now widely prescribed for obesity, has introduced millions of new patients to self-injection for the first time. This surge in demand for injectable therapies has dramatically shifted the patient landscape, with many individuals who may have never considered self-injecting now facing the task of regularly administering their own medication.

Understanding the role of behaviour design is fundamental to developing solutions that will offer tangible benefits and create real impact for patients. To develop effective connected devices and digital patient support materials, efforts should be focused on specific decision points in the user journey that have demonstrable impact on long-term engagement. The overarching user experience (UX) strategy, as well as the individual features of a product, must prioritise a set of target user behaviours that make a difference, while also respecting and complimenting the existing patient journey. This requires an understanding of user capabilities and motivations, as well as the potential barriers to achieving the desired outcome.

"THIS SURGE IN DEMAND FOR INJECTABLE THERAPIES HAS DRAMATICALLY SHIFTED THE PATIENT LANDSCAPE, WITH MANY INDIVIDUALS WHO MAY HAVE NEVER CONSIDERED SELF-INJECTING NOW FACING THE TASK OF REGULARLY ADMINISTERING THEIR OWN MEDICATION."

THE REALITY OF PATIENT ONBOARDING

Despite the growing prevalence of these devices, there are numerous challenges related to onboarding and use-related injection errors. It is known that access to training and education varies across patients, and that patient anxieties, learnings and expectations around device use create opportunities for injection errors to occur.

Most product labels outline the necessity for patients or caregivers to administer injections under the supervision of a healthcare professional (HCP), who should assess their suitability and willingness to self-administer injections, as well as provide instruction on proper injection technique. Despite this stipulation, 40% of HCPs acknowledge that they do not provide any training to patients on the use of injection devices.[1–3] In the many cases where manufacturers do not provide a training programme to onboard new users onto a self-administration therapy, it is down to the HCP's judgement on what level of training is deemed adequate. Furthermore, HCPs are not always trained on the devices themselves, with a survey reporting that 43% of HCPs have not received training on specific device use.[1]

Given these training inequalities, there is a need for accessibility, comprehensiveness, individualisation and emotional support when onboarding patients to a device. The prevailing aim for all device manufacturers should be to set their patients up for success – not only for new patients using a device for the first time but also those who are experienced and switching to a new device. There are very real risks that patients can be lost in the first weeks and months of using a device due to poor onboarding or user experience. The question is, what approaches can be taken to improve onboarding and long-term engagement?

BEHAVIOUR DESIGN

Behaviour design facilitates the development of products and interventions that are informed by behavioural and cognitive science principles. When applying behaviour design models, the aim is to design products based on an understanding of how people make decisions, behave and interact with the environment. This ensures that products encourage engagement in desired behaviours as much as possible.

To create products that are informed by applied behavioural science, it is crucial to adopt a behaviour design framework that ensures a systematic and balanced approach (Figure 1). The framework should integrate behavioural science principles with UX design, human factors engineering (HFE) and iterative testing methods. There are three core phases to consider – foundations, behavioural science and iterative design. Together, these represent a series of iterative and interconnected activities that streamline the design of connected devices and digital patient support materials.

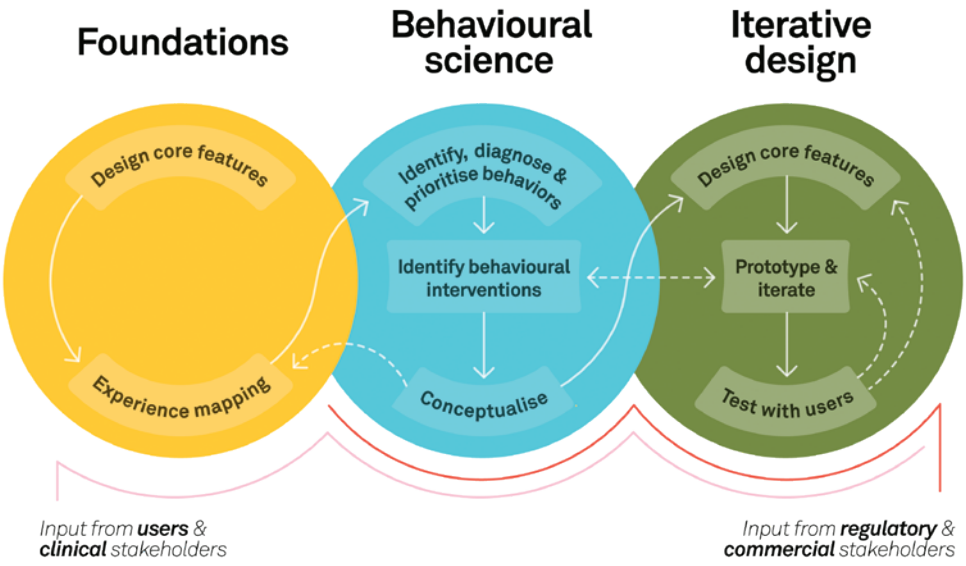

Figure 1: A behaviour design framework for a balanced approach.

> "IT IS EQUALLY IMPORTANT TO UNDERSTAND THE PATIENT'S PERSPECTIVE – THEIR CURRENT EXPERIENCE, PAIN POINTS AND THE TOOLS AND TECHNIQUES THEY RELY ON."

Phase 1: Foundations

Foundational research establishes a robust understanding of the patient experience in the context of the broader healthcare ecosystem. By combining exploratory research and experience mapping, it is possible to capture the standard of care, existing workflows and a detailed, evidence-based view of the patient journey. For instance, when examining challenges in training and onboarding, it is essential to define what a gold standard, HCP-led injection training session entails.

It is equally important to understand the patient's perspective – their current experience, pain points and the tools and techniques they rely on. This research should go beyond internal factors related to device use and encompass the surrounding and external influences that shape patients' learning experiences as they first engage with self-injection.

Depending on the information available, these insights can be gathered through a combination of semi-structured interviews, observational studies, analysis of previous validation studies, post-market surveillance and literature reviews. The research should be designed to systematically build an understanding of the circumstances that influence behaviours related to device interactions. Learnings can then be translated into a comprehensive experience map, highlighting clinical touchpoints, tools, pain points, emotions and decision points.

Phase 2: Behavioural Science

The foundational research can then be analysed through the lens of a behavioural science model, such as the COM-B model of behaviour developed at University College London.[4] The COM-B model is recommended in the development of connected medical devices and digital patient support materials as it provides a structured approach to understanding target behaviours and identifying relevant evidence-based interventions.

The first step of COM-B is to translate the research insights into prioritised target behaviours that have the greatest potential impact on clinical outcomes and are therefore the most relevant to address with the digital solution. These should be specific, measurable behaviours that contribute to patient engagement and adherence. These behaviours are then "diagnosed" based on data in the experience map.

In the COM-B model, a behaviour is defined as a culmination of factors relating to capability, opportunity and motivation. By identifying barriers related to these three factors, development teams can better understand where to focus digital interventions. For example, the foundational research may highlight that failure to wait for medication to reach room temperature increases pain perceptions and affects drop-off rates. The barriers preventing users waiting sufficiently may include both opportunity-related barriers, such as time constraints, and capability-related barriers, such as lack of knowledge of the consequences.

The COM-B model includes a taxonomy of behaviour change techniques (BCTs) and a guide on where they have shown success. Self-monitoring of behaviour, prompts/cues and information about consequences are examples of BCTs that are linked to specific behavioural barriers. By applying this approach, development teams can select BCTs based on literature citations, implementation feasibility and applicability

to the specific user demographic. These are not prescriptive and instead provide a starting point that helps to de-risk the innovation process and enable concept development that is informed by evidence. For example, BCTs and concepts could be related to specific mediums of educational material, informative packaging, connectivity features or companion apps.

Phase 3: Iterative Design

Once concepts have been generated, they can be iteratively designed, prototyped and tested. It is important to design specific features that bring the concepts to life, to test whether they have the intended impact with the specific patient demographic. Taking the example of patient training and onboarding, digital educational materials might include a video with a specific narrative. When working on a video concept, the first step is to break down the content into a storyboard of scenes and topics that need to be covered and to work as a cross-disciplinary team to embed the BCTs identified into the design. In this case, BCTs might include providing information about consequences to demonstrate why certain behaviours are important, whilst applying positive framing. Demonstration and self-monitoring techniques can also be incorporated through video voiceover and narrative, for example, as a dialogue between a patient and an HCP.

If a concept in development is a smart device with a connected app, the features should reflect specifically what kind of data will be useful for patients to monitor, what language should be used to present the data in the app and what kind of feedback patients need from the device. This can be informed by the BCTs and behavioural barriers established earlier in the framework. A blueprint of the digital product can then be outlined to demonstrate how behavioural techniques can be embedded into the UX.

Rapid prototyping techniques can be used to enable iterative refinement of product features with feedback from clinical and regulatory experts, as well as representative users, through functional, interactive code-free mock-ups of the digital interface (Figure 2). This process allows developers to validate screens and components to ensure they are being understood as intended.

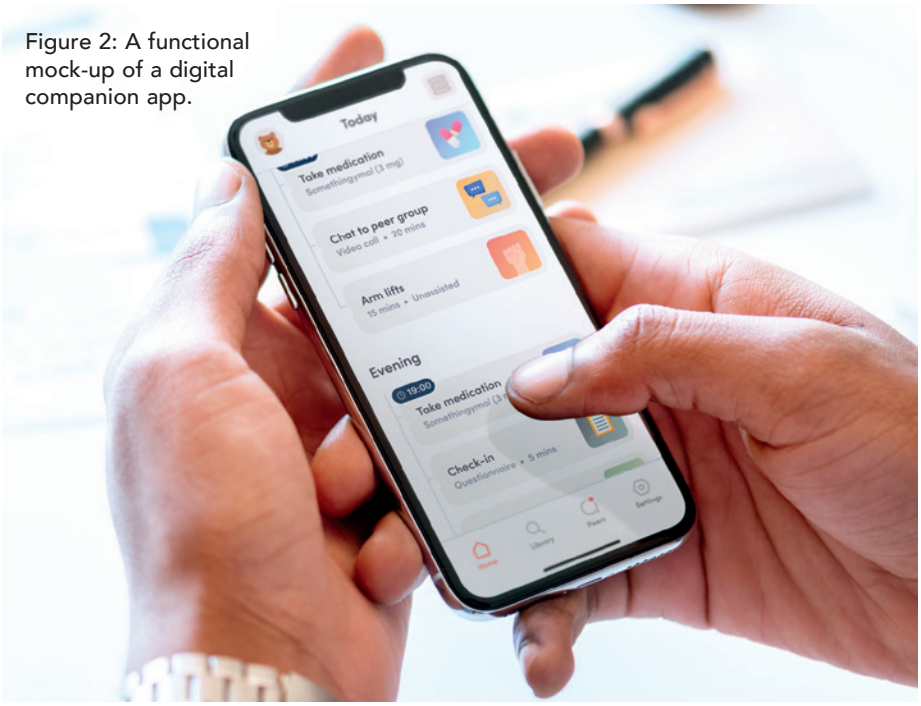

Figure 2: A functional mock-up of a digital companion app.

When creating digital educational materials, it is recommended to conduct multiple rounds of user testing with patients and HCPs, evaluating various learning methods and comparing designs against the gold standard of hands-on injection demonstrations. This approach allows for a thorough assessment of objectives related to injection performance, engagement, confidence and user experience, using a combination of qualitative feedback and performance data to build evidence.

Incorporating Stakeholder Input

Throughout the application of the behaviour design framework, the product design needs to be evaluated against clinical, regulatory and commercial requirements. Continuously consulting with subject matter experts and following a risk-based process can help to de-risk the development and result in a digital product that is safe and effective, but also compliant and marketable.

CONCLUSION

The continuous rise in self-injecting patient populations underscores the need for thoughtful behaviour design that enhances patient experiences, reduces injection errors and promotes the safe, effective use of therapies. Improved onboarding and tailored digital support can play a transformative role in helping patients feel confident, minimising barriers and supporting long-term adherence to treatment. As healthcare adapts to this shift, the importance of patient-centric design and comprehensive onboarding has never been greater.

"WHEN CREATING DIGITAL EDUCATIONAL MATERIALS, IT IS RECOMMENDED TO CONDUCT MULTIPLE ROUNDS OF USER TESTING WITH PATIENTS AND HCPS, EVALUATING VARIOUS LEARNING METHODS AND COMPARING DESIGNS AGAINST THE GOLD STANDARD OF HANDS-ON INJECTION DEMONSTRATIONS."

Despite the benefit these approaches can bring, connectivity and digitisation of patient support materials should not be an example of "technology push" and may not be the best solution for all use cases. Combining behavioural science with robust HFE and UX design practices can guide the selection of evidence-based principles, which can then be translated into concrete UX strategy, guidelines and features.

Ultimately, a behaviour design framework offers a structured approach to developing solutions, making the most of what digital devices and tools have to offer. By de-risking digital device development within the constraints of a highly regulated industry, adopting a balanced framework can streamline innovation and maximise the success of connected devices and digital patient support materials, driving meaningful advancements in patient care.

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ABOUT THE COMPANY

Team Consulting is a drug delivery technology design and development partner. For over 38 years, the company has helped its clients create elegant, sustainable solutions to complex healthcare challenges. Team Consulting's multidisciplinary team of experts brings a unique blend of human-centred design, engineering, science and regulatory expertise to every project, with an unparalleled track record in drug delivery technology development. Working with organisations ranging from leading pharma companies to emerging start-ups, Team Consulting empowers its clients to create high-quality products that improve patient lives.

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VERSATILITY, SUSTAINABILITY AND DIGITALISATION IN ONE SMART HANDHELD INJECTION PLATFORM

altek MED

Leonard Chu of **Altek Biotechnology** discusses three trends in self-administration that are aligned with emerging smart devices – device versatility, sustainability and digitalisation – and the benefits offered by the Alcee injection platform.

The public health crisis of covid-19 and the surging popularity of glucagon-like peptide-1 (GLP-1) injection for weight loss have inspired some thoughts on the potential of using smart injection devices. For example, smart devices could be the key enabling tools when the segregation of a population is required to control the spread of a disease. Collecting data from multi-variable dosing or high-frequency dosing could be useful for tracking treatment and evaluating the clinical outcomes. Three trends are aligned with the emerging smart devices – device versatility, sustainability and digitalisation.

The compatibility of primary containers with injection devices is one of the key decision-making factors for commercialising a combination product, especially when the corresponding fill-finish line is not readily available or compatible with the existing packaging. Thus, the first trend is exploring the versatility of an injection platform that can accept various primary containers with different volume size and shape.

The second trend is sustainability, which is negatively impacted by the increment of medical waste. While self-injection devices offer many use and safety benefits, a more sustainable approach to producing and using self-injection devices is desired. The third trend is the digitalisation of devices, which enables both automated device operation and connectivity for digital health management. Learning from historical events and current practices, a smart, versatile and sustainable injection platform could provide opportunities to address some of the unmet needs of self-injection.

"A SMART, VERSATILE AND SUSTAINABLE INJECTION PLATFORM COULD PROVIDE OPPORTUNITIES TO ADDRESS SOME OF THE UNMET NEEDS OF SELF-INJECTION."

THE ALCEE INJECTION PLATFORM

Alcee is a handheld injection platform operated on an electromechanical system. By harnessing the platform's versatility, Alcee is configured into three different types of handheld injectors, as shown in Figure 1. Each injector type is a platform itself that can be used to deliver a variety of drugs based on the chosen primary container. Taking advantage of the commonality across Alcee injectors, pharmaceutical partners have the freedom to choose suitable handheld injectors to address different dosing needs with a more efficient timeline and lower development cost. Any dosing requirements beyond the pre-assumed specification range can be discussed case by case.

Alcee injectors comprise a reusable power unit and a disposable unit. The power unit provides the electromechanical drive and is rechargeable. The reusability of the Alcee power unit can reduce the cost per injection compared with disposing of the whole device after a single use. The disposable unit can easily be customised to accommodate the required injection volume. Any volumes larger than 3 mL up to 10 mL are possible but may translate to a longer delivery time. For larger delivery volume beyond 3 mL, it is recommended to use the Alby large-volume wearable injectors instead.[1] All Alcee injectors offer the option of wireless connectivity for digital health management. An intuitive user interface with audible and visual feedback, and sharps protection features, are included as part of the standard models of Alcee.

Figure 1: An overview of the Alcee injection platform – (left to right) multi-variable-dose pen injector, single-dose vial autoinjector and single-dose prefilled syringe (PFS) autoinjector.

Figure 2: The designs of Alcee-V.

Single-Dose Vial Autoinjector

The Alcee vial autoinjector (Alcee-V) is a single-dose injector that uses a vial as the primary container (Figure 2). Among the three types of Alcee injectors, Alcee-V has the greatest flexibility in accepting the primary container (practically any vial shape and size having a crimp neck size between 13 and 20 mm). Although a total injection volume ranging from 0.5 mL to 10 mL is feasible, it is recommended to use the Alby large-volume wearable injector instead when the injection volume goes beyond 3 mL.[1] Vials and Alcee-V devices are not housed together and may be shipped or packaged separately. Therefore, user loading of a vial to an Alcee-V device will be required prior to injection.

Single-Dose PFS Autoinjector

The Alcee PFS autoinjector (Alcee-PFS) is a single-dose injector that uses a PFS as the primary container (Figure 3).

Standard Alcee-PFS models accept a 1 or 2.25 mL PFS. The housing of the Alcee-PFS can easily be customised to accept volumes other than 1 or 2.25 mL. The PFS filled with the drug is housed together with the disposable unit of Alcee-PFS; no user loading of the PFS is required.

Multi-Variable-Dose Pen Injector

The Alcee pen injector (Alcee-P) is a multi-variable-dose injector that uses a cartridge as the primary container (Figure 4). Standard Alcee-P models accept a 3 mL cartridge, but the housing of the Alcee-P can easily be customised to accept cartridge sizes other than 3 mL. The Alcee-P dialling knob is fixed at the rear end of the device and does not extend or move linearly when turned. The dial options of Alcee-P can easily be customised by software for setting a variety of doses, and for certain functional selections such as priming (flow check) and Bluetooth connection. Each dose can range from less than 0.1 mL to a much larger quantity – in theory, up to the maximum injection volume. The precision of each dose can be less than 0.1 mL.

Figure 3: The designs of Alcee-PFS.

THE VERSATILITY OF ALCEE-V AUTOINJECTOR

Although vials are the most commonly used containers for packaging pharmaceuticals, they rarely appear in self-injection devices, in part due to the complexity of drug handling from a vial and the involvement of more device operational steps. To enable and facilitate the use of vials in self-injection devices, Alcee-V offers a solution with high versatility and automated device operation.

Versatility is the core competency of Alcee-V. The cap of Alcee-V serves as an adaptor that holds the vial and provides the interface for drug transfer from the vial to the injector. The Alcee-V cap can be highly flexible in shape and size to accept any vials (e.g. 2–20 mL) with a crimp neck size between 13 and 20 mm.

> "THE CAP OF ALCEE-V SERVES AS AN ADAPTOR THAT HOLDS THE VIAL AND PROVIDES THE INTERFACE FOR DRUG TRANSFER FROM THE VIAL TO THE INJECTOR."

Alcee-V also provides an innovative solution that makes the preparation of a drug from a vial and the self-administration process simple, easy and safe. Since the vial filled with the drug and the Alcee-V device are not housed together, the user is able to access and clean the vial stopper prior to injection. After disinfecting the stopper, the user loads the vial into the cap of the Alcee-V. Aided by the automated function, the drug is automatically drawn

Figure 4: The designs of Alcee-P.

> "BY AVOIDING MANUAL OPERATION OF DRUG TRANSFER AND INJECTION, THE RISKS OF USER HANDLING ERRORS, DOSE INACCURACY CAUSED BY MANUAL TRANSFER, AND SHARPS INJURY ARE GREATLY REDUCED."

Figure 5: The reusable power units and the disposable units of the Alcee platform.

from the vial into the body of the injector. Upon completing the drug transfer process, the user removes the cap along with the vial, and then performs injection just like a typical autoinjector. Besides the automated drug transfer, the injection process is also powered by the automated drive system. By avoiding manual operation of drug transfer and injection, the risks of user handling errors, dose inaccuracy caused by manual transfer, and sharps injury are greatly reduced.

THE SUSTAINABILITY OF ALCEE INJECTION PLATFORM

Sustainability is increasingly important and relevant due to climate change. The growing demand for self-injection devices has continued to exacerbate the burden of medical waste. To reduce the environmental burden, the Alcee injectors are designed to have two distinctive device units with the goal of minimising the size and weight of the disposable unit relative to the reusable unit. Figure 5 illustrates how Alcee keeps the plastic parts of the disposable unit at a minimum while providing essential protection to the primary container and functional connection to other device parts.

Eco-friendly materials are being considered for mass production of Alcee to further increase sustainability. For smart devices that contain electronics, reusability is critical to avoiding excessive generation of electronic waste after each use. Although sustainability is a focus of the Alcee design, other elements, such as functionality, usability and safety, have also been carefully considered and balanced in creating sustainable, robust products.

"ALCEE SERVES AS A KEY ENABLER AND DIFFERENTIATOR FOR PHARMACEUTICAL PRODUCTS THAT REQUIRE SIMPLE, FAST AND CONVENIENT SELF-ADMINISTRATION."

NEW OPPORTUNITIES WITH SMART DEVICES

Digital technology has already become an integral part of daily life, yet smart devices are at an early adoption phase in the self-injection space. Digitalisation of injectors offers huge potential in the enablement of telemedicine, the automation of device operation and the enhancement of patient compliance.

Smart devices are capable of generating, storing and sharing data to inform both users and healthcare professionals about the dosing. When a large amount of data is generated within a relatively short period of time, as in the case of multi-variable dosing or high-frequency injections, the monitoring and management of data become more relevant. Besides telemedicine, using a mobile app as an extension of the device user interface could offer users more support when it comes to device usage.

For example, the app could display animated step-by-step visual instructions to guide users on proper preparation and device operations. When the app is in sync with the visual or auditory feedback from the device, users could have access to a larger, more comprehensive interface via the phone screen to better capture the dosing status. To enhance patient compliance, the app could also send reminders to users when the next dose is due.

Although artificial intelligence (AI) has yet to be built into Alcee, the advancement of the electronics hardware for AI is now paving the way for future applications in many industrial sectors, including drug delivery. The question of how AI could apply to drug delivery is an interesting topic for future discussion.

THE ENABLER AND PRODUCT DIFFERENTIATOR

Alcee serves as a key enabler and differentiator for pharmaceutical products that require simple, fast and convenient

self-administration. By combining device versatility, sustainability and digitalisation, Alcee introduces a whole new opportunity to address a variety of dosing needs, including single-dose, multi-variable dose or doses with a customised profile through three different types of handheld injectors that support vials, PFSs and cartridges. Since all forms of Alcee are operated based on the same principle, developing one type of Alcee injector also accelerates the development of the other types of Alcee injector. Such synergies in development could translate into efficiency, thus saving development time, cost and effort compared with developing the injectors individually. The readiness of functional prototypes and the preliminary laboratory dose accuracy data suggest that Alcee is now ready to take further steps to conduct feasibility studies and development with potential drug candidates.

Dr Leonard Chu

Leonard Chu, PhD, Deputy Director at Altek Biotechnology, holds a doctoral degree from the Georgia Institute of Technology (GA, US), focusing on developing dissolving microneedles. He has a variety of industry experience, serving in both technical and project management roles. Dr Chu has led customer projects from the design phase to the validation phase, involving fully automated assembly. Currently he leads the Drug Delivery Business Unit to develop a portfolio of smart injection devices, including autoinjectors, pen injectors, precision dosing on-body injectors and large-volume wearable injectors.

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- ✓ Delivery volume 0.5mL – 3mL (precision < 0.1mL)
- ✓ Reusable handheld injectors including:
  - Pen injector (cartridge, multi-variable dose)
  - Vial autoinjector (vial, single dose)
  - Autoinjector (PFS, single dose)
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- ✓ Built-in safety features and alarm system
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DEVICE SELECTION: INJECTION VOLUMES FOR SUBCUTANEOUS ADMINISTRATION

Nicolas Brandes, **Andrea Allmendinger** and **Hanns-Christian Mahler** of **ten23 health** explore the critical considerations for subcutaneous injection volume, beginning with the historical and scientific perspectives on injection volume before delving into the challenges of determining volume ranges and their associated fill volumes.

INTRODUCTION

The subcutaneous (SC) route is increasingly becoming the preferred route for the administration of biologics, especially in the context of patient-centric care. The advantages of SC injections are well documented – ease of self-administration, opportunities for at-home use and the avoidance of intravenous (IV) delivery – and contribute to an improved patient experience and lower costs for the healthcare system. Additionally, there may be pharmacological benefits for SC administration, such as when targeting the lymph nodes. All these benefits are supporting a growing market of drugs delivered via SC administration, not just as a therapeutic option for patients but also as a strategic choice for pharmaceutical companies during drug development.[1]

Determining the optimal dose volume for SC delivery is challenging, particularly in development and early clinical phases. Early in development, the "commercial patient dose" – the dose intended for the marketed product – is not yet defined in most cases. This uncertainty is due to several factors, including the evolving

understanding of the molecule's pharmacokinetic (PK) profile and efficacy, as well as the clinical programme's goals. Decisions about final dose and injection frequency are often a combination of the needs of the scientific drug product and the commercial market strategy. For instance, therapies aiming to reduce injection frequency, such as from weekly to monthly, often require higher injection volumes or more concentrated formulations, which may introduce technical challenges. At the same time, larger doses may enhance patient comfort due to the reduced number of injections.[2]

The physical and chemical properties of a drug product significantly influence the feasibility for SC delivery. Factors such as viscosity and stability play an important role in determining whether a molecule can be concentrated into a volume suitable for SC injection. Formulation decisions also directly affect the choice of the delivery device. Low-viscosity formulations align with prefilled syringes, needle safety devices and standard autoinjectors (Figure 1), whereas highly viscous drug products may require an enabling technology that is capable of delivering the drug at an acceptable injection force and speed. Other considerations for dose and device selection include the clinical and regulatory context, the target indication and target users, and the competitive environment. For example, needle size heavily impacts usability (injection forces) and is specifically critical for highly viscous formulations.

Figure 1: Example container (syringe) and autoinjector device, used for delivering injection volumes up to 2.25 mL.

"LARGER VOLUMES CAN BE INJECTED INTO THE SC TISSUE, AS DEMONSTRATED IN CLINICAL STUDIES."

In early clinical trials, dosing flexibility is key, as formulation and volume often evolve alongside emerging clinical data.[3] However, as SC administration becomes more prevalent, drug development must also address practical constraints such as manufacturing scalability, patient experience and regulatory requirements, ensuring that the selected approach is both scalable and market ready. These factors underline the importance of balancing scientific, commercial and patient requirements.

SC INJECTION VOLUME

Historical Perspective on Volume Tolerability

An SC delivery volume of 1–2 mL has been traditionally considered a common target (and assumed limit) for self-administration, with higher SC volumes historically believed to be unpleasant for patients and to lead to local tissue reactions, with no controlled studies or assessments available. Healthcare professionals were cautious about SC injections exceeding 1–2 mL, stating concerns about pain, swelling and erythema at the site of injection. These limitations were further aggravated by the absence of advanced devices capable of delivering larger volumes effectively – SC injections were mainly done manually or using small-volume prefilled syringes and autoinjectors.

However, perceptions began to shift as systematic studies evaluated the capacity of SC tissue to accommodate larger volumes, challenging traditional assumptions. In 2015, Mathaes *et al* reviewed the landscape of SC injections and concluded that larger volumes can be injected into the SC tissue as demonstrated in clinical studies, with SC injections of up to 5 mL typically not being of any concern.[4] These findings have broadened the opportunities for SC delivery, allowing higher-dose therapies to transition from IV infusion to SC injection.

Patient Insights

While technology has started to push the theoretical boundaries for larger-volume SC delivery, different patient studies have offered valuable insights into the practical limits of SC injection volume through assessing patient perceptions of SC injections ranging from 1 mL to 5 mL. It was concluded that higher volumes were well tolerated, especially when being delivered using appropriate injection techniques and devices. Injection speed and device ergonomics may also be relevant in mitigating discomfort, and the interplay between formulation properties and delivery technology is key.

While studies have shown the potential for larger SC volumes, physiological and practical constraints must be considered. Tissue elasticity, injection site and fluid viscosity are key factors influencing tolerability. For example, slower injection speeds and lower-viscosity formulations have been reported to reduce pain and swelling but may extend injection time, impacting patient acceptance.

Advanced Technology Supporting the Delivery of Larger Volumes

The use of permeation enhancers (PEs) such as hyaluronidase as a formulation component in SC products has been helpful in expanding SC injection limits toward 10 mL and beyond. PEs temporarily modify the extracellular matrix, degrading hyaluronic acid, thereby facilitating the dispersion of injected fluids due to diminished tissue backpressure. Nowadays, however, there is also clear scientific evidence that injection volumes of 25 mL can be injected subcutaneously without any relevant pain or injection site reactions, even in the absence of any permeation enhancers.[5] Additionally, a technological

advancement that has enabled the SC administration of large volumes is a novel class of large-volume autoinjectors and on-body delivery systems.

For drug product development, advanced technologies have opened up new possibilities for biologics and other high-dose therapies, allowing them to be delivered via the SC route rather than the IV route. However, introducing new device technologies comes with additional complexities, such as the need for combination product development, device complexity, regulatory considerations, higher unit cost and more complex supply chains.

Looking Ahead

The maximum SC injection volume is not a fixed value but a dynamic parameter shaped by advancements in formulation science and device engineering. New technologies are continually pushing the boundaries of what is possible, paving the way for new therapeutic modalities.

It is clear that the question of how much can be injected is only one piece of the puzzle. The interplay between injection volume, formulation properties and device design underlines the complexity of SC product development and sets the stage for deeper exploration.

DECIDING ON INJECTION FREQUENCY

When considering the SC injection volume, choosing the injection frequency is another critical aspect of developing injectable drug products. In general, the less frequent the injections, the more convenient it is for patients. However, reduced injection frequency requires a higher dose per administration, which presents two significant challenges. First, higher doses necessitate either larger injection volumes or higher drug concentrations, both of which pose technical difficulties, such as minimising irritation at the injection site. Highly concentrated formulations also often lead to increased viscosity, which can complicate both the handling of the formulation and the design of the injection device.

Another key decision is whether to use single or multiple injections for treatment. During clinical studies, it must be defined whether a larger dose will be delivered in a single injection or split across multiple smaller injections. For instance, treatment could involve either a single 4 mL injection or two 2 mL injections. This decision has several implications. On the one hand, multiple injections may lead to a different bioavailability than a single injection, potentially affecting the efficacy of the treatment. On the other hand, large injection volumes can impact bioavailability, also potentially affecting the efficacy of the treatment. From a development and timeline perspective, multiple smaller injections may be necessary if high-concentration formulations are not yet available or if a suitable device-drug combination product capable of delivering larger volumes is still under development.

DECIDING ON VOLUME RANGE AND PRODUCT PRESENTATION

The selection of product presentation – prefilled syringes, autoinjectors, wearable devices or vial-and-syringe systems – must balance considerations of intended use, human factors, patient population, user preference (including options for multiple injections) and patient compliance. However, there are considerations beyond the user's perspective comprising technical challenges related to product properties such as viscosity, device performance, compatibility with the primary packaging container, quality and regulatory aspects, cost of goods, sustainability considerations, technology maturity, supply chain security, and availability and capabilities of manufacturing partners. Furthermore, product presentations for products in clinical stages must consider additional aspects such as dosing flexibility and product losses.

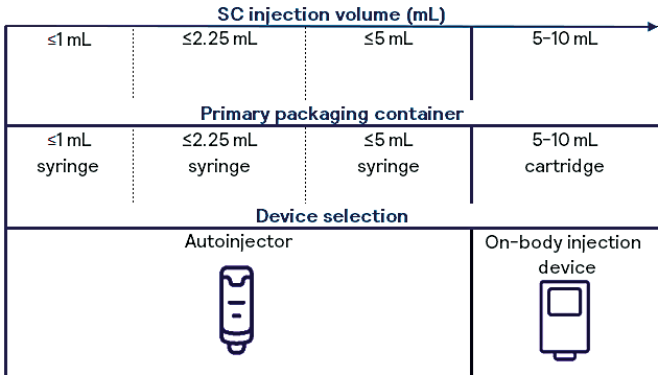

Figure 2: Selection of primary packaging containers and devices related to SC injection volume.

Figure 2 summarises current options for selecting primary packaging containers, associated functional containers and devices depending on the intended SC injection volume (for single use). Needle selection for SC injections is typically 27G (normal or thin wall), although, in rare cases, 25G or bigger needles are used, balancing injection time against potential patient discomfort. The needle size chosen depends on the indication, patient population and competitive product landscape. The choice of needle size also determines the acceptable viscosity, and therefore the maximum concentration, of the API in its formulation (including its upper specification limit), assuming a given target of injection force for that dedicated patient or user group.

The concentration of a drug product is a critical factor influencing both its technical manufacturability and clinical usability and must be carefully selected. High-concentration protein formulations present significant technical challenges, including higher viscosities that complicate

"THE MAXIMUM SC INJECTION VOLUME IS NOT A FIXED VALUE BUT A DYNAMIC PARAMETER SHAPED BY ADVANCEMENTS IN FORMULATION SCIENCE AND DEVICE ENGINEERING."

manufacturing processes, administration processes necessitating higher injection forces and stability challenges, such as higher aggregation propensity, accumulation of host-cell proteins that degrade polysorbates and other issues that relate to adverse product quality stability.[3]

Therefore, for high-viscosity products, the selection of primary packaging components is a key factor for usability. Conversely, lower-concentration formulations are easier to develop and manufacture due to improved stability and lower viscosity. However, they often present larger injection volumes or longer injection times, which may affect patient convenience. As a result, the interplay between formulation concentration and viscosity, injection volume, injection time and injection frequency introduces complex trade-offs in product development. Decisions must involve all elements, including formulation, manufacturing and device development, as well as clinical and marketing considerations. Optimising these variables is crucial to balancing clinical outcomes and the patient experience while also addressing manufacturability and stability constraints.

Selection of Fill Volume

The SC injection volume is not equal to but lower than the volume that is filled into the primary packaging material. Determining the optimal fill volume for parenteral products is a critical step influenced by multiple technical and regulatory considerations. Recent US FDA guidance emphasises minimising overfill, reducing waste during administration and drug product losses during manufacturing to improve the cost of goods and healthcare costs overall.[6]

Furthermore, overfilling can compromise safety by overdosing but can also lead to unacceptable and unauthorised product misuse, such as using residual formulation, possibly pooling from multiple vials, thereby increasing the risks of microbial and particulate contamination. Additionally, an excessive fill volume is economically undesirable, particularly for cost-intensive biologics.

> "BUBBLE-FREE FILLING AND STOPPER SETTING TO ENSURE A PRODUCT WITHOUT NON-ESSENTIAL HEADSPACE IS HIGHLY BENEFICIAL."

The excess volumes are meant to be sufficient to permit withdrawal and administration of the labelled volumes accounting for hold-up volumes in the container, as well as in the syringe or needle used for administration, especially in vial presentations. It also must consider the potential variability in the extractable volume test, as well as filling technology precision. Therefore, the overfill may vary, for example, when manufacturing in multiple facilities with varying fill precision. In multi-use device presentations, additional volume must account for priming, repeated withdrawals and ensuring the correct dose for each injection, and also ensure that the dose withdrawal does not compromise sterility or stability.

This is especially critical for syringes and cartridges – bubble-free filling and stopper setting to ensure a product without non-essential headspace is highly beneficial as the inclusion of air can disrupt dose accuracy, particularly in small-volume formats. This is specifically relevant for treatments that require the down-dosing of a product, in the case of multi-use applications, or for products where the product leaflet prescribes to push out the air bubble prior to injection, leading to potential error and accidental pushout of actual product. Absence of headspace can also eliminate the need for priming. Innovations in filling technologies and container design are thus essential to enable product improvements and meet evolving regulatory expectations. Consequently, strategies are needed to adequately determine and optimise fill volume operations and to meet both lower and upper fill volume limits, balancing safety, regulatory compliance and cost considerations.

WHY CHOOSE TEN23 HEALTH?

A contract design, manufacturing and testing organisation such as ten23 health is appropriately positioned to support its customers with technical and regulatory experience when taking crucial decisions for selecting product presentations, including device and primary packaging container selection for SC drug products. ten23 health's team of experts can design an adequate strategy from early-stage development to commercialisation to de-risk the development approach.

ten23 health offers end-to-end services for sterile drug products, including IV and SC formulation development, drug-device selection, integration and testing, manufacturing process development, comparability studies, analytical development, clinical and commercial GMP fill-finish and quality control release and stability testing. ten23 health provides its GMP fill-finish of complex and high-precision containers (including bubble-free filling) at its facility in Visp (Switzerland), including syringes, vials and cartridges, including the capacity to handle both glass and polymer containers on the same line. Transitioning from a vial to a syringe or cartridge configuration requires no transfers to other lines or facilities, ensuring a seamless process when integrated with the necessary technical evaluations.

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Dr Nicolas Brandes

Nicolas Brandes, PhD, has been Director Business Development & Sales at ten23 health since March 2024. Prior to ten23, Dr Brandes spent 15 years at West Pharma in Business Development, Product Management and Research & Development, working on integrated packaging containment and drug delivery systems. Dr Brandes studied Biology at the University of Wuerzburg (Germany) and the Universidad de Salamanca (Spain), and holds a PhD in Biochemistry from the University of Michigan (Ann Arbor, MI, US).

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Dr Andrea Allmendinger

Andrea Allmendinger, PhD, has been Chief Scientific Officer at ten23 health since November 2021. Dr Allmendinger is also Adjunct Professor and Group Leader at the University of Freiburg (Baden-Württemberg, Germany), researching novel parenteral drug formulations and device solutions to improve stability, usability and cost of goods. Between 2010 and 2021, she was Principal Scientist, Pharmaceutical Development at Roche, working on inter alia manufacturability and injectability of high-concentration formulations, syringe and high-volume drug/device combination products, particulates and surfactant strategy. Dr Allmendinger studied Pharmacy at the University of Heidelberg (Germany) and University College London (UK), and holds a PhD in Pharmaceutical Sciences from the University of Basel (Switzerland). She obtained the venia legendi (German Habilitation) from the University of Freiburg in 2021 and served as Editor-In-Chief for the AAPS Open journal from 2021 to 2024.

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Prof Dr Hanns-Christian Mahler

Professor Hanns-Christian Mahler, PhD, is Chief Enablement Officer and Board Member of ten23 health. He previously built and led the Drug Product Services Business Unit at Lonza AG (2015 to 2021), led different organisations involved in sterile product development and sterile manufacturing at F Hoffmann-La Roche (2005 to 2015) and worked as Principal Scientist and Chemistry, Manufacturing and Controls Leader at Merck KGaA (2000 to 2005). Prof Mahler is additionally Lecturer and Adjunct Professor at the University of Basel and University of Frankfurt/Main, Editor for various scientific journals, and serves as an Expert at the European Pharmacoepeial commission. He studied Pharmacy and holds a PhD in Pharmacology & Toxicology from the University of Mainz (Germany) and obtained his venia legendi and title as extraordinary Professor from the University of Frankfurt/Main. (Germany).

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The complexity and diversity of modern therapeutics is increasing. Medical research is facing growing challenges of stability, usability, and consistent manufacturing.

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- Formulation development for liquid and lyo
- Sterile drug product development for different modalities
- Sterile manufacturing under cGMP (vials, syringes, cartridges)
- Administration compatibility testing
- Syringe development, manufacturing, testing
- Primary packaging material characterisation

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Interview: Sustainability at the Heart of Aptar Pharma's Expansion

Audrey Chardonnet discusses the centrality of sustainability to **Aptar Pharma**'s expansion strategy, going into detail on how, by improving its practices and investing in its infrastructure, the company works towards reducing the environmental impact of injectable drug delivery solutions manufacturing.

Q What is Aptar Pharma's strategy when it comes to sustainability?

A At AptarGroup, sustainability is at the centre of what we do. Most notably, this has been recognised by leading institutions through a series of awards, including Forbes' "World's Top Companies For Women 2024", Time Magazine's "World's Most Sustainable Companies 2024" and USA Today's "America's Climate Leaders" in 2023 and 2024. Aptar is also an active member of the United Nations Global Compact, the Ellen MacArthur Foundation and the World Business Council for Sustainable Development.

Aptar is a global leader in drug and consumer product dosing, dispensing and protection technologies across multiple markets, including pharmaceutical, beauty, food, beverage, personal care and home care. As a leader in the development and manufacturing of more sustainable closure solutions, Aptar is also leading the way in designing innovative drug delivery solutions with our Futurity® platform, which features solutions for improved sustainability, such as recyclable products, waste reduction, CO_2 footprint reduction and the use of alternative materials, including bio-feedstock.

The Futurity platform includes pressurised metered dose inhaler technology for low global warming potential propellant use, nasal spray pumps, and ophthalmic and dermal drug delivery solutions that embody our commitment to sustainability and circularity for addressing the waste crisis. Beyond product development, Aptar Pharma is also dedicated to making its manufacturing operations landfill free, saving energy at every step of its manufacturing processes and promoting inclusion, equity and belonging at work.

Q For injectables, how do you align with the company's global sustainability strategy?

A Contrary to other drug delivery solutions in Aptar's portfolio, which are mostly plastic based, Aptar Pharma's injectables solutions are made of rubber (Figure 1). These closure solutions are in direct contact with the drug and must be used in conjunction with glass containers. As these containers come into contact with patients – whether via the intravenous, intramuscular or subcutaneous route – packaging for injectables is considered biohazard waste and treated as such. Under the current pharmaceutical waste management situation, rubber components are highly unlikely to enter any recycling route after being used.

We must therefore find other levers to fulfil our sustainability objectives, which we do by focusing on ensuring that our operations are more sustainable. All of Aptar Pharma's injectables manufacturing sites are certified landfill free through our internal programme, which was achieved through the establishment of a vulcanised rubber waste recycling network, allowing us to recycle at least 90% of our rubber waste each year.

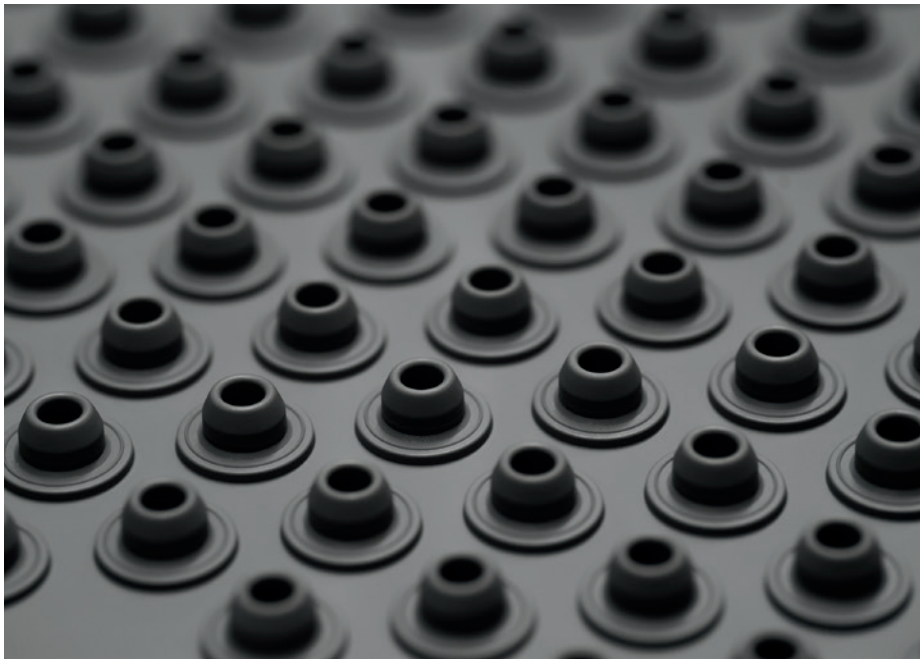

Figure 1: Aptar Pharma vial stopper sheet. Downstream vulcanised rubber scraps enter a recycling network.

Audrey Chardonnet

Global Business Development Director

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Audrey Chardonnet is the Global Business Development Director for prefilled syringe components at Aptar Pharma's Injectables division and is responsible for driving the strategy for the company's PFS segments. She previously held various positions within the Aptar Pharma sales organisation, most recently as Director, Global Strategic Customers, with a particular focus on business development with syringe manufacturers and global accounts. Ms Chardonnet graduated with a master's degree in Chemistry and has over 15 years of experience in the injectables industry.

"ALL OF APTAR PHARMA'S INJECTABLES MANUFACTURING SITES ARE CERTIFIED LANDFILL FREE THROUGH OUR INTERNAL PROGRAMME, WHICH WAS ACHIEVED THROUGH THE ESTABLISHMENT OF A VULCANISED RUBBER WASTE RECYCLING NETWORK, ALLOWING US TO RECYCLE AT LEAST 90% OF OUR RUBBER WASTE EACH YEAR."

Additionally, all of the electricity we use within our injectables sites comes from renewable sources. Most importantly, as part of our global expansion, we have been implementing energy-saving initiatives, aiming to reduce natural gas consumption at our facilities worldwide. These changes have resulted in significant reductions in natural gas consumption at some of our sites, reducing the greenhouse gas emissions associated with our operations.

Q **How do you manage your energy use at the site level?**

A In order to meet our energy targets, we set up dedicated teams and launched a series of projects around four key pillars. First, we performed comprehensive energy assessments at the site level. During these assessments, tracking indicators were defined for all our processes and benchmarked against other manufacturing sites within the company and the industry. We then developed an energy-saving culture within our factories and implemented short-term action plans to reduce unnecessary energy use throughout the factories.

To take this initiative further, we brought in external agencies to perform an energy audit for us to identify long-term energy-saving opportunities and prioritised high-impact actions. At some of our sites this was done in collaboration with the French CertiNergy agency, a governmental partner that supports French-based industries in transitioning towards cleaner manufacturing.

Based on this audit, we identified new technologies with high energy-saving potential and launched a series of projects to modernise our utilities. Once again, the CertiNergy agency partnership played a central role in supporting the implementation of these new utilities and ensuring that results were in line with expectations.

Q **Can you provide an example of an energy savings project and the results you have seen?**

A One of the most energy-intensive processes in our factory is the production of hot water to transport heat. This is used for both the production of water for injection (WFI), which is the primary element for washing all of our rubber components, and for heating the factory during the cold months of the year.

In our Granville (France) factory, this process was handled by two independent boilers, which were replaced by a single state-of-the-art steam boiler. In addition to having twice the capacity of previous boilers in tonnes of steam produced per hour, it is also digitally regulated to optimise energy consumption. Most importantly, new air compressors and chillers were installed and equipped with heat recovery mechanisms, allowing the heat to be redirected to the primary boiler to further reduce the consumption of natural gas.

By reducing the number of boilers, modernising our utilities and implementing heat-recovery mechanisms, we reduced the consumption of energy for building heating by 99.7% and for WFI production by 15%. This energy was formerly coming from natural gas, so these savings equated to an estimated reduction of 814.5 tonnes of CO_2.

Following the success of this project, we have initiated a similar project for upgrading the boiler systems in our other manufacturing site in Brécey (France) and are continuing to upgrade our utilities to eliminate energy waste. This is a key objective of our global expansion, and we are committed to growing sustainably.

Q **Could you offer further insight into how Aptar Pharma is expanding?**

A In October 2022, Aptar Pharma announced a global expansion to address the growing needs of the injectable market. This growth relates to both

"FOLLOWING THE SUCCESS OF THIS PROJECT, WE HAVE INITIATED A SIMILAR PROJECT FOR UPGRADING THE BOILER SYSTEMS IN OUR OTHER MANUFACTURING SITE IN BRÉCEY AND ARE CONTINUING TO UPGRADE OUR UTILITIES TO ELIMINATE ENERGY WASTE."

Figure 2: Aptar Pharma's new factory is intended to be a flagship for sustainable manufacturing.

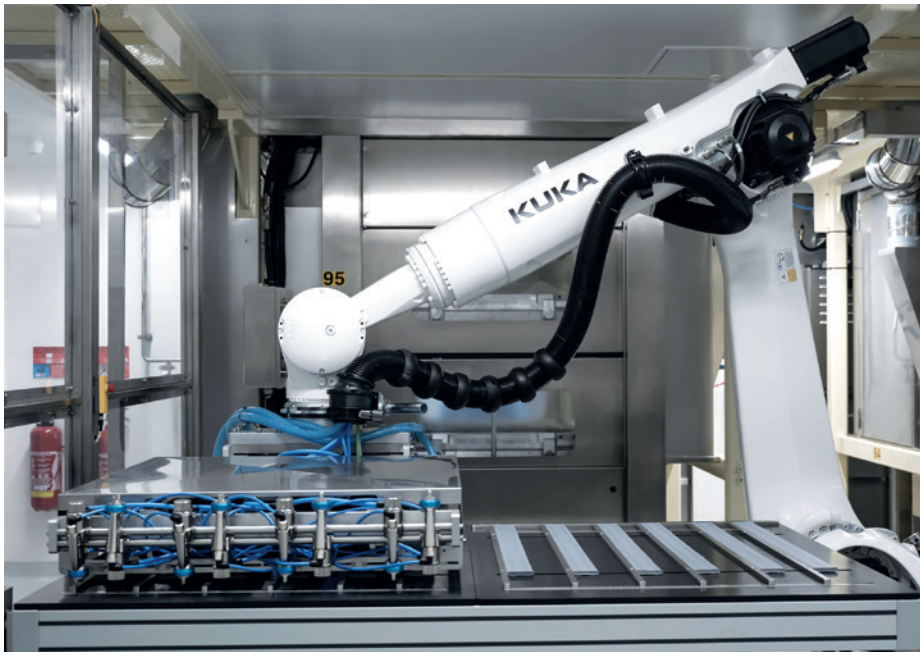

Figure 3: Automation and ergonomics are key features of Aptar Pharma's expansion plan.

the number of injections administered globally and to the quality of packaging required for increasingly sensitive drugs. This expansion was initiated by upgrading our existing manufacturing sites in Granville and Brécey, with the notable addition of an extension to the Granville factory, dedicated to the production of PremiumFill® and PremiumCoat® injectable components. Our manufacturing site in Congers (NY, US) was also expanded to increase the production capacity for PremiumCoat® film-coated solutions.

Most importantly, Aptar Pharma's expansion programme includes the construction of a new 19,000 m² factory in Granville, dedicated to the production of vial and prefilled syringe components All the knowledge and experience acquired with the expansion and upgrading of the existing sites has been applied to make our new factory the flagship for Aptar Pharma's sustainable manufacturing (Figure 2).

Q What makes the new factory different?

A Only one boiler, with a capacity of three tonnes per hour, was installed in the new factory. Heat recovery was implemented by default on all relevant equipment, as well as digital tracking of all energy expenditure. Additionally, 2,500 m² of solar panels were installed on the roof of the factory, enabling the production of electricity corresponding to the yearly consumption of 100–200 households. Rainwater collection has also been implemented and would allow the saving of the equivalent of 300 m³ of sanitary water each year.

In order to promote wellbeing at work, the factory was also designed to maximise the use of natural light and focus on ergonomics, improving the health and safety of our employees. During building design, all processes were rethought to reduce the need for carrying heavy loads, exposure to powders and repetitive tasks (Figure 3). This was greatly enabled by the implementation of state-of-the-art automation at all stages of the manufacturing process.

We're increasing our capacity and capabilities in a big way

...to help you deliver billions of essential doses.

Big health challenges require transformative thinking. At Aptar Pharma, we're transforming expectations of what an injectables partner can be.

Our expansion program of close to $180 million USD is already derisking drug development pipelines, and enhancing quality and service. We're deploying advanced robotics and digital systems, adding more clean rooms, and expanding our global manufacturing footprint to deliver billions of additional injectable components each year.

With our increased capacity and agility, together we can meet the world's biggest health challenges, today and tomorrow. Join us.

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Shaping the future of injectables, together

Aptar pharma

All these sustainability initiatives were recognised by the US Green Building Council's Leadership in Energy and Environmental Design (LEED) rating system with the silver certification.

Q What is LEED certification and how did you obtain it?

A LEED is a green building certification that promotes lower-impact material selection and energy-efficient systems and architecture. The LEED certification is a globally recognised symbol of sustainability achievement, backed by an entire industry of committed organisations and individuals paving the way for market transformation in building design and construction. To achieve LEED certification, a project must earn points and address key areas of sustainability, such as carbon, energy, water, waste and transportation, all of which were considered for this expansion project.

The LEED certification also considers the type of land used for building new facilities. Our new factory was built on land that was previously occupied by another factory and therefore did not require the conversion of agricultural or natural fields, demonstrating Aptar's commitment to reducing the project's environmental impact.

Q Do you have any concluding remarks?

A As Aptar Pharma continues to expand its injectables manufacturing capabilities worldwide, sustainability remains at the heart of our projects. Beyond manufacturing, we are continuing to develop internal expertise in conducting lifecycle assessments leveraging Aptar's own Eco Design Tool. This capability supports discussions and preliminary work with customers, helping us collectively identify key levers for enhancing environmental efficiency and create action plans to reduce the environmental footprint of our products.

Whether it is by working on new product designs, sourcing of raw materials or mass balance approaches, we are committed to reducing our impact on the environment so that we can continue to deliver life-saving solutions to patients around the world responsibly.

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NOVEL SOLUTIONS FOR ULTRA-LARGE-VOLUME WEARABLE AND PORTABLE SUBCUTANEOUS INJECTORS

MicroMED
Precision Drug Delivery Platform

Dr Hong-Jun Yeh of **MicroMED** and **Jiunn-Ru Lai** and **Tsung-Chieh Cheng** of **Kaohsiung University of Science and Technology** discuss the need for novel approaches to the challenge of delivering high volumes of biologics while also addressing patient centricity, and introduce MicroMED's two innovative gas-powered approaches that leverage micro-electromechanical systems to drive the injection.

INTRODUCTION

The subcutaneous (SC) drug delivery system landscape is rapidly evolving, driven by the increasing demand for higher-dose biotherapeutics and patient-centric considerations, such as increased treatment tolerability and quality of life. Two key trends are emerging to address these unmet needs:

1. Advancements in formulations, including higher-concentration biologics and the inclusion of recombinant human hyaluronidase (rHuPH20) as a dispersion and permeation enhancer to improve the tolerability of large-volume SC injections
2. Innovative device technologies enabling larger volumes and higher concentrations for SC delivery.[1]

Advancements in drug delivery system technologies have pushed the boundaries of commercial delivery devices, such as autoinjectors and on-body injectors (OBIs), toward higher doses of biotherapeutics through increased volumes and/or drug concentrations, with or without rHuPH20. While significant strides have been made in developing devices for moderate-volume (up to 20 mL) SC injections, challenges persist in addressing the growing need for ultra-large-volume (ULV) SC delivery devices, particularly for volumes exceeding 25 mL. This ULV range includes devices such as OBIs and ambulatory syringe pumps with deliverable volumes between 20 and 60 mL per use, considering drug concentration, wearability and portability.

COMMERCIAL CASES AND CHALLENGES

An important trend to understand is the transition from intravenous (IV) to SC administration. In 2010, the first immune globulin infusion (20%) HIZENTRA from CSL Behring was approved with a syringe pump for delivery volumes of up to 100 mL. In 2019 and 2020, Genentech's Herceptin HYLECTA® (Trastuzumab/hyaluronidase 5 mL) and PHESGO® (Pertuzumab/trastuzumab/hyaluronidase 10 mL and 15 mL) were approved for manual syringe injections. These successful IV to SC transitions align with the healthcare system's needs for reductions in resource use, time and cost, along with patient preferences. However, manual syringe injections still require healthcare provider assistance and are typically administered in clinical settings. Moreover, manual injections lasting several minutes can be challenging for healthcare providers and painful for patients.

Currently, the commercial market primarily features autoinjectors with capacities up to 2.25 mL due to short injection duration requirements. Using these devices, higher doses of biotherapeutics can only be achieved by leveraging higher drug concentrations with smaller delivery volumes. Although there are ongoing efforts to develop larger-volume (5–10 mL) autoinjectors from companies such as SHL (Zug, Switzerland), Ypsomed (Burgdorf, Switzerland), Kaleo (Richmond, VA, US) and SMC (Somerset, WI, US), it is widely understood that the advancement of large-volume autoinjector development is reaching its limits in terms of delivery volume and injection duration (approx 30 sec), even with rHuPH20.[2–4]

On the commercial OBI combination product side, devices such as West Pharmaceutical's (Exton, PA, US) 10 mL SmartDose OBI for SC Pharmaceuticals' Furoscix® (furosemide) and Enable Injections' (Cincinnati, OH, US) 20 mL EnFuse OBI for Apellis' Empaveli® (pegcetacoplan) represent the most recent advancements in higher dose delivery. While numerous OBIs are under development, ranging from 5 mL to 20 mL and leveraging conventional drive mechanisms, such as mechanical springs, electromechanical motors, pressure-based systems or elastomeric material, fundamental challenges remain for ULV applications with 20–60 mL delivery volumes. These challenges, based on different drive mechanisms, include:

"WHILE NUMEROUS OBIs ARE UNDER DEVELOPMENT, RANGING FROM 5 mL TO 20 mL AND LEVERAGING CONVENTIONAL DRIVE MECHANISMS, FUNDAMENTAL CHALLENGES REMAIN FOR ULV APPLICATIONS WITH 20–60 mL DELIVERY VOLUMES."

1. Insufficient and inconsistent force/pressure (delivery rate) over the entire injection duration:
   - Mechanical drive mechanisms, particularly those relying on springs and elastomeric materials, are susceptible to this challenge due to their inherent strong-to-weak driving force profile. This can lead to issues for drugs that require precise injection duration control and is exacerbated with ULV dose delivery as backpressure increases over time.
   - Larger containers require significantly higher driving forces that may exceed the capabilities of springs, elastomeric materials or motors, limiting the selection of standard containers.

2. Bulky size due to standard container availability and drive mechanism design constraints:
   - Standard containers are not space-efficient for wearable and portable device design, especially for delivery volumes exceeding 25 mL. The space around a standard cylindrical container creates unavoidable dead volume for the overall injector size. The addition of a plunger rod further increases the overall device length for syringe pump applications.
   - Motor-based drive mechanisms require additional components, such as a gearing system, to handle motion and force transition, increasing the size and weight of the device.

3. Lack of scalability:
   - A platform approach is crucial for both drug and device companies to optimise product lifecycle management, design verification and validation, commercial manufacturing, regulatory submission strategy and complaint handling. Most conventional drive mechanisms lack the scalability to cover a 10–60 mL delivery volume range.

4. Energy consumption:
   - Motor-based drive mechanisms require significant energy consumption to handle the larger driving forces required due to the container size, especially for repeatable injections.

5. Lack of reusability for mechanical drive mechanisms:
   - Mechanical systems, such as springs and elastomeric material, cannot offer reusability, making them less sustainable, due to their inherent limitations on design for recharging the energy required for mechanical OBI applications.

Despite these challenges, OBIs offer more flexibility in terms of drug concentration, injection volume and duration. Considering wearability (size and weight limitations), delivery volumes of up to 60 mL are feasible in an ideal OBI design. This means that the goal of high-dose biotherapeutic delivery with slow and steady delivery rates (long injection durations) and up to 60 mL delivery volumes is achievable. This was further demonstrated through a clinical study by Eli Lilly, which showed the feasibility and tolerability of a low-pain formulation (without rHuPH20) for an abdominal injection of 25 mL at a delivery rate of 0.5 mL/min in both lean and non-lean subjects.[5]

Considering the current drug delivery system market and the underlying challenges, there is a clear demand for ULV injectors to address the growing need for high-dose therapies while prioritising patient comfort and convenience.

"CONSIDERING THE CURRENT DRUG DELIVERY SYSTEM MARKET AND THE UNDERLYING CHALLENGES, THERE IS A CLEAR DEMAND FOR ULV INJECTORS TO ADDRESS THE GROWING NEED FOR HIGH-DOSE THERAPIES WHILE PRIORITISING PATIENT COMFORT AND CONVENIENCE."

Considering key factors, from drug formulation to device design and patient preferences, it is essential to focus on developing innovative solutions that can meet the unmet requirements of a space-efficient ULV OBI and syringe pump device that possesses the following characteristics:

1. A compact and scalable design in terms of wearability, portability and a platform approach
2. A powerful, uniform, controllable and reusable driving mechanism
3. Low energy consumption
4. Low manufacturing cost.

MicroMED has developed two novel approaches based on a micro-electromechanical system (MEMS)-enabled gas-pressure-driven actuator that possesses these qualities to address the unmet needs in ULV injector devices:

1. Dual-bag wearable injector for OBI and ambulatory pump applications
2. Gas-bellows-actuated compact/portable syringe pump for ambulatory pump applications.

WORKING PRINCIPLES OF THE MEMS-ENABLED GAS MICROPUMP

MEMS technology enables the integration of mechanical and electrical components on a microscopic scale, allowing for miniaturised high-performance systems. The MEMS-enabled gas micropump offers a simple, compact, flexible, robust and powerful energy source to address emerging unmet needs in ULV SC drug delivery systems.

With its simplicity and low component count for integrating the actuator into the final delivery device, the gas micropump grants the flexibility to adjust the device's form factor based on the requirements of the final products. The gas micropump employs MEMS technology and electrochemical principles to convert electrolytes into gas pressure in a fast and controlled manner. Inside the micropump, the MEMS microelectrodes, controlled by a printed circuit board assembly, interact with the electrolytes to initiate instantaneous gas generation. This precise control over gas generation enables accurate gas pressure output from the gas micropump.[1]

The gas pump can be configured as a non-linear actuator, where the actuation is directly performed by the gas micropump system. This flexibility allows the system to adapt to different drug delivery system designs and requirements, such as OBI and ambulatory pump applications.

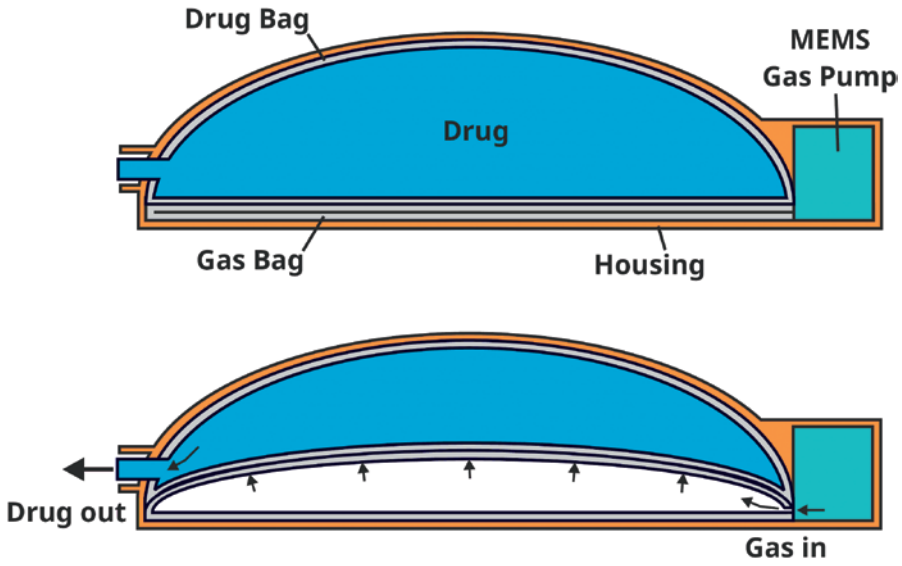

Figure 1: Dual-bag OBI schematics with working principles.

dBOBi DUAL-BAG OBI – A NOVEL SOLUTION FOR ULV WEARABLE OBIs

MicroMED has developed the dBOBi™, a compact, wearable OBI using dual-bag actuation. Powered by patented MEMS-enabled gas pump technology, the dBOBi OBI surpasses traditional drive mechanism technologies, enabling the SC administration of UVL biotherapeutics. The compact dBOBi OBI device can also replace the existing devices used for ambulatory pump applications.

Key Characteristics

- **Dual-Bag Actuation Approach:** As illustrated in Figure 1, two flexible bags (similar to IV bags except for the shape) are constrained inside a half-dome-shaped shell. The MEMS-enabled pneumatic pump pumps gas into the first bag, transferring the pressure to the second, drug-filled bag to initiate the delivery process. The drug can be manually transferred from a vial or syringe through a vial adaptor or a Luer-lock connector to the bag.

"THE MEMS-ENABLED GAS MICROPUMP OFFERS A SIMPLE, COMPACT, FLEXIBLE, ROBUST AND POWERFUL ENERGY SOURCE TO ADDRESS EMERGING UNMET NEEDS IN ULV SC DRUG DELIVERY SYSTEMS."

Figure 2: dBOBi dual-bag OBI functional prototype for 50 mL delivery (dimensions: 100 x 90 x 25 mm).

- **Space-Efficient and Lightweight Design:** With very few components inside the half-dome shell, this design enables ULV capacity and scalability for a platform approach to device design. The half-dome design maximises the use of space, enabling delivery volumes that other OBI designs struggle to achieve.
- **Controlled Pressure Output:** This ensures that the target injection duration is achieved and compensates for the higher SC backpressure associated with ULV applications.
- **Simple Modular Design:** This keeps the cost of goods low and makes manufacturing easier.
- **Sustainability:** This system can accommodate a design with a separate reusable power module and a disposable drug bag and fluid path system to minimise waste.

Key Components

Figure 2 shows a functional prototype of a 50 mL dBOBi dual-bag OBI. The size of the 60 mL OBI is comparable to a typical gaming mouse with an even lower height of 25 mm (1 inch).

- Two flexible bags (half-dome shaped) – one for gas, one for liquid (drug)
- One rigid shell (half-dome shaped)
- Battery-powered MEMS gas micropump integrated with the rigid shell and flexible bag for the OBI
- Liquid-transfer connector for transferring the liquid drug from a vial or prefilled syringe into the device
- Needle insertion unit that connects to the drug bag outlet through the OBI.

Key Functions and Operating Steps

- Drug can be manually transferred from a vial or prefilled syringe to the drug bag through the connector
- MEMS gas micropump starts to pump gas into gas bag (volume expansion)
- The volume expansion in gas bag starts (injection starts), squeezing the liquid bag against the rigid shell until the liquid bag is completely empty (injection completes)
- The flow rate is controlled by the MEMS gas micropump
- The liquid bag can be disposed of after use
- The MEMS engine and rigid shell can be reused.

Key Advantages

- Low cost and easy to manufacture due to modular design with minimal components
- Space efficient and lightweight
- Scalable platform approach able to handle doses from 10 to 60 mL
- No risk of drug contamination with dual-bag design separating gas and drug
- Reusable power module with frame
- Replaceable/disposable drug bag with fluid path system
- Low energy consumption – 300 mW (3V, 100mA), 95 mAh per injection of 50 mL deionised water with a 26G thin-wall (TW) needle at 1 mL/min flow rate.

dBOBi DUAL-BAG ULV OBI – PERFORMANCE AND DISCUSSION

Figure 3 and Table 1 present the delivery volume and delivery duration of the dual-bag OBI prototype using 26G (TW), 27G (TW) and 30G needles with a 50 mL bag of deionised water (1cP) and 60% glycerine solution (10 cP). With a

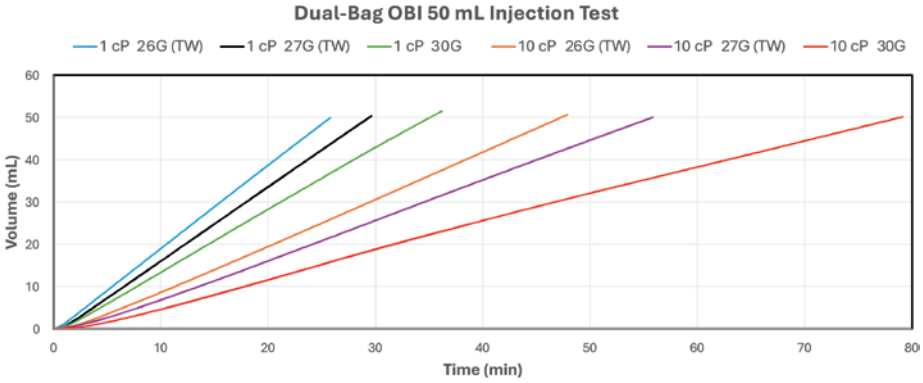

Figure 3: Dual-bag OBI preliminary study results – volume versus time with three different needle gauges and two viscosities.

Test #	Needle	Solution	Viscosity (cP)	Injection volume (mL)	Injection time (min)	Average Flow rate (mL/min)
1	26G (TW)	DI water	1	50.2	25.9	1.94
2	27G (TW)	DI water	1	50.4	29.6	1.70
3	30G	DI water	1	51.6	36.3	1.42
4	26G (TW)	60 % glycerine	10	50.5	50.4	1.00
5	27G (TW)	60 % glycerine	10	50.1	55.9	0.90
6	30G	60 % glycerine	10	50.0	79.0	0.63

Table 1: Dual-bag OBI – test results of 50mL delivery of solutions (1 & 10 cP) based on three different needle gauges.

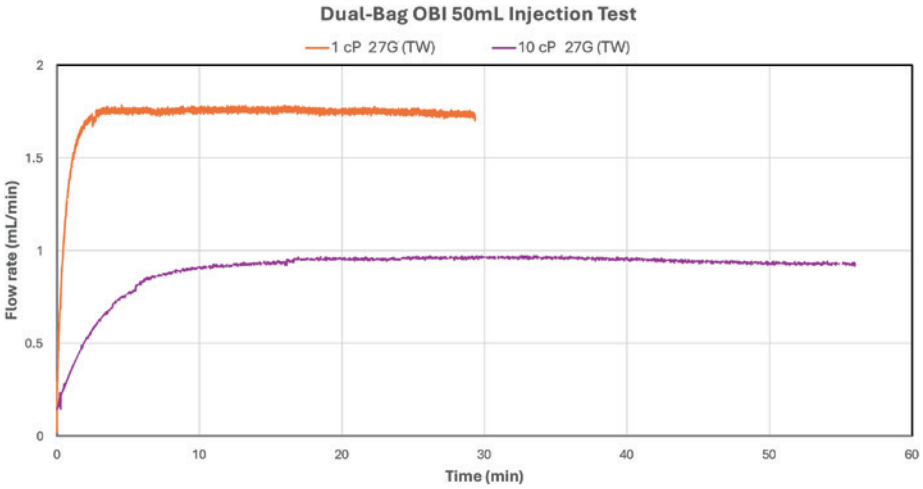

Figure 4: Dual-bag OBI - consistent flow rate over time delivering 50 mL deionised water and 10 cP solution with 27G (TW) needle.

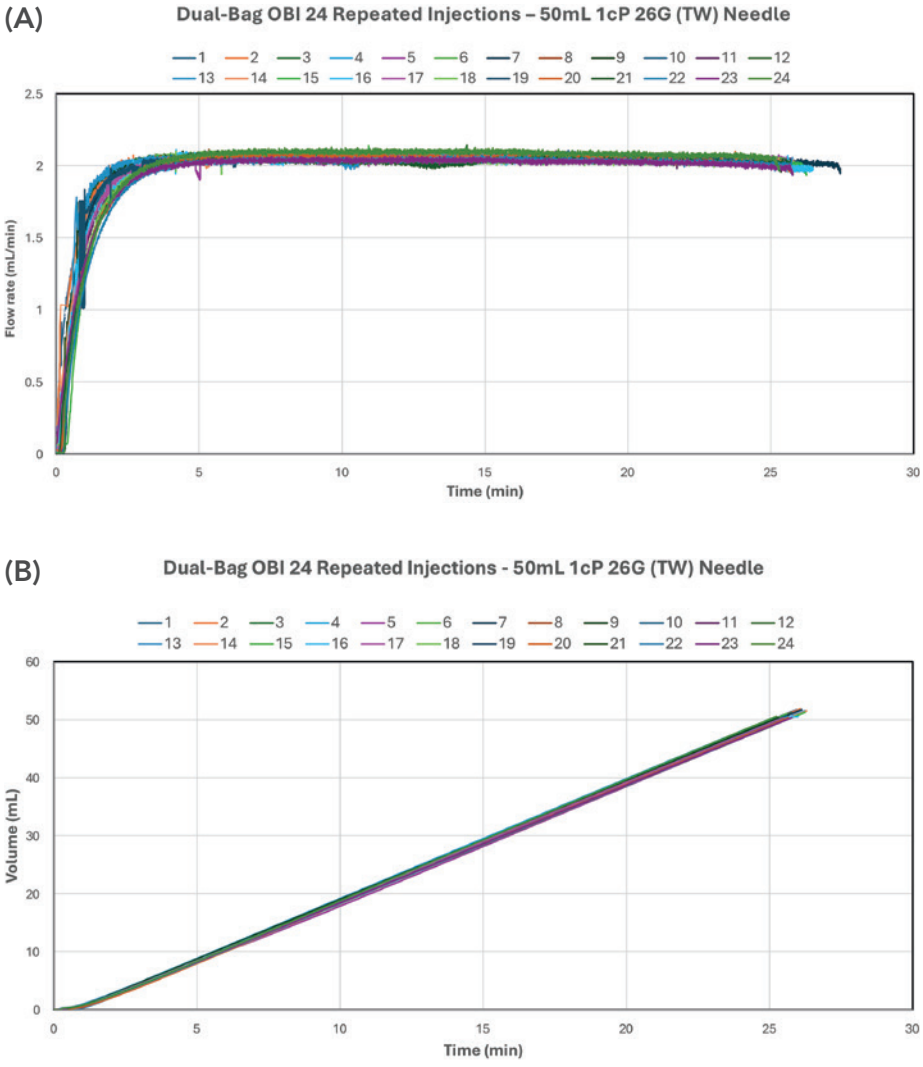

Figure 5: Dual-bag OBI – consistent repeated injections for delivering 50 mL deionised water with 26G (TW) needle: (a) flow rate over time and (b) delivery volume over time.

low power input, flow rates ranged from 0.63 mL/min (79 minutes with 10 cP solution and a 30G needle) to 1.94 mL/min (26 minutes with 1 cP solution and 26G (TW) needle) respectively. As shown in Figure 4, the flow rates remained consistent throughout the injection duration for both 1 cP deionised water and 10 cP solutions using 27G (TW) needle.

Figure 5 illustrates the results of multiple 50 mL deionised water injections at a target flow rate of 2 mL/min using the 26G (TW) needle. This test demonstrated 24 successful deliveries leading up to the publication deadline. Continued development of the gas micropump is expected to yield a significantly higher number of repeatable injections. These results demonstrate the micropump's reusable nature and consistent flow-rate performance, fulfilling sustainability requirements.

GAS-BELLOWS SYRINGE PUMP – A NOVEL SOLUTION FOR ULV AMBULATORY SYRINGE PUMPS

The MEMS-enabled gas micropump can efficiently drive a compact, portable syringe pump capable of delivering ULV SC injections with drug volumes over 60 mL.

Key Characteristics

- **Gas-Bellows Actuation Approach:** The MEMS-enabled pneumatic gas micropump delivers gas pressure directly to the plunger stopper through an extendable bellows, eliminating the need for a plunger rod.
- **Reduced Device Size:** The gas-bellows device size can be significantly reduced in comparison and become more portable by leveraging gas pressure through bellows to directly move the plunger stopper in the syringe without a plunger rod.
- **Constant Pressure Output:** This compensates for the higher backpressure associated with ULV applications.
- **High Compatibility:** The device can connect with commercially available infusion sets and flow rate controllers.
- **Reduced Cost:** The gas-bellows approach reduces costs due to its simple design, easy manufacturability, low component count and compact size.

Current commercial portable ambulatory syringe pumps for SC immunoglobin are bulky, with a very long length of approximately 25.4 cm (10 inches). By eliminating spring-related components and the syringe plunger rod, a 60 mL syringe pump based on a gas-bellows design can achieve a size reduction of approximately 40% compared with existing spring-driven syringe pumps for SC immunoglobin applications.

"BY ELIMINATING SPRING-RELATED COMPONENTS AND THE SYRINGE PLUNGER ROD, A 60 mL SYRINGE PUMP BASED ON A GAS-BELLOWS DESIGN CAN ACHIEVE A SIZE REDUCTION OF APPROXIMATELY 40% COMPARED WITH EXISTING SPRING-DRIVEN SYRINGE PUMPS FOR SC IMMUNOGLOBIN APPLICATIONS."

Key Components

- One 60 mL disposable Luer-lock syringe with a removable plunger rod
- Gas bellows connecting the plunger/stopper of the syringe and the gas micropump outlet
- Rechargeable battery-powered MEMS gas micropump integrated with an outer shell accommodating the gas bellows and syringe.

Key Advantages

- Low cost
- Patient comfort with consistent delivery rate
- Compact, portable and lightweight
- Ability to handle 10 to over 60 mL
- Reusable gas-bellows pump
- Replaceable/disposable syringe
- Low energy consumption.

Future Directions and Work

MicroMED has embarked on the development of a gas-bellows syringe pump, integrating a MEMS-enabled gas micropump into a compact, efficient design. This innovative approach uses indirect gas pressure from the micropump, channelled through an expandable gas bellows, to actuate a syringe plunger. Precise control of the gas pressure allows the micropump to achieve accurate and adjustable injection rates. Eliminating the plunger rod significantly reduces the overall length of the gas-bellows syringe pump system, resulting in a low-cost, portable and reusable device. Functional prototypes based on MicroMED's initial design concepts are currently under development, and the company plans to present its design and preliminary findings in a forthcoming issue of ONdrugDelivery Magazine.

CONCLUSION

This article highlights the current market demand for ULV SC drug delivery systems capable of administering higher-dose

"THESE INNOVATIVE APPROACHES OFFER NOVEL AND VIABLE SOLUTIONS FOR ULV SC DRUG DELIVERY, PARTICULARLY IN APPLICATIONS SUCH AS OBIs AND AMBULATORY PUMPS."

medications. The challenges associated with conventional drug delivery systems have been identified and addressed through a MEMS-enabled pneumatic actuation system. These innovative approaches offer novel and viable solutions for ULV SC drug delivery, particularly in applications such as OBIs and ambulatory pumps. By overcoming the limitations of traditional driving technologies, the dual-bag OBI and gas-bellows pump approaches demonstrate the potential to deliver high-dose biologics while addressing patient-centric considerations.

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The **dBOBi™** on-body injector offers a platform approach to meet biologics product requirements and patient needs

— Wide range of bag volumes: 10, 20, 25, 50, 60 mL
— Slender profile and light weight
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Photo of 50mL Device

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Precision Drug Delivery Platform

The dBOBi™ on-body injector:

Compact, scalable, low-cost OBI for high-dose drug delivery

MicroMED has developed the dBOBi™, a compact, wearable on-body injector utilizing Dual-Bag actuation. Powered by patented MEMS-enabled gas pump technology, the dBOBi™ OBI surpasses traditional driving technologies, enabling the subcutaneous administration of ultra-large volumes (up to 60mL) of biotherapeutics.

Compact size

The unique half-dome drug bag design is space-efficient, lightweight, and maximizes drug dosage capacity, surpassing traditional OBI limitations.

Accuracy – consistent delivery

Controlled pressure ensures precise delivery rates and injection durations, even for high-concentration drugs, compensating for the increased subcutaneous backpressure in ultra-large-volume applications.

Scalability – Platform approach

Supports 10 to 60 mL volumes, offering a versatile platform for optimizing lifecycle management, design validation, manufacturing, regulatory submissions, and complaint handling.

Low energy consumption

Consumes just 300mW (3V, 100mA) and 95mAh per 50mL of injection at 1mL/min, easily powered by a small of-the-shelf battery.

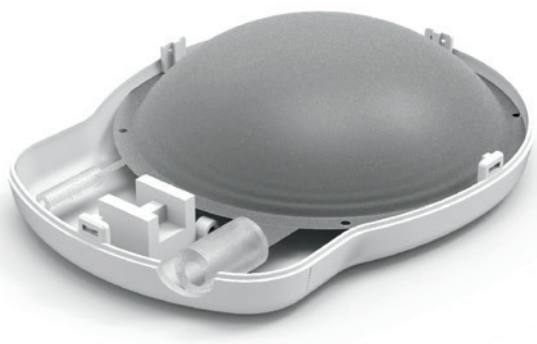
Reusability for sustainability

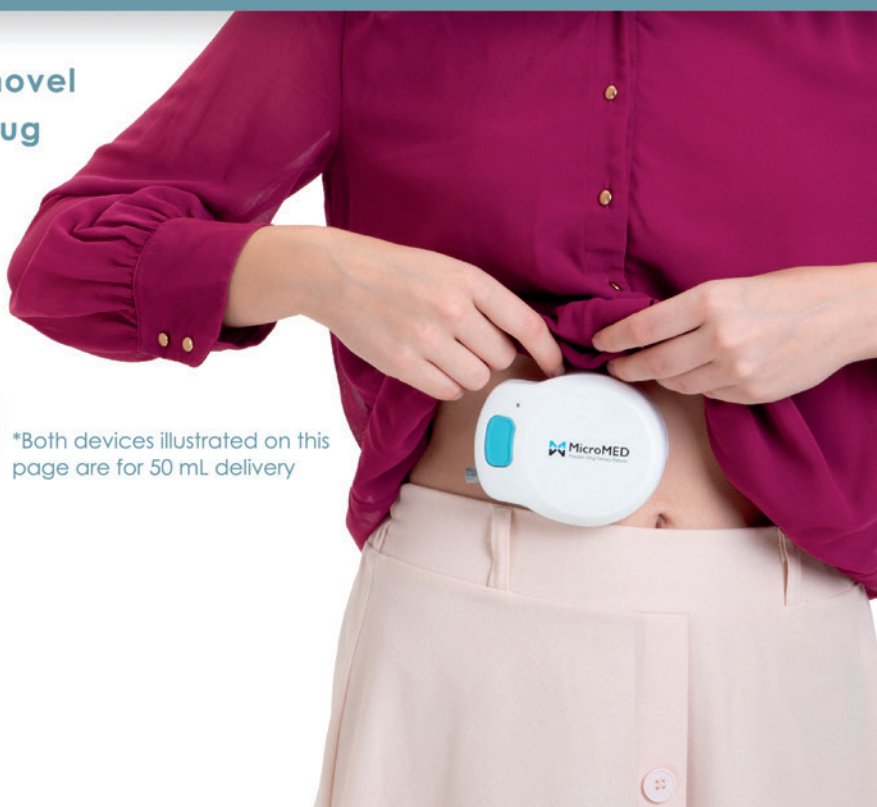
Incorporates a reusable power module with a disposable drug bag and fluid path system to reduce waste.

Low COGs and easy to manufacture

A streamlined, modular design, with minimal components to manufacture and assemble, the Dual-Bag approach reduces manufacturing costs and enables us to compete effectively with mechanical OBIs.

MicroMED provides cost effective novel solutions to address your unique drug delivery needs





*Both devices illustrated on this page are for 50 mL delivery

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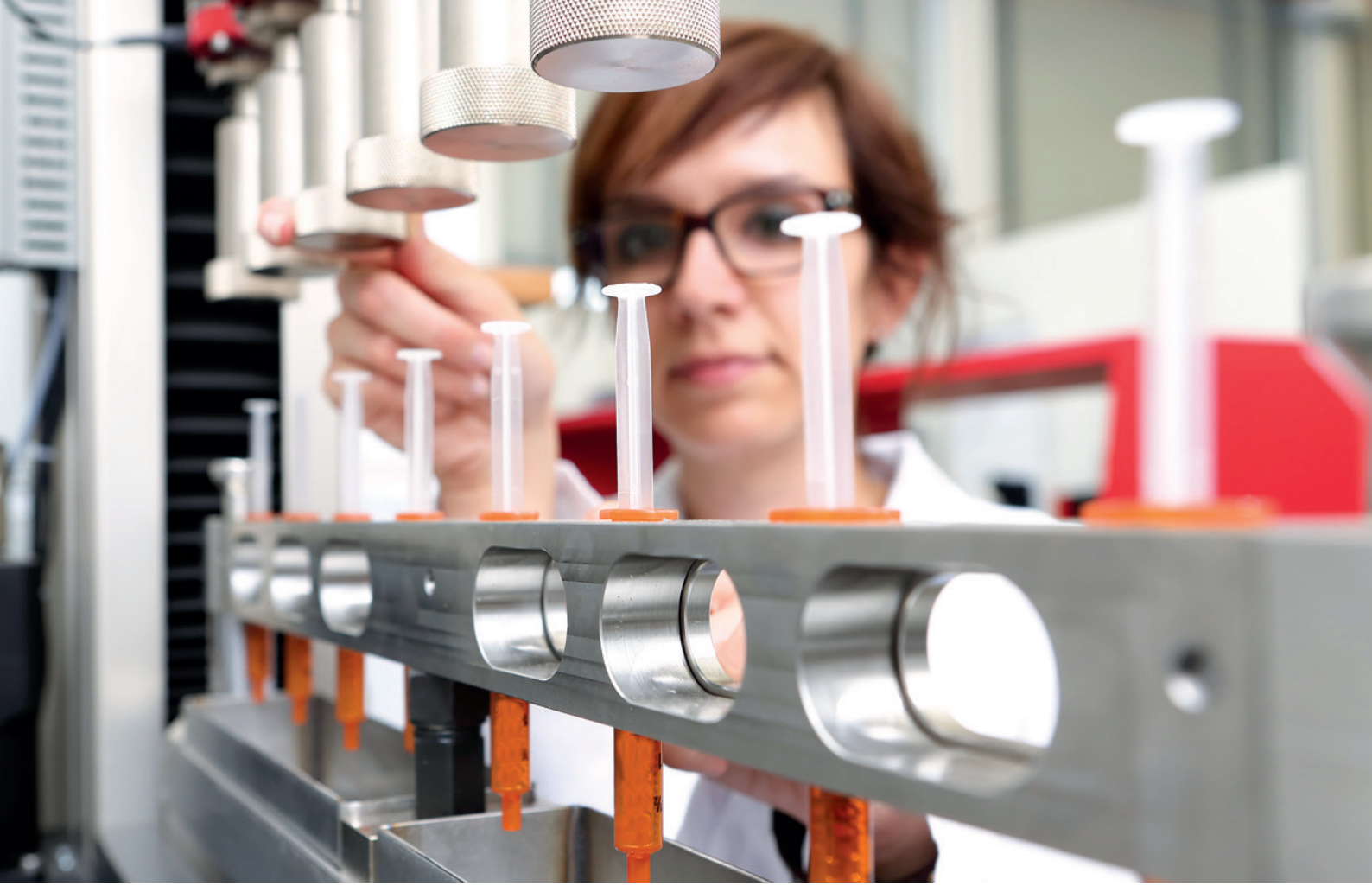

TESTING SYRINGES & INJECTION DEVICES: SOLUTIONS THAT BOOST EFFICIENCY

Zwick / Roell

Peter Schmidt of **ZwickRoell** discusses the company's offerings in the arena of testing systems for injectable drug delivery systems, in particular highlighting the advantages of automation for providing reliable, reproducible results.

When testing disposable and prefilled syringes, the smallest influences can change the test results. An error in the quality assurance process can not only lead to disastrous consequences for the quality of the results but also disrupt factory shipments and incur additional costs. Accounting for this is especially critical when using prefilled syringes in autoinjectors.

Automated processes reduce operator influence and can produce transparent and reliable test results. Additionally, they significantly increase specimen throughput and reduce the cost to test each specimen. Both are important considerations when it comes to efficiency.

With these factors in mind, global market leader ZwickRoell offers various testing solutions to provide results with both semi-automated and fully automated systems.

SEQUENTIAL TESTING: ONE TEST RUN, ONE SPECIMEN, ALL THE RESULTS

Consider an autoinjector – all functions must be tested in the manner in which the patient is expected to use the device.

> "AUTOMATED PROCESSES REDUCE OPERATOR INFLUENCE AND CAN PRODUCE TRANSPARENT AND RELIABLE TEST RESULTS."

Here, different results must be determined for each user action, from removal of the safety cap to activation, as well as functions that occur after the injection. If each result were to be obtained from a separate test or from different specimens, they would not be comparable, which would have significant implications for the validity and reproducibility of the results. ZwickRoell has therefore developed a testing system that determines all the necessary results in a single run with a single specimen – guaranteeing comparable and reproducible test results (Figure 1).

SERIAL TESTING: TESTING SEVERAL SPECIMENS IN SUCCESSION

Larger numbers of test specimens, such as syringes or cartridges, can be tested in series and without user influence using quick-load interchangeable magazines. ZwickRoell offers several different magazine solutions, such as the precision X-Y table for 64 specimens (Figure 2) or a rotary magazine for 15 syringes (Figure 3),

Figure 2: Serial testing with X-Y table for breakaway and glide force testing.

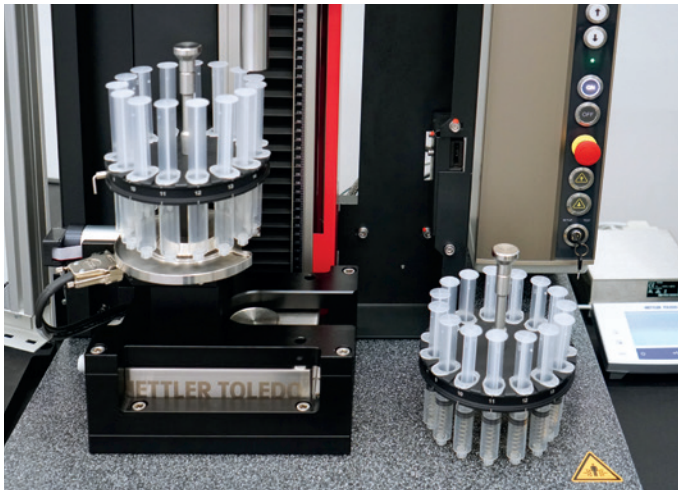

Figure 3: The rotary magazine is used to automatically test 15 syringes one after the other; another magazine can be loaded in parallel.

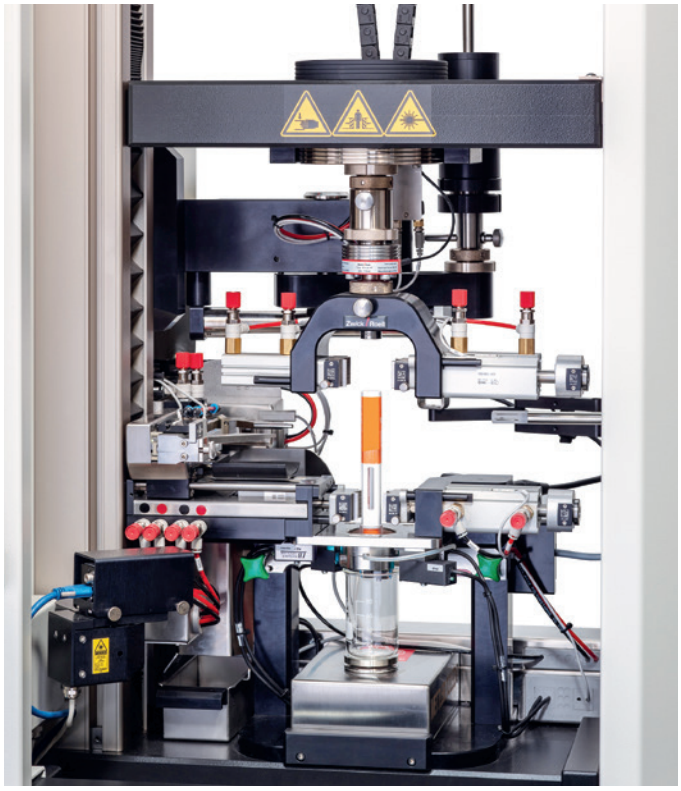

Figure 1: Sequential testing on a single autoinjector – all results are determined in a single test run.

> "IN ORDER TO REDUCE THE TEST TIME FOR MULTIPLE SYRINGES, ZWICKROELL'S TESTING MACHINES CAN BE EXTENDED TO TEST SIX TO EIGHT SPECIMENS SIMULTANEOUSLY."

depending on the respective requirements of the test throughput and the desired modularity of the testing system. All systems are controlled via ZwickRoell's testXpert testing software with a specimen-specific test programme, always in accordance with US FDA 21 CFR Part 11. With both solutions, operator influence is significantly reduced or eliminated.

PARALLEL TESTING: TESTING SEVERAL SPECIMENS SIMULTANEOUSLY

In cases where a drug is administered slowly via a syringe, such as in syringe pumps, individual tests take a comparatively long time. As such, achieving high throughput by testing a batch of syringes simultaneously tends to be an attractive scenario. In order to reduce the test time for multiple syringes, ZwickRoell's testing machines can be extended to test six to eight specimens simultaneously (Figure 4). The test results for each syringe are recorded individually and clearly displayed in the results matrix of the testXpert testing software.

Figure 4: Eight syringes tested simultaneously, with individual test results and values recorded separately.

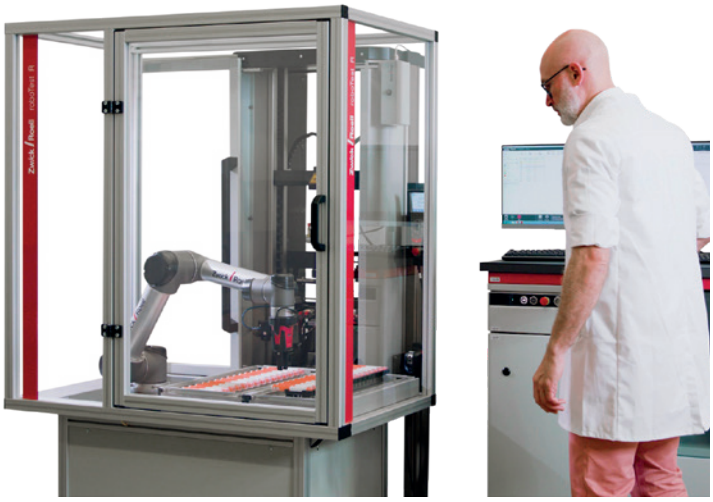

Figure 5: A robotic system can handle a very high test volume with 24/7 operation.

FULLY AUTOMATED TESTING SOLUTIONS WITH INTEGRATED ROBOT

For high test volumes where the capacity of serial solutions has been exhausted, it makes sense to expand the testing machine with a mobile robot system (Figure 5). This complete system guarantees safe and economical testing of autoinjectors, insulin pens or vials with the maximum testing throughput. Depending on the requirements, collaborative robots (smart robots) or industrial robots can be used. Graphical visualisations can be used to display system status in real time via mobile devices such as tablet PCs. Visualisation increases the efficiency of the robotic testing system by reducing idle time. Additionally, the modular design of the robotic testing system enables manual tests to be performed with the machine whenever required.

"FOR HIGH TEST VOLUMES WHERE THE CAPACITY OF SERIAL SOLUTIONS HAS BEEN EXHAUSTED, IT MAKES SENSE TO EXPAND THE TESTING MACHINE WITH A MOBILE ROBOT SYSTEM."

Peter Schmidt

Peter Schmidt, Product Manager Medical/Pharma at ZwickRoell, has several decades of experience in the pharmaceutical and medical technology industry. Mr Schmidt is a product specialist for testing solutions for injection devices and primary packing.

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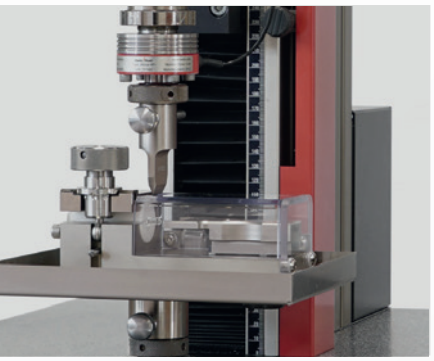

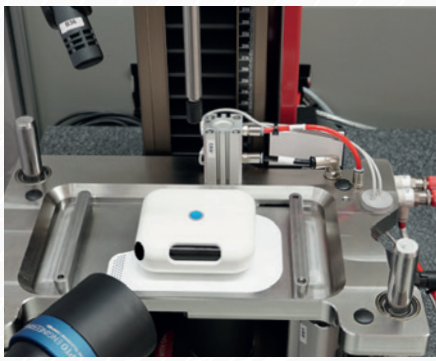

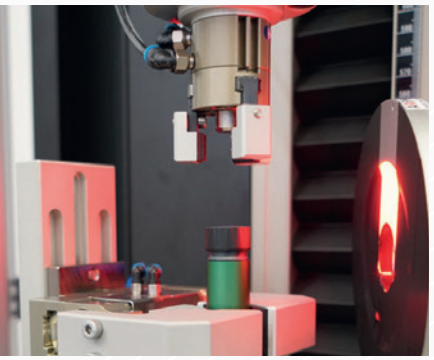

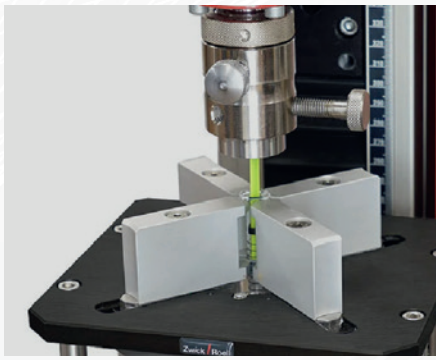

- Manual, semi-automatic and fully automated testing solutions for therapy systems (needles, (pre-filled) syringes, insulin pens, auto injectors)
- Traceable and tamper-proof test results in accordance with FDA 21 CFR Part 11
- ZwickRoell supports customers with DQ, IQ and OQ services

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HIGH-DOSE DRUG DELIVERY – HOW FAR CAN AUTOINJECTORS GO?

Phillips Medisize
a molex company

Iain Simpson of **Phillips Medisize** reviews the development of autoinjectors for self-injection and explains that, despite significant emerging trends for biologics, new developments in formulation and autoinjector technology may enable them to continue to be the dominant delivery device for these medications.

INTRODUCTION

Autoinjectors have been on the market for the injectable delivery of therapeutics for chronic diseases since the 1990s; however, the market has grown more rapidly over the past 10 years, driven both by the introduction of new innovative biologics and the launch of biosimilars. To date, as shown in Figure 1, nearly 100 combination products that include an autoinjector have been approved, of which around 80% are mechanical disposable devices, with the rest of the market split between reusable mechanical and electromechanical autoinjectors. More specifically, spring-powered devices, with manual needle insertion and removal, shield-triggered activation and passive needle protection have become the preferred disposable design.

Commercially available mechanical disposable autoinjector platforms currently dominate the market, having been approved for multiple combination products and offering economies of scale and confidence regarding development timelines and reduction of regulatory risk. Presently, standardisation is being favoured over differentiation so, even when other device designs offer potential benefits (such as automated needle insertion and retraction to improve comfort or the ability to provide higher injection forces to reduce injection time), trade-offs around cost, size, complexity, development time and regulatory risk need to be considered, meaning they may only enter the market for niche applications.

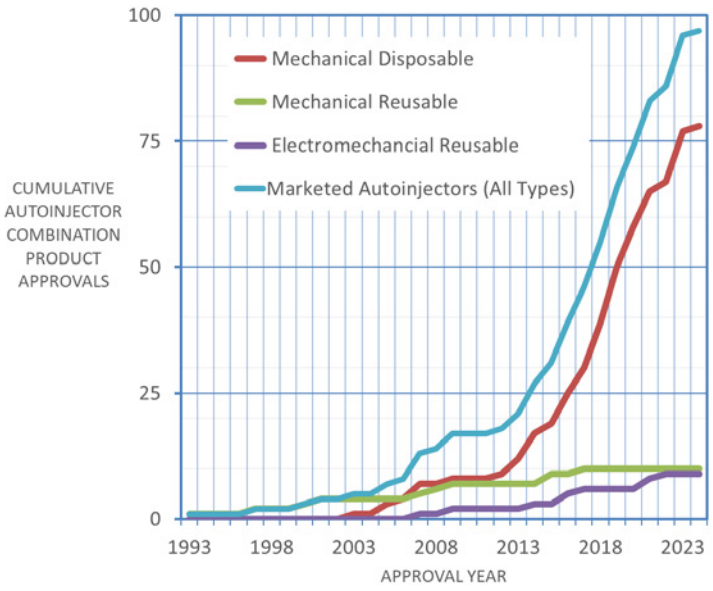

Figure 1: Cumulative autoinjector approvals by year (Data from PharmaCircle, Aug 2024).

EMERGING TRENDS IN INJECTABLE DELIVERY DEVICES

Although the trend towards mechanical disposable device platforms looks set to continue, several emerging trends may start to challenge the status quo and disrupt the market.

Environmental Sustainability

Back in 2006, when the first disposable devices entered the market, sustainability was not a major area of concern for the pharmaceutical industry. The benefits of increased self-administration of medication and a focus on ease of use for patients outweighed the negative impact of single-use mechanical devices in terms of cost per dose and sustainability. The same view prevailed in the insulin pen market. However, today, many leading pharmaceutical companies have comprehensive sustainability policies and goals, some of which highlight the need to reduce waste from medical packaging, including delivery devices. As such, more sustainable device solutions are becoming of increasing interest to pharma companies, particularly where large patient populations are involved.

Connectivity

By adding connectivity to drug delivery devices, real-time medication use data can be reliably captured and used to gather information on adherence and drive digital services that can dynamically adapt to changing use patterns, providing patients with personalised support and feedback. Although adding the electronics needed for connectivity can add to the environmental footprint of the device, the ability to provide timely support and coaching can potentially reduce disease complications and hospitalisations, which can help reduce the total environmental impact of the treatment, as well as improve healthcare outcomes.

Applying Device Technology Across Multiple Drug Products

Although current mechanical autoinjector platforms are being used across broad drug portfolios, this requires the drug formulation to be confined to a limited range of volumes and viscosities, or for the device to be customised for different fill volumes. While some of the newer mechanical autoinjectors under development can deliver higher volumes and others can be more easily adapted to different primary containers and fill volumes, there are still limitations to their flexibility, but current designs have limitations that might drive the need to look for new technical solutions.

TECHNOLOGY OPTIONS FOR AUTOINJECTORS

One way of categorising autoinjectors is to consider them as being either:

- Single-use or reusable, and
- Having either an electromechanical or non-electromechanical drive mechanism.

The reason for the second classification is that electromechanical devices already incorporate electronics that can enable significant additional functions, such as audible and visual user feedback and inbuilt connectivity, as well as offering benefits for delivery performance. For non-electromechanical devices, electronics could still be added but will not improve the delivery performance of the device. Figure 2 summarises the advantages and disadvantages of the four device options. At present, there are no single use electromechanical autoinjectors as they would have an unacceptably high cost and poor sustainability, although it is worth noting that this approach has been adopted for some on-body devices.

THE CHALLENGE OF DELIVERING BIOLOGICS – HISTORICAL PERSPECTIVE

In 2008, the prevailing view was that the maximum volume that could be delivered by an autoinjector was 1 mL and the

"BY ADDING CONNECTIVITY TO DRUG DELIVERY DEVICES, REAL-TIME MEDICATION USE DATA CAN BE RELIABLY CAPTURED AND USED TO GATHER INFORMATION ON ADHERENCE AND DRIVEDIGITAL SERVICES THAT CAN DYNAMICALLY ADAPT TO CHANGING USE PATTERNS, PROVIDING PATIENTS WITH PERSONALISED SUPPORT AND FEEDBACK."

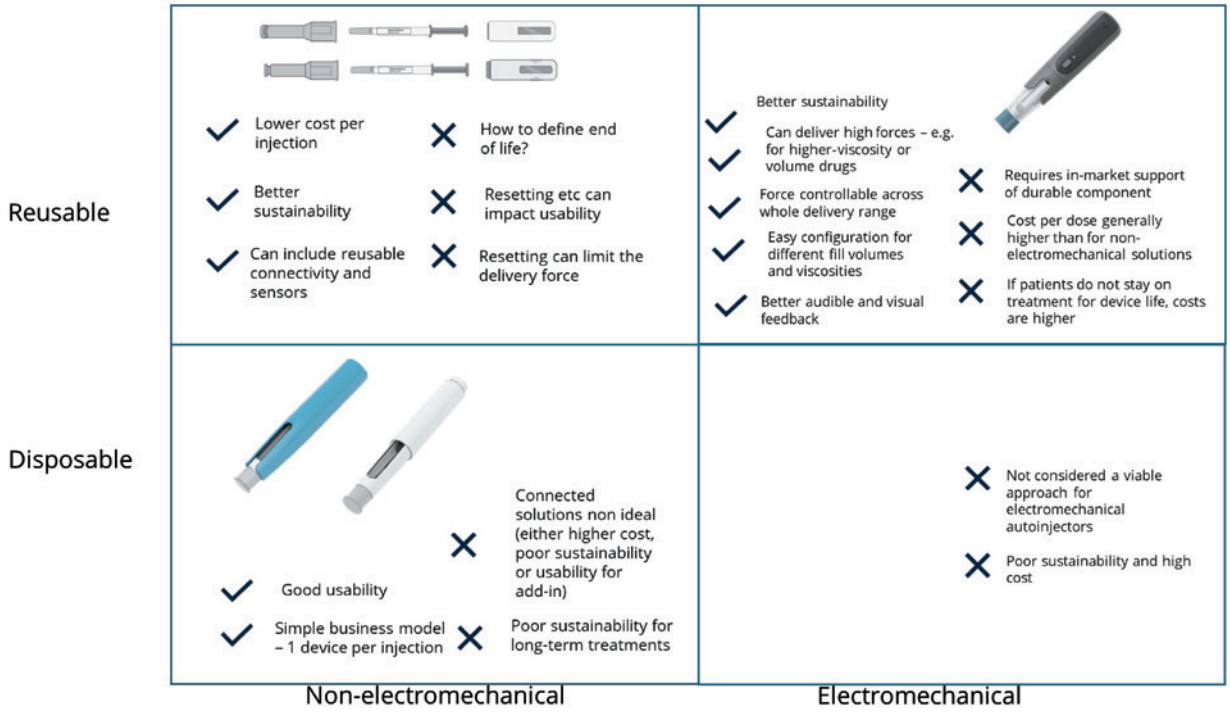

Figure 2: Technology options for autoinjectors.

maximum concentration that could be achieved for a stable, injectable monoclonal antibody (mAb) formulation was around 100 mg/mL, suggesting a maximum dose of 100 mg. A drug pipeline analysis from that period suggested that more than 50% of drugs under development would require a higher dose than this, leading to the conclusion that a different type of delivery device would be required to support future self-injection needs if the drug was not to be delivered as an intravenous (IV) infusion.

It was suggested that, to facilitate the longer injection times required for these larger doses, wearable on-body devices would be required, and several such devices have been developed or are currently under development to address this need. However, 15 years later, fewer than 10 such drug-device combinations have entered the market and, in contrast to autoinjectors, no dominant design has been established. Figure 3 shows that some of the needs of high-dose delivery anticipated in 2008 have been addressed by increasing drug concentrations up to 150 mg/mL and drug volumes of up to 2 mL.

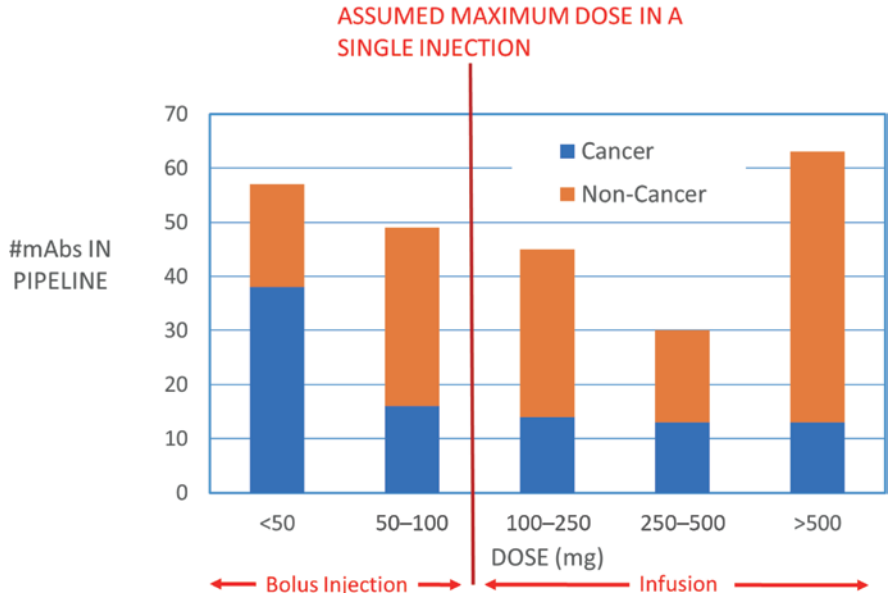

Figure 3: Drug pipeline data from 2008 by dose.

More recently, there has been increasing interest in moving drugs that are currently delivered as an IV infusion to subcutaneous (SC) injection at a local clinic, or even in patients' homes. With this trend in mind, a recent systematic review of clinical-stage and approved IV and SC biopharmaceuticals identified 186 biopharmaceutical candidates that would potentially be suitable for large-volume SC delivery with volumes of >2 mL, representing around 15% of all IV and SC biopharmaceuticals.[1]

It then becomes a question of what the best way is to deliver these doses. On-body devices can deliver a wide range of drug volumes over a variety of delivery times, so could address this need; however, compared with autoinjectors, their usability is less well established and the technology less well proven. To support ease of use, current devices usually have an integrated cannula insertion mechanism and an adhesive means of attaching the device to the body during use.

These features mean that reusability is harder to achieve than for an autoinjector, and electromechanical on-body injectors fall into the single-use/electromechanical category shown in Figure 2 where sustainability is poor and cost per use high.

Arguably, if autoinjectors can deliver higher drug payloads than currently available, they may well compete advantageously with on-body injectors. Given the high level of acceptance of autoinjectors in the market today, it makes sense to consider how much further in terms of dose they are able to go, either by considering higher-injection volumes or considering higher-concentration formulations.

OPTIONS FOR HIGHER-DOSE DELIVERY FROM AUTOINJECTORS

Large-Volume SC Drug Delivery

Schneider *et al* (2023) conducted a systematic review of the literature relating to the high-volume SC bolus injection of therapeutics.[2] They highlighted three key considerations relevant to developing large-volume autoinjectors:

- Injection tolerability
- Suitability for self-administration
- Pharmacokinetic equivalence with existing dosing options.

They concluded that high-volume autoinjectors look to be feasible and that further work should be conducted to support their development.

More recently, Calderwood and Lindner presented data at the 2024 PDA Universe of Pre-Filled Syringes conference that showed that large-volume SC injections are clinically feasible and tolerable, higher-capacity mechanical injection systems are technically feasible and that users are capable of handling the longer injection times required to deliver these doses. They concluded that a 5 mL injection from a mechanical autoinjector using conventional drug formulations appears feasible and such a device is under development.

Permeation enhancers offer further options for high-volume injection. Halozyme (San Diego, CA, US) has developed ENHANZE®, a proprietary enzyme that temporarily degrades glycosaminoglycan hyaluronan in the SC layer, allowing a co-administered drug to flow more freely from the injection site, thereby allowing larger drug volumes to be injected successfully without discomfort or risk of drug leakage from the injection site. Using this approach and a new proprietary high-volume autoinjector, Halozyme was able to demonstrate successful injection of 10 mL of representative biologic product co-formulated with its ENHANZE drug delivery technology in 23 healthy volunteers.[3] The injection time was around 30 seconds and well tolerated with minimal or mild erythema and swelling that resolved after 90 minutes. All but one of the participants indicated that they would be comfortable receiving the injection again.

> "ARGUABLY, IF AUTOINJECTORS CAN DELIVER HIGHER DRUG PAYLOADS THAN CURRENTLY AVAILABLE, THEY MAY WELL COMPETE ADVANTAGEOUSLY WITH ON-BODY INJECTORS."

High-Concentration SC Drug Delivery

The alternative to delivering higher volumes is increasing the concentration of the drug formulation. A key challenge in doing this, especially for biologics, is that molecular interactions can result in poor stability and the viscosity of the formulation increases rapidly with concentration. However, as Figure 4 shows, this is an area of increasing interest and several companies are actively developing formulation technology to address this need, for example:

- Elektrofi (Boston, MA, US) claims that its technology can produce stable and syringeable mAb formulations with concentrations up to 700 mg/mL.[4]
- Xeris (Chicago, IL, US) has reported successful formulation and testing of a large molecule at concentrations in excess of 450 mg/mL using its XeriJect technology.[5]
- Qprotyn (St Petersburg, FL, US) has published results showing reductions in viscosity in a range of mAbs using its HILOPRO formulation compared with the originator at the same concentration.
- Arecor (Chesterford, UK) has developed an aqueous formulation technology, Arestat, that can improve stability and reduce the viscosity of large-molecule formulations.

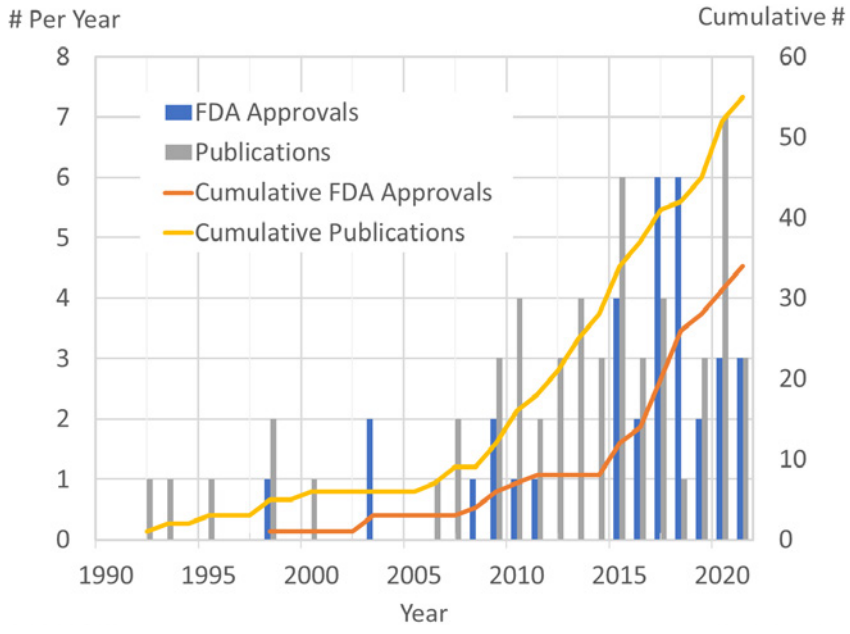

Figure 4: Interest in high-dose formulations from publications and US FDA approval.

"ELECTROMECHANICAL AUTOINJECTORS COULD GENERATE LARGER AND MORE CONTROLLABLE FORCES THAN SPRING-BASED SYSTEMS CAN."

The aim of these approaches is to develop stable, high-concentration formulations that can be delivered using conventional autoinjector technology; however, ultimately, viscosity and the associated longer injection times will limit what can be achieved using a mechanical drive mechanism. That said, as Phillips Medisize has presented in previous publications,[6] electromechanical autoinjectors could generate larger and more controllable forces than spring-based systems can. Figure 5 shows modelled data for a range of drug viscosities and 1 and 2.25 mL injection volumes. The results demonstrate that high-viscosity formulations can be delivered in acceptable times. Furthermore, the superior audible and visual feedback that can be provided by an electronic system may provide better user confidence before and after the injection has taken place.

What is the Dose Limit for Autoinjectors?

If work on developing high-volume and high-concentration SC delivery is successful, then dose ranges that can be delivered using autoinjector technology can be significantly increased through a combination of considering high-volume injection, high-concentration formulations and the possibility of two successive injections. Figure 6 shows some possible approaches that could potentially address nearly 90% of the high-dose drug pipeline, offering a credible alternative to moving towards on-body injector devices.

CONCLUSION

Since 2006, there has been rapid growth in the use of autoinjectors for self-administration of injectable drugs. This approach to drug delivery offers good usability, patient satisfaction and safety. Looking to the future, there is increasing interest in delivering high drug doses by SC injection, rather than IV infusion, with around 15% of the candidate drug pipeline estimated to require injections greater than 2 mL.

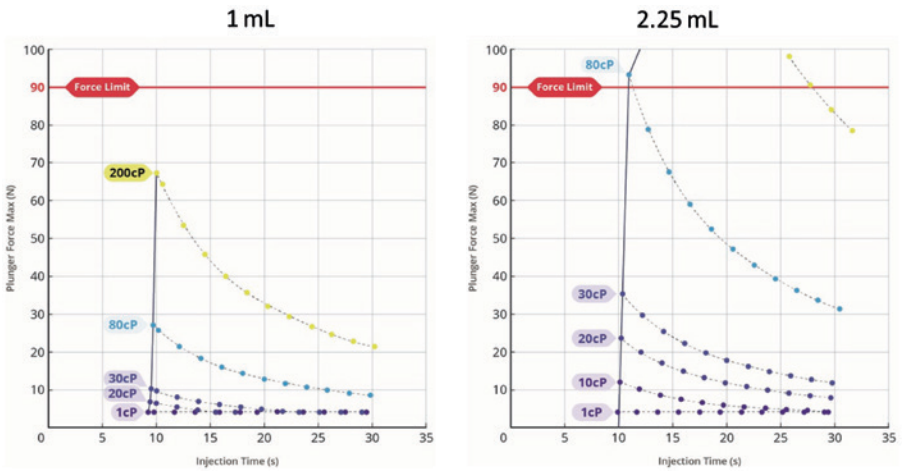

Figure 5: Force-injection time profiles for 1 and 2.25 mL injections. Modelled for an electromechancial autoinjector.

It has been argued that this can only be achieved by increasing drug volumes above those that can be delivered by a handheld autoinjector, which has driven the development of on-body devices that can deliver drug volumes of 3–20 mL in a reasonable timeframe (minutes). However, recent developments in autoinjector and formulation technology have the potential to increase the range of doses that autoinjectors can deliver, potentially making them a viable alternative to on-body injectors. Achieving this requires the development of higher-dose autoinjectors and demonstration of their clinical feasibility.

Both higher concentrations and higher volumes will require longer injection times to deliver the dose. Compared with mechanical devices, electromechanical autoinjectors can offer superior and more flexible delivery performance. Furthermore, the ability to provide clear audible and visual feedback may increase user confidence and reduce use errors associated the longer injection times. In choosing an appropriate delivery device, several factors need to be considered, including:

- The maturity of technology (device, primary packaging and formulation)
- Usability/user preference
- Cost of goods and sustainability.

"COMPARED WITH MECHANICAL DEVICES, ELECTROMECHANICAL AUTOINJECTORS CAN OFFER SUPERIOR AND MORE FLEXIBLE DELIVERY PERFORMANCE."

Approach				Max. Deliverable Dose (mg)
#	Volume	Conc. mg/mL	# of Injections	
7	2 mL	600	Two	2,400
6	10 mL	150	One	1,500
5	5 mL	150	Two	1,500
4	2 mL	600	One	1,200
3	5 mL	150	One	750
2	2 mL	150	Two	600
1	2 mL	150	One	300

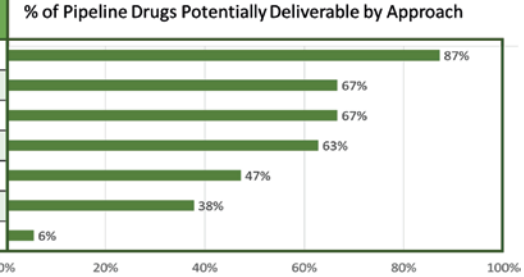

Figure 6: Options for autoinjector delivery of high drug doses.

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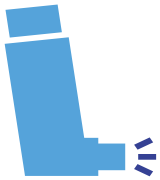
ENGINEERING CONFIDENCE IN DRUG DELIVERY DEVICES

Design, development and manufacturing capabilities for drug delivery systems

Autoinjectors, syringe systems and needle safety devices

Wearable on-body injectors



Inhalation devices

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There is no one size that will fit all, but the strong pedigree of autoinjectors in the market over the past 20 years suggests that they will continue to play a significant role in supporting self-administration of medicines outside a clinical setting.

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Iain Simpson, PhD, is a Director in the Global Pharma Segment Team at Phillips Medisize, where he is part of a global team developing industry-leading solutions and platforms for drug delivery, digital medicine and connected health. Dr Simpson has more than 35 years' experience in multi-disciplinary technology and product development; the last 25 years of which have been in healthcare and increasingly focused on the use of devices and digital technologies to support better therapeutic delivery, create product differentiation, improve patient engagement and better measure clinical outcomes in the real world. He has a degree and PhD in Physics, both from University College London (UK), and an MBE in Technology Management from the Open University. Dr Simpson has published and presented at conferences on drug delivery, digital biomarkers, healthcare technology and technology licensing. He is an associate lecturer at the University of Cambridge (UK) in Bioscience Enterprise.

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Expert View

EFFICIENTLY PRODUCING INJECTABLES IN SMALL BATCHES

Klaus Brinkrode and **Ulrik Keldke** of Syntegon discuss industry challenges in injectable production – and how to efficiently produce small batches of injection devices.

Efficient and rapid scaling is crucial for injectable device production to keep pace with fluctuating demands. This necessity is fuelled by the drive for faster market entry, a surge in new product launches and the "fail fast" mindset, all of which significantly boost the demand for versatile and scalable manufacturing solutions.

The global injectable drug delivery market is growing rapidly, driven by advancements in biologics and personalised medicine. According to a 2023 report by MarketsandMarkets, the injectable drug delivery market is projected to reach $902 billion (£711 billion) by 2028, fuelled by the increasing prevalence of chronic diseases, growth in self-administration practices and demand for biologics (Figure 1). This trend underscores the importance of efficient production systems that can cater to varying demands, from large-scale manufacturing to smaller, specialised batches.

Large automated systems, capable of assembling hundreds of pens and autoinjectors per minute, are often the go-to choice for high-volume production. However, such systems may not be ideal for low-volume production runs, such as those needed for clinical trials, specialised medications or early product launches. This gap has led to an increased focus on manual assembly platforms specifically

Figure 1: Medical devices, such as autoinjectors, safety devices and pens, contribute to beneficial patient outcomes, as they support easy administration and therapy adherence.

INDUSTRY CHALLENGES IN INJECTABLE PRODUCTION

The production of injectable drugs presents unique challenges, including stringent sterility requirements, complex formulation processes and diverse global regulatory standards. The need to maintain sterility throughout production is paramount, with contamination posing significant risks to patient safety and product efficacy. Additionally, the supply chain for critical components such as vials, syringes and stoppers, has been under strain in recent years, requiring manufacturers to adopt adaptive and resilient strategies.

Small-batch assembly solutions must adhere to stringent regulatory requirements and quality control standards, matching the precision and reliability of their high-capacity automated counterparts. Additionally, these systems should blend automated functions with human interaction, enhancing production efficiency while maintaining safety. Key considerations for such systems include ergonomics, usability and adaptability to new device types from various manufacturers. These features are essential for efficient production transitions and overall versatility in addressing evolving market demands.

SEAMLESS SCALABILITY ACROSS PRODUCTION STAGES

Pharmaceutical manufacturers and contract development and manufacturing organisations are increasingly recognising the need for a range of production solutions. These include manual platforms that complement high-volume automated assembly systems, providing the flexibility required to produce small batches efficiently. Starting

"BY INTEGRATING ROBUST DESIGN PRINCIPLES, SMALL-BATCH SYSTEMS CAN FACILITATE EFFICIENT SCALING, ENSURING CONSISTENT QUALITY ACROSS ALL PRODUCTION STAGES."

with small clinical trials and advancing to market introduction, such systems support a streamlined ramp-up to full-scale mass production. This approach enables organisations to meet rapidly changing market demands while maintaining regulatory compliance and product quality.

Scalability is a critical factor, as it ensures a seamless transition from clinical stages to commercial scale without the need for extensive revalidation processes. By integrating robust design principles, small-batch systems can facilitate efficient scaling, ensuring consistent quality across all production stages. Real-world examples illustrate the benefits of scalable solutions.

For example, a European biotech firm leveraged modular assembly platforms during the development of a new biologic drug. The initial set-up allowed for small-batch production for clinical trials, which then seamlessly transitioned to higher-output machines as the product moved to commercialisation, reducing time-to-market by 30%.

ENHANCING FLEXIBILITY FOR DIVERSE APPLICATIONS

Modular design is a cornerstone of effective small-batch production systems. This design approach provides the versatility needed to accommodate new devices from various manufacturers, ensuring consistent assembly across different device sizes and types. By adhering strictly to assembly specifications, including precise measurements of distance, force and resistance, these systems can deliver uniform and repeatable outcomes. This modularity also enables operators to execute quick and error-free changeovers, ensuring smooth and efficient transitions between formats or devices.

The rise of RNA-based therapies has further highlighted the need for flexible production systems. Such therapies often require specialised handling and small-batch production capabilities due to their complexity and cost. Modular systems equipped with advanced monitoring and control technologies can ensure precise assembly and adherence to regulatory standards, even for these cutting-edge applications.

"THE RISE OF RNA-BASED THERAPIES HAS FURTHER HIGHLIGHTED THE NEED FOR FLEXIBLE PRODUCTION SYSTEMS."

OPERATOR-CENTRIC DESIGN AND EASE OF USE

Ease of operation is a vital consideration for any manual assembly platform. Intuitive interfaces, clear operator guidance and ergonomic designs contribute to enhanced accuracy and efficiency. For example, height-adjustable screens, polycarbonate enclosures for visibility and safety, and angled table plates for effortless component feeding and removal are all features that improve operator engagement. These design elements reduce errors and increase processing speed, ensuring that small-batch production remains both efficient and reliable.

Figure 2: Systems that integrate advanced human-machine interfaces and ergonomic features can lead to a 25% reduction in operational errors.

A study by the International Society for Pharmaceutical Engineering in 2022 emphasised the importance of operator-centric design in minimising human error. Systems that integrate advanced human-machine interfaces and ergonomic features can lead to a 25% reduction in operational errors, improving overall equipment effectiveness (OEE) and product quality (Figure 2).

MAINTAINING HIGH EQUIPMENT EFFECTIVENESS

High OEE is another important goal for small-batch production systems. Features such as lifetime lubrication on actuators, drives and gears can minimise maintenance requirements, allowing operators to focus on achieving optimal performance. Additionally, systems designed for easy monitoring and reporting enhance traceability and compliance with industry standards such as CFR 21 Part 11.

Automation in monitoring and reporting is also advancing rapidly. For instance, integrated batch reporting systems that track variables such as force and distance can ensure traceability and facilitate compliance with stringent regulatory

requirements. This capability is particularly crucial for biologics and other high-value injectable products, where consistency and reliability are non-negotiable.

MEETING THE NEEDS OF A DYNAMIC MARKET

As the pharmaceutical industry continues to evolve, the demand for flexible, scalable and efficient production solutions grows increasingly important. Small-batch assembly platforms that integrate advanced design principles and operator-focused features are becoming essential for meeting the dynamic needs of the market. These systems enable rapid changeovers, allowing manufacturers to switch between device formats with minimal downtime, ensuring efficient responses to shifting market demands while maintaining high standards of quality and compliance.

"THE FUTURE OF INJECTABLE DRUG PRODUCTION LIES IN ADAPTABILITY, PRECISION AND CUTTING-EDGE TECHNOLOGY."

The future of injectable drug production lies in adaptability, precision and cutting-edge technology. Innovations such as integrated batch reporting systems offer unparalleled traceability, meeting stringent regulatory standards effortlessly. As the industry moves forward, advancements in artificial intelligence and robotics, including predictive maintenance tools and real-time quality control systems, promise to further enhance the efficiency and reliability of injectable production systems. These developments will continue to empower manufacturers to meet the evolving demands of the injectable drug market, ultimately contributing to improved patient care and more efficient healthcare delivery.

ABOUT THE COMPANY

Syntegon is a packaging solutions provider for the global pharmaceutical and food industries. In the pharma sector, the company offers solutions for the processing, filling, inspection and packaging of liquid and solid pharmaceuticals. Syntegon has a comprehensive service portfolio that covers the entire machine lifecycle from spare parts management to digital line optimisation.

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THE ROLE OF METAL DEEP-DRAWN PARTS IN MEDICAL DEVICES FOR DRUG DELIVERY

STÜKEN MEDICAL

Dennis Gossmann of **STÜKEN MEDICAL** discusses the benefits of using deep-drawn metal components in drug delivery devices and how STÜKEN MEDICAL, as an established expert in this field, can be an ideal partner for manufacturing and supplying these parts.

In the field of drug delivery, the choice of materials and manufacturing processes plays a critical role in ensuring device reliability, safety and performance. Deep-drawn metal components, particularly those made from stainless steel and titanium, have become indispensable in this respect due to their exceptional biocompatibility, strength and corrosion resistance. These properties are crucial for components that must withstand contact with bodily fluids, resist mechanical stress and endure sterilisation processes – typical requirements for drug delivery systems such as autoinjectors, inhalers and insulin pumps.

The deep drawing process is ideal for manufacturing metal components for the medical device industry, as it enables the production of parts with highly precise tolerances and complex geometries. This precision ensures that critical

> "THE DEEP DRAWING PROCESS IS IDEAL FOR MANUFACTURING METAL COMPONENTS FOR THE MEDICAL DEVICE INDUSTRY, AS IT ENABLES THE PRODUCTION OF PARTS WITH HIGHLY PRECISE TOLERANCES AND COMPLEX GEOMETRIES."

"AS A LEADING PARTNER IN THIS FIELD, STÜKEN MEDICAL IS RENOWNED NOT ONLY FOR ITS EXPERTISE IN MANUFACTURING DEEP-DRAWN METAL COMPONENTS FOR THE MEDICAL INDUSTRY BUT ALSO FOR OFFERING A COMPREHENSIVE RANGE OF VALUE-ADDED SERVICES."

Figure 1: STÜKEN MEDICAL ensures required cleanliness with validated cleaning processes and Class 7 cleanrooms.

components such as canisters, housings and drug reservoirs maintain consistent performance, which is essential for the accurate dosing and delivery of medication. Additionally, the seamless design provided by deep drawing eliminates potential contamination points, offering enhanced reliability in devices where any failure could compromise patient safety.

Moreover, the deep drawing process is highly scalable and cost-efficient. Once the tooling is in place, manufacturers can produce large volumes of parts with minimal material waste, making it a practical choice for mass production. This scalability ensures that even intricate parts remain cost effective over time, which is vital in the competitive landscape of the drug delivery market.

As a leading partner in this field, STÜKEN MEDICAL is renowned not only for its expertise in manufacturing deep-drawn metal components for the medical industry but also for offering a comprehensive range of value-added services. These include passivation according to industry standards, ensuring optimal corrosion resistance, as well as plating and laser welding for customised component finishes and functionality. STÜKEN MEDICAL also provides packaging in ISO Class 7 cleanrooms (Figure 1), which is essential for maintaining the cleanliness of parts used in sensitive drug delivery devices.

Additionally, STÜKEN MEDICAL is ISO 13485 certified, affirming its commitment to meeting the highest quality and regulatory standards in medical device manufacturing (Figure 2). The company's full suite of capabilities – from deep drawing to post-processing and assembly – makes

Figure 2: STÜKEN MEDICAL operates Class 7 cleanrooms in accordance with DIN EN ISO 14644 and EU GMP Class C guidelines.

it a one-stop partner for producing not just components but complete, ready-to-use solutions tailored to the stringent requirements of drug delivery systems.

STÜKEN MEDICAL's innovative production techniques and state-of-the-art facilities enable the manufacturing of complex, custom-designed components tailored to meet the specific needs of drug delivery systems (Figures 3 & 4). Its commitment to quality, coupled with its capacity for cost-efficient, high-volume production, positions STÜKEN MEDICAL as a trusted partner for medical device manufacturers worldwide. On top of this, STÜKEN MEDICAL has a dedicated team ensuring that the focus is always on the customer's requirements – for example, with comprehensive customer service and innovative technical support in the development phase.

In conclusion, deep-drawn metal components offer unmatched advantages for drug delivery devices. With their superior material properties and the precision offered by the deep-drawing process, these parts ensure device safety and performance. STÜKEN MEDICAL's expertise, coupled with its wide range of value-added services and ISO 13485 certification, makes it the go-to partner for manufacturers looking to create reliable and effective drug delivery systems.

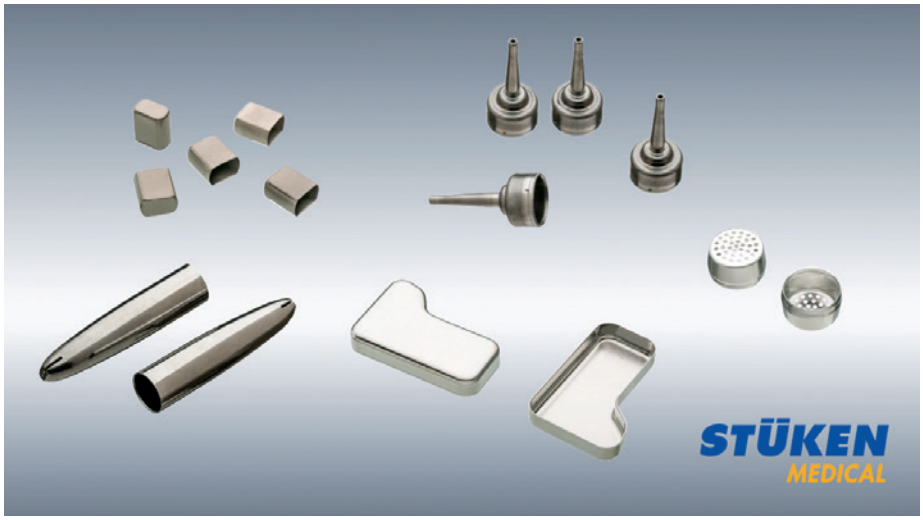

Figure 3: STÜKEN MEDICAL delivers a wide range of product sizes and geometries.

Figure 4: STÜKEN MEDICAL produces deep-drawn components with dimensions <1–92 mm in length.

"STÜKEN MEDICAL HAS A DEDICATED TEAM ENSURING THAT THE FOCUS IS ALWAYS ON THE CUSTOMER'S REQUIREMENTS – FOR EXAMPLE, WITH COMPREHENSIVE CUSTOMER SERVICE AND INNOVATIVE TECHNICAL SUPPORT IN THE DEVELOPMENT PHASE."

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Expert View

CUSTOM INTEGRATED CIRCUITS ENABLING ADVANCEMENTS IN IMPLANTABLE DRUG DELIVERY SYSTEMS

Asheesh Divetia of Cirtec Medical looks at how custom electronics are advancing implantable drug delivery systems – with precise drug administration, seamless connectivity to other devices and real-time monitoring of drug levels and patient responses. These device innovations are driving key improvements in therapeutic efficiency and patient outcomes.

"IMPLANTABLE DRUG DELIVERY DEVICES ARE PROVING INVALUABLE IN PROVIDING A WIDE RANGE OF MEDICAL THERAPIES, INCLUDING PAIN RELIEF AND CHRONIC DISEASE MANAGEMENT."

The advancement of implantable drug delivery systems is transforming medication administration, driven by breakthroughs in the miniaturisation of electronics and sensor technology and the growing need for tailored, long-term therapeutic solutions. Unlike conventional drug delivery methods, these systems emphasise precision, personalisation and automation, focusing on delivering the right dose at the right time and effective drug management. Implantable drug delivery systems, engineered for long-term operation within the body, use advanced technologies to ensure consistent and controlled dosing that enhances treatment accuracy and reduces the need for frequent interventions.

Customised electronics and integrated circuits (ICs) play a key role in this technology by enabling miniaturisation, improving power efficiencies and enhancing the functionality of these systems. Recent advancements in sensing and wireless technologies have also enabled real-time monitoring, improved data collection and seamless communication of this data to healthcare providers. Implantable drug delivery devices are proving invaluable in providing a wide range of medical therapies, including pain relief and chronic disease management.

THE EVOLUTION OF IMPLANTABLE DRUG DELIVERY SYSTEMS

The healthcare industry is increasingly recognising the need for more targeted, personalised and automated drug delivery systems. Conventional drug delivery methods, such as oral, topical or injectable delivery, generally deliver drugs in fixed doses without continuous monitoring or control, which can lead to undesired variability in drug levels in the body, wastage of the drug due to systemic administration and unnecessary side effects.

The development of implantable medical devices, such as pacemakers and neuromodulation systems, has paved the way for innovation in drug delivery. Recent advancements in engineering and manufacturing methods have made these devices more affordable and accessible, while they have also become more standardised and widely adopted, facilitating further developments in related fields, including implantable drug delivery. These manufacturing technologies, originally developed for other specific applications, are now being repurposed and customised for broader therapeutic uses.

Among the most transformative advances in implantable medical devices over the last two decades has been the integration of wireless communication within hermetically sealed packaging. Wireless components embedded in implanted electronics enable communication between the implanted device and external monitoring systems, allowing for easier data retention and retrieval, as well as higher bandwidth for data transfer. This functionality enables healthcare providers to monitor patients remotely, making it easier to track long term treatment efficacy and make necessary adjustments without requiring in-person visits.

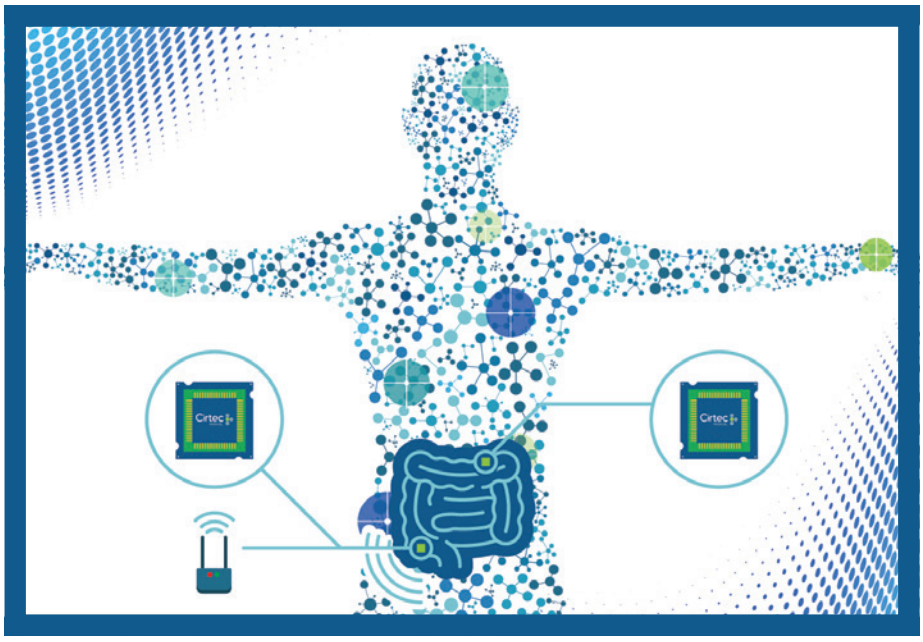

Figure 1: Advanced sensing chips enable precise health monitoring and treatment.

"WITH ADVANCEMENTS IN IC TECHNOLOGY ENABLING GREATER PRECISION, MINIATURISATION AND POWER OPTIMISATION, IMPLANTABLE DELIVERY SYSTEMS ARE REACHING NEW LEVELS OF FUNCTIONALITY AND PERFORMANCE."

CUSTOM IC TECHNOLOGY ENHANCES CLOSED-LOOP DRUG DELIVERY

With advancements in IC technology enabling greater precision, miniaturisation and power optimisation, implantable delivery systems are reaching new levels of functionality and performance. Custom ICs also enable the integration of various sensors to create a closed-loop system between the sensors and the implantable device. These miniaturised sensors allow real-time data collection on key physiological parameters, such as blood glucose levels, oxygen levels, blood pressure, temperature and hormone levels. These data can then be processed within the implanted device and directed to automatically adjust medication dosage in response to certain physiological changes and tailor it to individual patient needs (Figure 1).

For example, in an implantable insulin delivery system used for diabetes management, implanted sensors monitor blood glucose levels and relay that information to the insulin pump, which can then adjust the dosage as needed. This ensures that patients receive accurate, timely treatment without requiring constant supervision.

THE IMPACT OF SMART DRUG DELIVERY ON PATIENT OUTCOMES

Custom IC technology and miniaturised electronics play a pivotal role in advancing smart drug delivery systems that adapt to specific patient needs – a cornerstone of personalised healthcare. By integrating custom electronics that are engineered for high accuracy, low power consumption, wireless communication and extended durability, these systems can offer dependable, long-term performance within the body. This enables automated, fine-tuned administration of medications at optimised therapeutic levels, tailored specifically to individual needs, and significantly reduce the need for human intervention, thereby minimising the risk of dosage errors and enhancing overall patient safety.

Furthermore, the surging demand for smart drug delivery systems is prompting more manufacturers to develop and innovate in this space, driving competition and accelerating advancements in device technology. Such smart systems can extend their relevance across numerous healthcare applications, from managing chronic conditions to delivering highly targeted therapies. This versatility is instrumental in addressing the varied demands of personalised medicine and equipping healthcare providers with the tools to tailor treatment plans effectively. Implantable drug delivery systems can improve patient adherence, enhance treatment efficacy, reduce adverse side effects and contribute to lowering healthcare costs.

LOOKING AHEAD: ENHANCED DRUG DELIVERY

Looking ahead, advancements in custom electronics are set to drive more efficient, affordable and accessible monitoring and control capabilities, especially in healthcare. One promising application is implantable contraceptive devices, providing long-term birth control solutions in regions with limited access to conventional contraceptives. By reducing the cost and complexity of developing custom drug delivery devices, IC technology can help to make personalised medicine more globally attainable.

"ADVANCEMENTS IN CUSTOM ELECTRONICS ARE SET TO DRIVE MORE EFFICIENT, AFFORDABLE AND ACCESSIBLE MONITORING AND CONTROL CAPABILITIES."

Today, the development cycle for custom IC solutions is faster and more cost-effective than before. Manufacturers can create compact, sophisticated systems on a single chip, facilitating new implantable drug delivery devices. This makes specialised devices faster and cheaper to produce, broadening accessibility to diverse patient populations.

Custom ICs are paving the way for the future of implantable drug delivery, supporting precise and personalised administration. This technology is driving innovation as manufacturers respond to the growing demand for custom, automated healthcare solutions, intensifying competition and accelerating advancements. The road ahead holds immense potential, with IC-driven solutions continuing to break down barriers – offering better, more accessible healthcare for all.

Dr Asheesh Divetia

Asheesh Divetia, PhD, General Manager at Cirtec Medical, has over 20 years of experience in medical devices and a proven track record of driving strategic growth, fostering innovation and delivering high-quality engineering and manufacturing solutions. He holds a PhD in Biomedical Engineering from the University of California Irvine (US) and a BS in Electrical Engineering from the Indian Institute of Technology.

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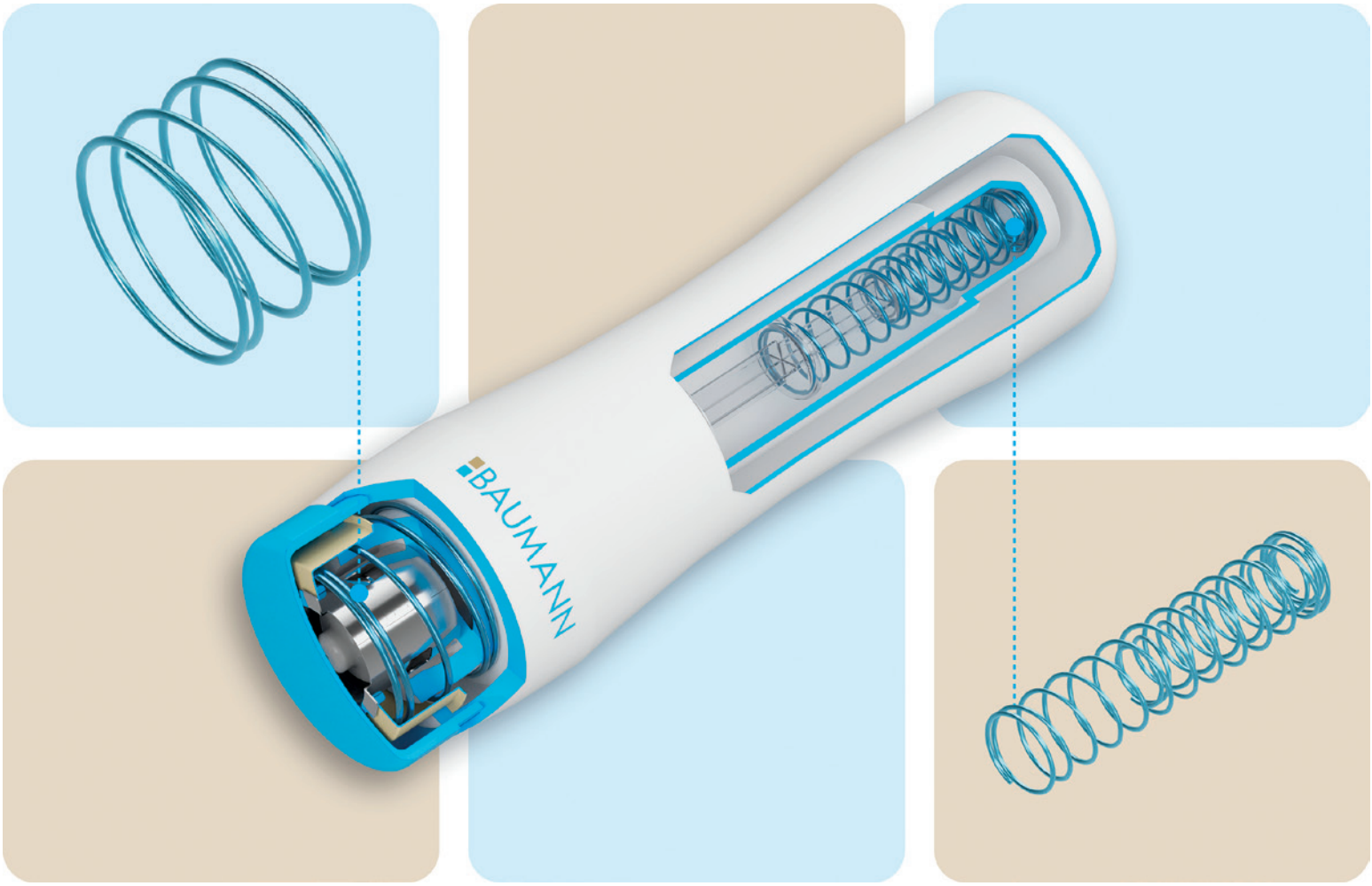
ABOUT THE COMPANY

Cirtec helps customers bring therapies to market quickly and cost effectively, from start-ups to Class II or III medical device manufacturers. The company offers services at every stage of the product development cycle, including design/development, pilot and clinical build, manufacturing and finished device assembly. Cirtec has a 30-year track record of developing medical devices fabricated under 21 CFR 820 and ISO 13485 quality standards. Cirtec helps customers bring products from concept to commercialisation on time, on budget and as seamlessly as possible.



UNLOCK VALUE: KEY COST DRIVERS IN SPRING AND STAMPING DESIGN

BAUMANN MEDICAL

Rolando Abaroa Martinez and **David Pircher** of **BAUMANN MEDICAL** highlight how a metal parts supplier can help to optimise costs – not only for springs and stampings but also in later production stages of a medical device. With a focus on the design phase, they emphasise that not only the costs associated with the metal product but also the total costs can be managed effectively with the right support from experts.

Medical device design is a complex and highly regulated field. BAUMANN MEDICAL's value chain begins with the initial customer contact, where foundational ideas and design concepts are discussed collaboratively. This progresses to decisions regarding which types of springs and materials are suitable, followed by process design and series production. The goal is to enhance value creation sustainably.

Partnering with experienced designers can help involved parties to not only develop a successful product but also manage total costs effectively. For example, a spring that contributes to high overall equipment effectiveness (OEE) on the assembly line without issues may result in a much better total cost balance, even if its initial product price is slightly higher.

BAUMANN MEDICAL aims to collaborate, where feasible, in the earliest possible development phase of a new device. It is scientifically proven – using the analogy of project management – that good planning at the beginning of a project can lead not only to success but also to significant cost savings in the development process.

This applies to most situations, whether a new platform is being developed by a design-consulting company, a specific device is being created with a pharma company or replacement products for existing devices are in development. In every design project, everything begins with thorough preparation: the clearer the strategy is at the outset, the smoother implementation will be.

BAUMANN MEDICAL frequently encounters two scenarios: 1) customers either present the company with a finished design for a new product or seek to replicate an existing one or 2) they approach the company at the initial stages of the development process for expert support. These situations significantly impact product costs. In the first scenario, opportunities for optimisation are limited, whereas the second offers substantial potential for cost reductions – sometimes up to 70% compared with the original concepts.

The measures for this are simple but not always clear to everyone involved. Selected focus points include:

- **Risk minimisation:** thorough planning helps to identify potential risks early and develop strategies to minimise them. This prevents problems that could later become costly
- **Better time and cost control**: by planning early, the project can be scheduled realistically, avoiding time pressure and unforeseen costs
- **Early identification of dependencies**: during the planning phase, dependencies and bottlenecks between tasks or teams can be identified and accounted for before they hinder project progress.

WHAT MAKES AN EXPERT?

BAUMANN MEDICAL supports customers in optimally developing their components and associated production processes, knowing that no two springs are exactly the same. Historically, the company's experience is reflected in successful collaborations with medical device and pharmaceutical companies over more than two decades, working with customers with low- to high-volume devices. Additionally, going further back, for more than 135 years, the company's springs and stampings have been increasing the health, comfort, efficiency and safety of a considerable number of people.

BAUMANN MEDICAL's engineering excellence and comprehensive process coverage are what truly set it apart. The company's team of engineers works closely with clients to develop advanced technological solutions that improve lives (Figure 1). Understanding that each project is unique, BAUMANN MEDICAL adopts a bespoke approach, tailoring its services to meet the specific needs of every client. From the initial concept to serial production, the team meticulously manages and optimises every step of the process. This dedication to customisation and excellence drives the company's innovation and keeps it at the forefront of the medical device industry.

Figure 1: Experts at work.

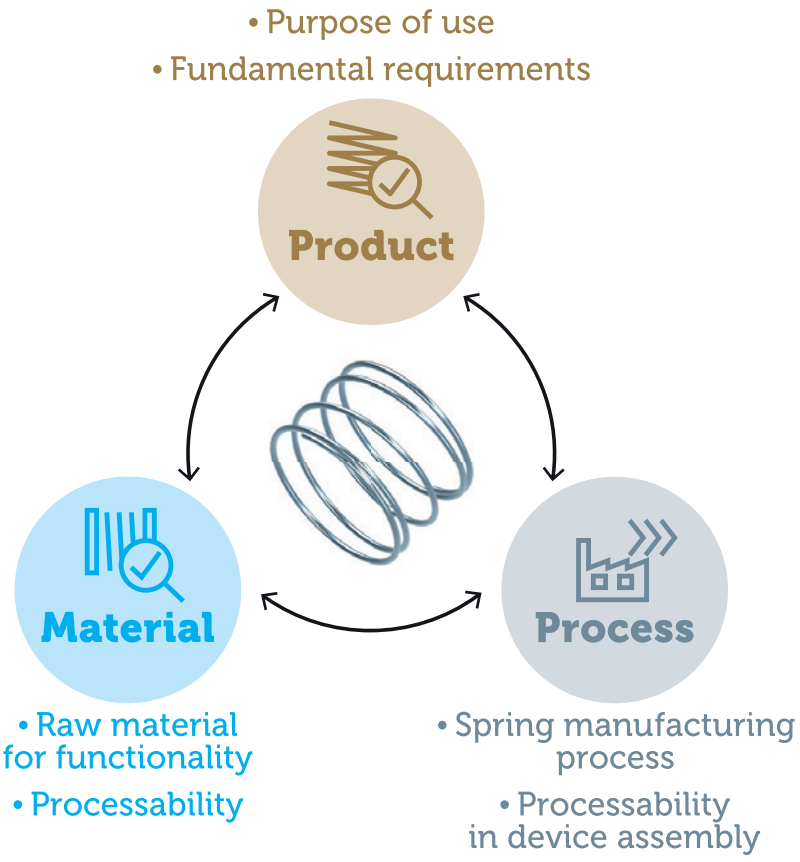


Figure 2: High-level trigger points for a cost-efficient design.

"THE CHOICE OF RAW MATERIAL DEPENDS ON FACTORS SUCH AS GEOMETRIC BOUNDARY CONDITIONS, CORROSION RESISTANCE, RELAXATION AND THE NUMBER OF USE CYCLES."

DESIGN FUNDAMENTALS

One of BAUMANN MEDICAL's areas of expertise is advising and supporting clients during the design iterations between spring/stamping design and the development of medical devices. To achieve the best results, reduce risks and identify dependencies, this process ideally occurs as a collaboration between the device designers and the spring/stamping designers.

In addition to many other important factors in the development of springs and stamped parts for medical devices, this article focuses on three main aspects of the design process: raw materials, product design and process design. Each of these areas presents opportunities to identify cost advantages, which are explored further (Figure 2).

RAW MATERIALS

All types of springs and stamped components can be produced using either stainless or carbon steel. The choice of raw material depends on factors such as geometric boundary conditions, corrosion resistance, relaxation and the number of use cycles. The cross-sectional shape is determined by the spring type or other required properties. Generally, it can be assumed that over 50% of the volume of springs and stamped parts in medical devices could be made from carbon steel.

However, in practice, stainless steel is often specified due to a general consensus that medical devices and equipment should be made from this material, primarily because of cleanliness concerns. When specifying materials, several factors must be considered, including exposure to liquids or humidity, storage conditions and duration, shininess and contact with other materials or patients. Nevertheless, the main driver for material selection remains the relaxation of the spring (Figure 3).

For an approximate idea of potential cost savings – depending on the volume purchased – consider that a basic soap-coated carbon steel costs around €3.5 (£2.80) per kg, compared with stainless steel at €7 per kg (lowest price found on October 9, 2024). In this context, it is useful to critically evaluate and challenge the choice of raw material to achieve cost efficiency. The following example of spring relaxation for carbon steel demonstrates the implications.

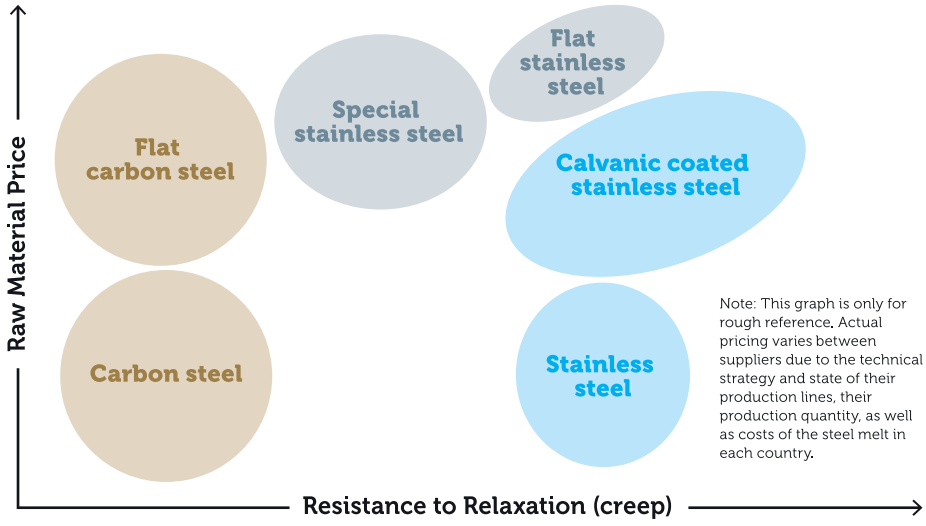


Figure 3: The main driver for material selection remains the relaxation of the spring.

Spring relaxation is the phenomenon in which a spring, after being deformed and held in that state for an extended period (shelf life), loses some of its stored energy and, consequently, its ability to return to its original shape or length. Due to its inherent material properties, carbon steel has a higher relaxation rate compared with stainless steel. Factors such as temperature, duration of load and initial stress state influence the extent of a spring's relaxation.

The implications for performance and, ultimately, costs are as follows:

- **Consistency:** if a spring relaxes too much, it may not perform as expected in its application, leading to reduced load-bearing capacity or changes in spring rate
- **Design considerations:** engineers must account for potential relaxation when designing springs for specific applications to ensure that they maintain their performance over time.

In summary, relaxation in springs refers to a gradual loss of tension, which can affect the performance and reliability of the final product. Understanding this phenomenon is crucial for designers and engineers to ensure the long-term functionality of springs in their intended applications.

PRODUCT DESIGN

Beyond material selection, the spring and stamping type and design are critical cost factors. Key questions include aspects such as stiffness-to-weight ratio, natural geometric variations during serial production and performance during energy release. Designs often have oversized springs, which not only increase costs but also result in bulky products that

"FACTORS SUCH AS TEMPERATURE, DURATION OF LOAD AND INITIAL STRESS STATE INFLUENCE THE EXTENT OF A SPRING'S RELAXATION."

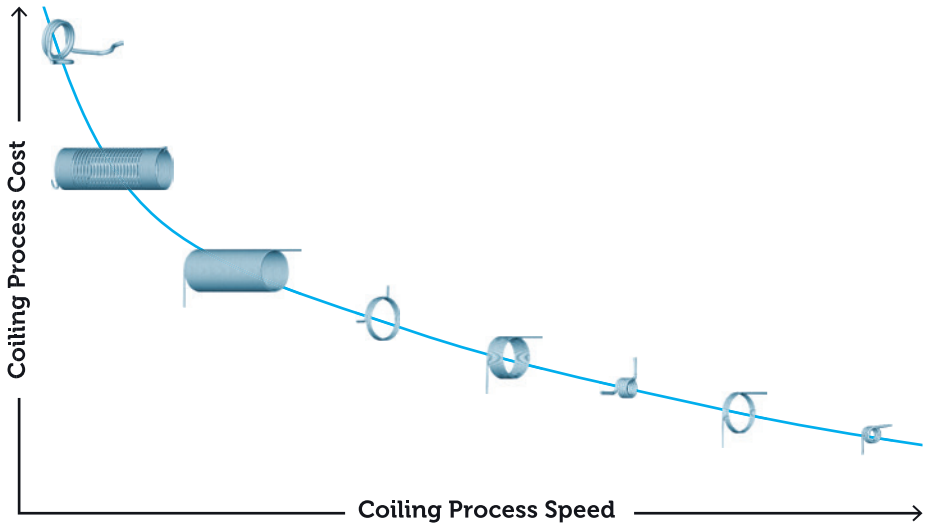


Figure 4: Visualisation of the dependency of coiling costs versus production speed.

complicate transport and raise sustainability concerns. By refining these elements, BAUMANN MEDICAL helps to optimise both performance and cost efficiency.

Using a torsion spring as an example of the key points that indicate an optimum design for minimum coiling costs, torsion springs featuring a small coil ratio, few coils, tangential legs and closed coils are the most cost effective in terms of coiling. However, several factors affect production speed (Figure 4):

- **Wire length:** longer wire results in slower production speeds
- **Leg complexity:** more intricate leg designs reduce manufacturing speed
- **Spring body complexity:** a more complex spring body also contributes to slower production
- **Radial stiffness:** lower radial stiffness in the coils slows down production
- **Coil ratio and pitch:** a large coil ratio combined with a small pitch ratio results in lower radial stiffness, further affecting speed
- **Spring length:** the longer the spring, the lower the production speed.

The following are real-life product design examples:

- **Detangling behaviour:** spring geometry may lead to the tangling of springs with different modes and depth. The degree of detangling success has a direct impact on the assembly line OEE.
- **Deformation behaviour during assembly:** a certain geometry can create challenges during subassembly of the spring. Geometry-related non-linearities during the loading operation in the assembly process may lead to lower assembly machinery performance, as the spring being deflected must be controlled.

PROCESS DESIGN

The journey from early-stage product development to industrialisation is a crucial process. BAUMANN MEDICAL excels in creating and designing unique solutions from scratch or enhancing the performance of existing parts to improve medical device performance and total costs. Its product engineers, in co-ordination with the development team, create production processes that meet client needs, ensuring the most efficient process.

It is useful to critically reflect on a few points where the basic design influences the process design. Cost drivers in spring production offer a different degree of automation. Or vice versa – the more complex a product, the more process steps and the higher the costs.

Key factors in spring design that ensure an efficient production process include material selection, precise tolerances, and a design that reduces complexity and machining effort. However, customer requirements must not be overlooked. For example, adding inactive coils at the ends of springs increases material consumption and costs but, at the same time, it simplifies handling for the customer during spring feeding and eases BAUMANN MEDICAL's production process. Another example involves spring wire: stainless wire with drawing soap has lower costs and is more readily available than polished wire. For the manufacturing process, "impure" wire is more economical and easier to handle in coiling; however, it can cause soap residue build-up on customers' assembly lines, leading to production downtime.

Therefore, it is crucial to have a detailed conversation with the customer on these issues early in the process to reach a consensus between both parties and outline mutual dependencies. This ensures that the spring manufacturing process is as efficient as possible without neglecting customer requirements (Figure 5).

BAUMANN MEDICAL's extensive expertise in process, machine building, process optimisation, manufacturing and quality management ensures a seamless and precise shift from prototypes up to triple-digit production. With global manufacturing capabilities across the North American Free Trade Agreement region, Europe and Asia, the company can support projects locally while providing the same high standards at all locations.

CONCLUSION

Spring production involves various cost drivers, each offering different levels of automation. As the complexity of the requirements increases, so does the production process. The key factors influencing spring production costs include:

- **Wire costs:** the cost of the wire depends on several factors, including the type of alloy used, the shape of the cross-section, and the surface quality and coating of the wire. Smart material selection can save up to 50% of pure material costs.
- **Product design and geometric factors:** these influence both the feasibility of production and the speed at which springs can be produced. An integral and well-thought-out design of the springs can save more than 30% of total costs.
- **Process costs:** these are driven by the type of spring, process complexity, geometric factors and specific features, such as cleanliness, surface conditions or the envelope, hooks and legs. With a customised and streamlined process, it is possible to achieve double-digit percentage savings in total costs.

By understanding these factors, manufacturers can better manage production efficiency, costs and risk mitigations.

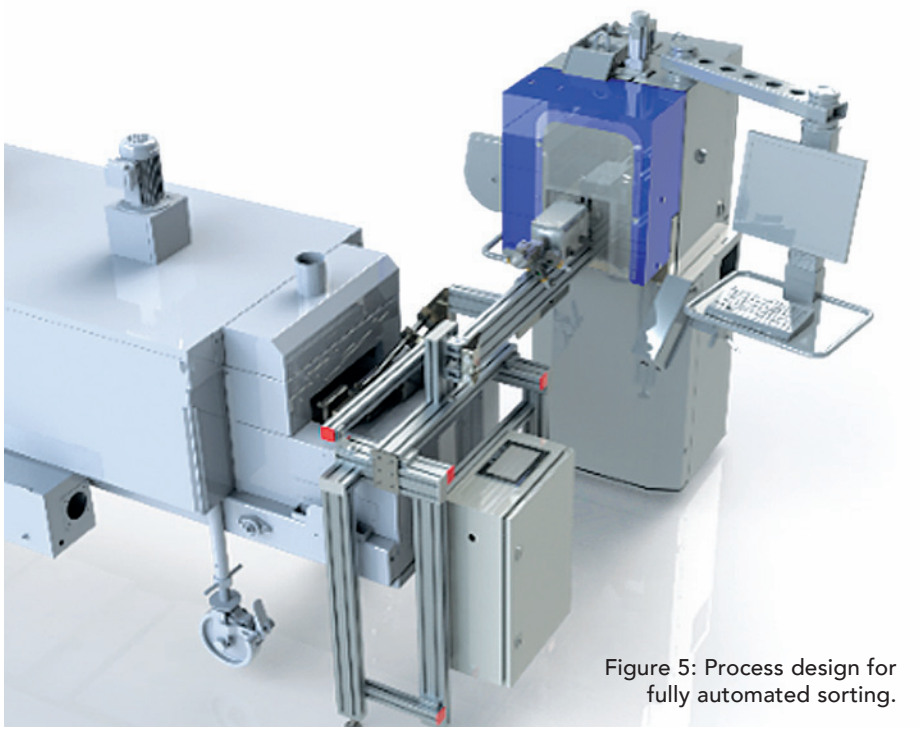


Figure 5: Process design for fully automated sorting.

Rolando Abaroa Martinez

Rolando Abaroa Martinez, Global Head of Product Design at BAUMANN MEDICAL, is a specialist in spring design with more than two decades of experience. He has a BSc in Mechanical Engineering and has gained practical experience in various positions within the BAUMANN Group. Compression, extension and torsion springs are his passion, and he has successfully worked with BAUMANN MEDICAL's stakeholders for over 10 years.

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David Pircher is Global Head of Business Development at BAUMANN MEDICAL. He holds an EMBA, an MAS in Business Consulting and an Engineering degree. As a member of the executive medical board, he is responsible for strategy, marketing and business intelligence. Mr Pircher has over 25 years of professional experience, including more than 15 years in management. He has worked in the medical devices sector for the past 10 years. Throughout his career, he has successfully led several significant strategic projects in a global context.

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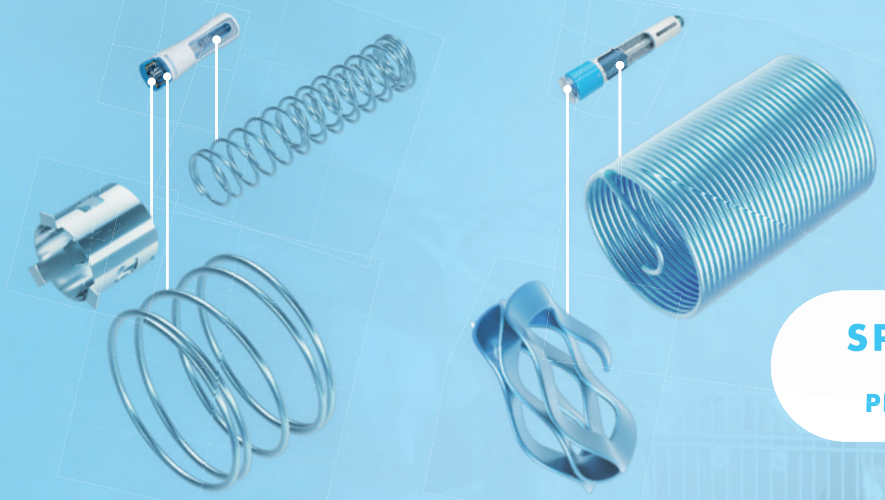

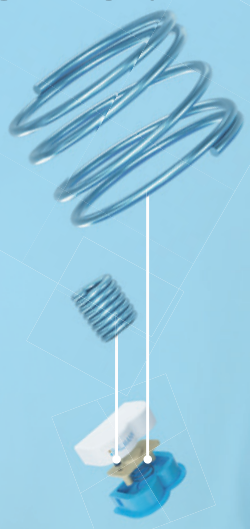

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TUB & NEST – PRECISION AND EFFICIENCY IN DRUG DELIVERY

FISCHER
LIFE SCIENCE. PACKAGING SOLUTIONS.

Ivana Thiesson at **Fischer Söhne** and **Jörg Sander** at **sam|sander applied marketing** discuss the benefits of Fischer Söhne's "Tub & Nest" format for packaging prefilled syringes, including design flexibility and precise cleanroom manufacturing.

Fischer Söhne, a Swiss plastics specialist with over 100 years of experience, is widely known for its innovative solutions in the life science market. The company's "Tub & Nest" system is a prime example of its commitment to precision and efficiency in drug delivery. Designed to address the growing demand for prefilled syringes (PFSs), Tub & Nest offers a streamlined approach to aseptic handling, ensuring the sterility and integrity of injectable therapies. According to Iwan Tresch, CEO of Fischer Söhne, "Fischer Söhne's rebranding marks a new era for our company. With over 100 years of expertise, we're focused on the future of life sciences and committed to delivering innovative solutions for the life science industry."

THE RISE OF PREFILLED SYRINGES

PFSs are rapidly gaining popularity due to their advantages for precise dosing, ease of use and reduced risk of contamination. However, these advancements require sophisticated packaging solutions to maintain product integrity throughout the supply chain (Figure 1). Fischer Söhne's Tub & Nest system directly addresses these challenges.

Tub & Nest: A Comprehensive Solution

The Tub & Nest system simplifies the aseptic handling of PFSs while ensuring their sterility and integrity. By offering a packaging system that seamlessly integrates into automated processes, Fischer Söhne supports the industry's move toward more efficient injectable solutions.

Figure 1: Tubs and nests for medical syringes.

Figure 2: Cleanroom production facility.

Figure 3: Standard Fischer Söhne Tub & Nest configuration.

TECHNICAL CAPABILITIES AND CLEANROOM STANDARDS

Fischer Söhne's state-of-the-art cleanroom production facilities are ISO 13485 certified, ensuring top-tier quality (Figure 2). Fischer Söhne operates injection moulding machines with clamping forces of up to 500 tons, enabling efficient multi-cavity moulding and manufacturing of both standard and customised packaging solutions. This versatility allows for handling complex projects, such as syringe plungers ranging from 0.5–50 mL, and both customised and standard Tub & Nest configurations (Figure 3).

Unmatched Precision and Cleanroom Manufacturing

Fischer Söhne's Tub & Nest products are manufactured under strict GMP Class C (ISO 7) cleanroom conditions (Figure 4), ensuring the highest standards of cleanliness and reliability. Their low-particle, scratch-free and unbreakable design provides exceptional protection for sensitive pharmaceutical products, such as PFSs. In the initial phase, the tubs and nests are equipped with glass or polymer syringes in a highly automated process, then sealed and sterilised. Once sterilised, these filled tubs and nests are delivered to pharmaceutical companies or their contract fillers.

When delivered to their destination, the tubs and nests can be opened under sterile conditions and the syringes filled with the intended drugs. These packaging solutions are directly integrated into customer pick-and-place machines, allowing for sterile filling and aseptic packaging processes. To further enhance quality, Fischer Söhne uses advanced polymer materials like polypropylene and polystyrene, which are highly durable and compatible with various sterilisation methods.

EXCELLENT DIMENSIONAL STABILITY

The Tub & Nest system reduces the risk of glass breakage, particle contamination and scratch marks during production. This precision facilitates smoother operations, enhances the processing speed of automated systems and maximises overall efficiency and output. The system's innovative design ensures that

syringes remain securely in place during transportation, preventing damage or misalignment. Additionally, Fischer Söhne collaborates closely with its clients to optimise the dimensional stability of its Tub & Nest products for specific syringe formats. This ensures seamless integration into existing processes and equipment, minimising downtime and operational costs.

Flexible and Certified Solutions

Available as standard items with short delivery times, Fischer Söhne's Tub & Nest products are compatible with common filling and loading systems, making them versatile and cost-effective.

Figure 4: Nest during cleanroom production.

Certified according to ISO 13485 and designed in adherence to ISO 11040-7 standards, these solutions ensure unparalleled quality and reliability while complying with GMP requirements. According to Iwan Tresch, "Our cleanroom production runs around the clock. That's why we are always ready to deliver, for smaller and also for very large quantities."

PARTNERING FOR SUCCESS

Fischer Söhne's customer-centric approach goes beyond delivering high-quality products. The company's technical team works closely with clients to provide tailored solutions, from initial concept development to production and delivery. Offering both standard Tub & Nest systems with short delivery times and the ability to develop customer-specific nests, Fischer Söhne ensures flexible solutions that meet individual requirements.

The company's expertise extends to designing entire systems, including trays and lids, delivering versatile, cost-effective products that are compatible with common filling and loading systems. By leveraging decades of experience and a deep understanding of industry trends, Fischer Söhne empowers its partners to stay ahead in a competitive market.

CONCLUSION

With its Tub & Nest solutions, Fischer Söhne demonstrates its commitment to innovation, quality and sustainability in the pharmaceutical packaging sector. As the market for PFSs and injection devices continues to grow, the company remains a trusted partner for pharmaceutical manufacturers worldwide. Fischer Söhne's unique combination of advanced technology, customer focus and environmental responsibility positions it as a leader in life science packaging solutions.

Ivana Thiesson

Ivana Thiesson is Marketing Manager for Fischer Söhne and a proactive and adaptable marketing professional. Having started her career with Fischer Söhne as an apprentice, she has contributed to the company in various roles for more than 12 years. Since rejoining the company in 2019, Ivana has demonstrated exceptional organisational skills, a structured work approach and a talent for fostering collaboration in dynamic environments. Her commitment to delivering impactful results and her ability to adapt to evolving market demands make her an integral part of Fischer Söhne's continued success.

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Jörg Sander is an experienced management consultant with over 26 years of expertise in advising companies on growth strategies, marketing and sales optimisation. He has a proven track record of helping businesses develop and implement customer-centric strategies, leveraging marketing technologies and building high-performing teams. His clients include Fischer Söhne, AstraZeneca and Siemens Healthineers.

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2025 Pharma Event Calendar

PharmaED RESOURCES, INC

Cleaning Validation Summit 2025
March 10-11, La Jolla, CA

Extractables and Leachables 2025
April 23-24, Philadelphia, PA

Combination Products Summit 2025
May 12-13, Philadelphia, PA

Process Validation & Data Integrity Summit 2025
June 10-11, Philadelphia, PA

Microneedle & Transdermal Delivery Forum 2025
September 10-11, Philadelphia, PA

Connected Devices & Digital Health
September 16-17, Philadelphia, PA

Aseptic Processing Summit 2025
October 8-9, Philadelphia, PA

Extractables & Leachables West 2025
November 5-6, La Jolla, CA

Pre-filled Syringes & Injection Devices 2025
December 9-10, La Jolla, CA

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Expert View

FROM PLATFORM TO PRODUCT: ACCELERATING TIME-TO-MARKET FOR PLATFORM TECHNOLOGIES

Fran Pencliffe of Cambridge Design Partnership explores the benefits of platform devices for parenteral delivery and outlines the challenges, risks and best practices when bringing a combination product to market in this way.

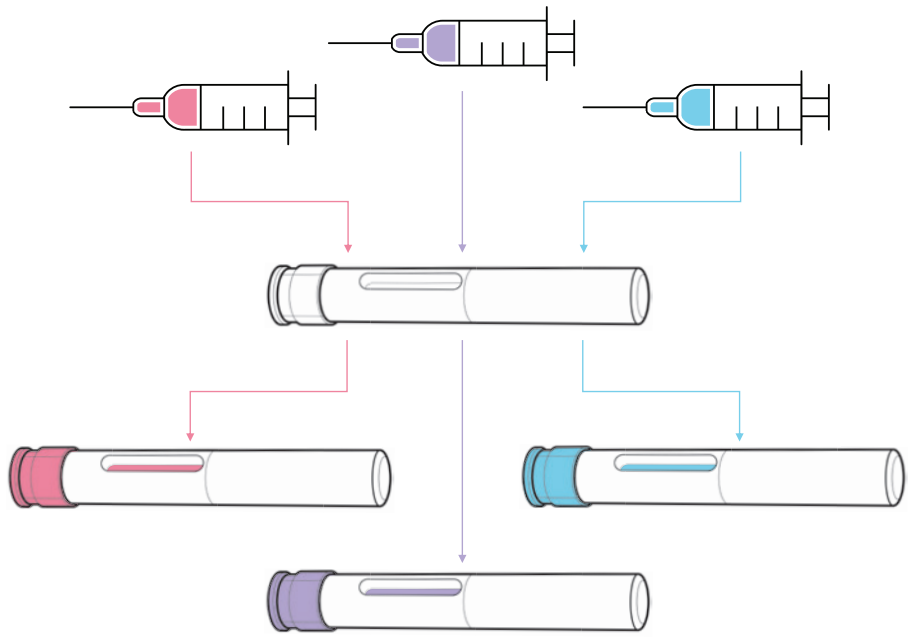

Figure 1: Platform devices are designed to support delivery of multiple formulations.

Platform devices have long been considered the "holy grail" of drug delivery device design. The appeal of platforms is clear, with companies looking to create innovative platforms to meet the evolving requirements of new therapies, while pharma companies are looking to use these technologies to expediate combination product development.

DEFINING PLATFORM DEVICES IN DRUG DELIVERY

In the drug delivery industry, the term "platform devices" encompasses off-the-shelf prefilled syringes, fixed- or variable dose pen injectors, autoinjectors for "standard" volumes of "low"-viscosity formulations and higher-volume on-body delivery systems. Platforms are also being developed to handle high-viscosity formulations or support automatic drug reconstitution, making technology selection increasingly complex.

Unlike devices developed for a single formulation, platforms are designed for use with multiple drug assets with varying requirements, such as different dose volumes, viscosities, user groups and use environments (Figure 1). The core feature of a platform is a consistent device architecture, with customisation options to accommodate varying assets, user groups or branding. Platforms vary from "narrow" (devices catering to very similar drug profiles) to "broad" (those intended for diverse therapy areas, user groups and drug properties). Broader platforms, while targeting a larger market, present greater technical challenges and risks during both platform and combination product development.

When designed and implemented correctly, platform devices offer numerous benefits for both device developers and pharmaceutical companies.

"THE CORE FEATURE OF A PLATFORM IS A CONSISTENT DEVICE ARCHITECTURE, WITH CUSTOMISATION OPTIONS TO ACCOMMODATE VARYING ASSETS, USER GROUPS OR BRANDING."

THE BENEFITS AND RISKS OF PLATFORM DEVICES

For those designing a platform device, the benefits are clear. A common architecture can be used with multiple drug products, increasing the potential market size for a single development effort. This reduces the investment cost per marketed drug and simplifies the process of navigating the intellectual property landscape for each new asset. Additionally, economies of scale in manufacturing components lower the cost per device, making the device more attractive to potential partners. However, high rewards often come with high risk, depending on the targeted platform.

Proper development and characterisation of a platform technology often requires significant upfront investment from the device developer, which may be made at risk prior to establishing a partnership with a pharmaceutical company. This can be challenging and relies on an "if you build it, they will come" mentality, often involving millions of dollars with no guaranteed return.

For pharmaceutical companies, platform devices offer a *near* "off-the-shelf" solution to deliver their assets. Using an existing (and hopefully already marketed) device can minimise time-to-market and the risks associated with developing a new device by building the combination product on proven technology. However, selecting the wrong device can lead to extensive device modifications or starting over with a new device, both of which may extend the development timeline and delay product launch. There are, however, ways to mitigate these risks and realise the benefits of platform devices.

KEY STRATEGIES FOR SUCCESSFUL PLATFORM DEVELOPMENT

To maximise return on investment when designing a platform technology, there are two key recommendations: understanding the target market to define an achievable platform boundary and preparing a data pack to minimise the effort required for potential partners to use the device.

The first challenge in platform device development is often generating the necessary investment required. To demonstrate a potential return on investment, it is critical to research upcoming drug pipelines and identify groups of assets that are likely to have similar delivery requirements. This can be done by examining Phase I and II trial data and monitoring trends in growing therapy areas. A broad potential portfolio strengthens the case for creating a platform design and maximises the likelihood of securing development investment.

Once this target drug portfolio is identified, use the likely delivery requirements to define the platform's boundaries. For example, consider whether the target therapies are intended for intramuscular or subcutaneous delivery, the expected volumes and viscosities that the platform will need to accommodate, and whether a fixed or user-selectable dose is needed. A platform with a broad performance envelope is likely to have the largest market potential but will be riskier and costlier to develop. A device concept is unlikely to gain significant attention from potential partners until functional performance can be readily proven, so clearly defining the platform performance envelope early and sticking to it throughout development will be the fastest route to market.

When developing a platform, it is also recommended to develop a data pack for potential partners to review as part of a technical due diligence. Sharing test data is the most compelling argument when selling a technology. Demonstrating that the device can, for example, deliver the correct volume and viscosity in the correct time instils confidence in its performance, which cannot be replicated through modelling or simulation. Although this requires effort in prototyping and developing test methods, the increase in "selling power" from having this real-world data increases the likelihood of a return on investment.

For a platform product, it is good practice to create a platform test plan with low-fidelity testing at the edges of the performance range to give confidence in the platform boundaries and high-fidelity (verification) testing on one or two specific configurations that represent the most likely assets in the target pipeline. Figure 2 shows an example of how the fidelity of testing can be adjusted to provide confidence in the platform envelope while focusing effort on the lead asset. Offering potential partners the opportunity

"A PLATFORM WITH A BROAD PERFORMANCE ENVELOPE IS LIKELY TO HAVE THE LARGEST MARKET POTENTIAL BUT WILL BE RISKIER AND COSTLIER TO DEVELOP."

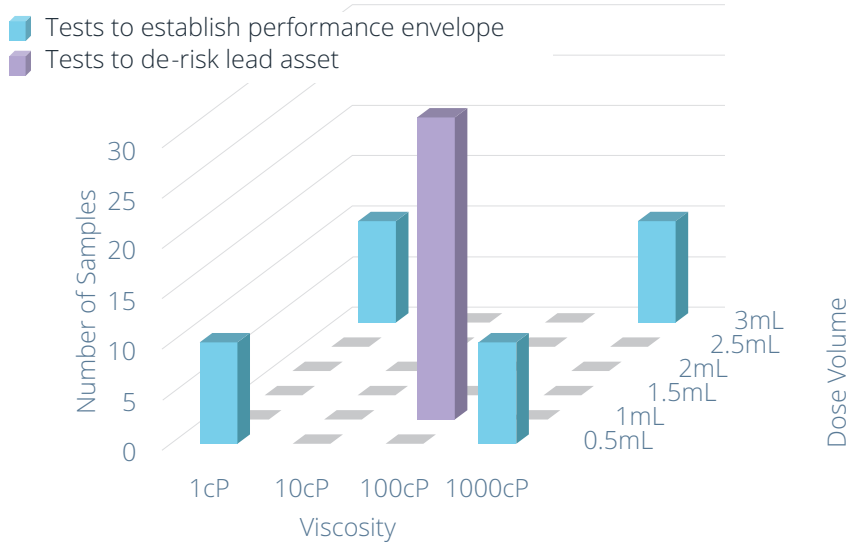

Figure 2: Example platform test plan (for each precondition) to provide confidence in the performance envelope.

"BEFORE SEARCHING FOR A DEVICE TECHNOLOGY, IT IS VITAL TO UNDERSTAND THE REQUIREMENTS OF THE TARGET DRUG ASSETS."

to test their formulation in the device, with sample devices available for filling and existing test methods, allows for quick and cost-effective testing.

Of course, there is no such thing as a truly "off-the-shelf" platform product, so the second critical aspect of the data pack to share with potential partners is the bridging plan. Minimising and clearly defining the design work and associated testing to be repeated for each new asset reduces time-to-market and further increases confidence in the device developer's ability to deliver on a combination product development programme. Figure 3 shows an example of a bridging test plan to convert from a platform injection device to a combination product – note that the specifics will be highly dependent on the drug and device in question.

By understanding the target market and device boundaries and creating a data pack to convey the platform's benefits to potential partners, the potential market size for a platform can be maximised and the potential return on the initial development effort increased.

CHOOSING THE RIGHT PLATFORM FOR THE TARGET DRUG PIPELINE

For pharmaceutical companies seeking a platform device to fit the delivery requirements of as many assets as possible in a drug pipeline, the critical activities are understanding the formulations, the available and applicable technologies and using existing data to minimise time-to-market.

Before searching for a device technology, it is vital to understand the requirements of the target drug assets. Pharmaceutical companies should identify groups of assets with similar characteristics and intended use profiles across their portfolios, for example, all those intended for subcutaneous injection in a home environment. This enables them to search for platforms with the correct performance envelope, assessing technologies not just for the lead asset but with the wider portfolio in mind, thereby offering the potential to minimise time-to-market for future assets.

It is also crucial to understand what the drugs require from a device as much as possible. What is the dose volume? What is the formulation viscosity, and how does it change with temperature and shear rate? What is the target delivery time? Answering as many questions about the required performance of a platform as early as possible can help optimise the search process and enable the device developer to gather and present the most relevant data during the due diligence process.

Another important process for pharmaceutical companies to undertake is to survey the technology landscape by searching for existing devices that meet the formulation's needs. This creates a shortlist of devices to be investigated further through supplier contact and deeper dives into the device data package. The primary focus during this survey is to establish device compatibility with the lead asset, with a secondary focus on compatibility with the wider drug wider pipeline.

To gain confidence in a device's ability to support the lead asset, pharmaceutical companies should look for empirical evidence wherever possible. Clear usability and test data supported by robust test methodology is the strongest indicator of device performance, while tolerance analyses and mathematical models can evidence a device's ability to perform at scale. Ideally, the test data should showcase a device's ability to deliver a formulation similar to the lead asset across all appropriate preconditions, for example, free-fall is often a point of failure for injection devices, or else provide explanations for any expected risks and mitigations.

The next step is to review the manufacturing and assembly plan to ensure that device supply can scale reliably and securely to meet expected market volumes at the required price point. Where possible, all evidence in the design history file should be reviewed for direct applicability to the asset under development, such as which test results can be used as part of a combination product submission, which need to be repeated and how well defined the scope of any work that needs to be repeated is.

To assess the platform as a whole, pharmaceutical companies should focus on the boundaries of performance, such as range of volumes and viscosities supported, and how well the device developer understands these boundaries. Can both the maximum volume and viscosity be delivered in the required time by a single device under all conditions? What evidence supports this? What parts need to be changed to support different configurations, and how much investment is needed to meet those requirements within the desired timeline? A strong device partner will demonstrate a clear and in-depth understanding

Test	Conditions/Precondition
Cap removal force	Cool, standard and warm
Needle attachment	Free fall
Dialling torque	Dry heat
Button activation force	Cold-storage
Dose accuracy	Vibration
Injection time	Transport
End of dose indication	Functional stability
End of pen indication confirmation	

Must be repeated May be repeated Not repeated

Figure 3: Example bridging test plan for injection device.

of their platform and technology, with readily available evidence or a plan to gather this evidence and the expected risks. Replacing test data with simulation data is adequate for early stage devices but does not fully mitigate the risk of a device underperforming and requiring more development work. If test data is not provided or fully documented, it indicates that the device is early in the development process and not "ready to use". Any first-time tests are likely to show failures and trigger a design loop. If this testing has not been conducted properly, extensive development work is likely still required within the platform development, posing a risk to time-to-market and increasing costs.

"A STRONG DEVICE PARTNER WILL DEMONSTRATE A CLEAR AND IN-DEPTH UNDERSTANDING OF THEIR PLATFORM AND TECHNOLOGY, WITH READILY AVAILABLE EVIDENCE OR A PLAN TO GATHER THIS EVIDENCE AND THE EXPECTED RISKS."

INTEGRATING DEVICE AND DRUG: STEPS TO MARKET READINESS

Once compatibility between a device and a drug has been established, a risk assessment should be conducted as part of the creation of a plan for customising and verifying the combination product. Existing test results can be used if there is sufficient evidence that the drug will not influence the outcomes, such as cap removal force if the same components are being used, or free-fall preconditioning if the drug density matches that used in testing. The tests that are likely to need to be repeated in all cases include dose accuracy under standard, warm and cool preconditions (Figure 3). However, methods, fixtures and processes can be reused if dose accuracy testing has been conducted previously. This process allows for the minimum viable test plan, drastically reducing the time and effort required to verify combination product performance compared with a custom development.

As platform devices are required to meet an ever-widening set of market demands, there is an increasing need to simplify the process of developing these devices and adopting them for combination products. Through independent characterisation of both device and drug, combination product development can be greatly simplified, reducing the time and investment required to bring a new therapy to market.

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 start-ups 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 an direct-to-organ delivery.

Fran Pencliffe

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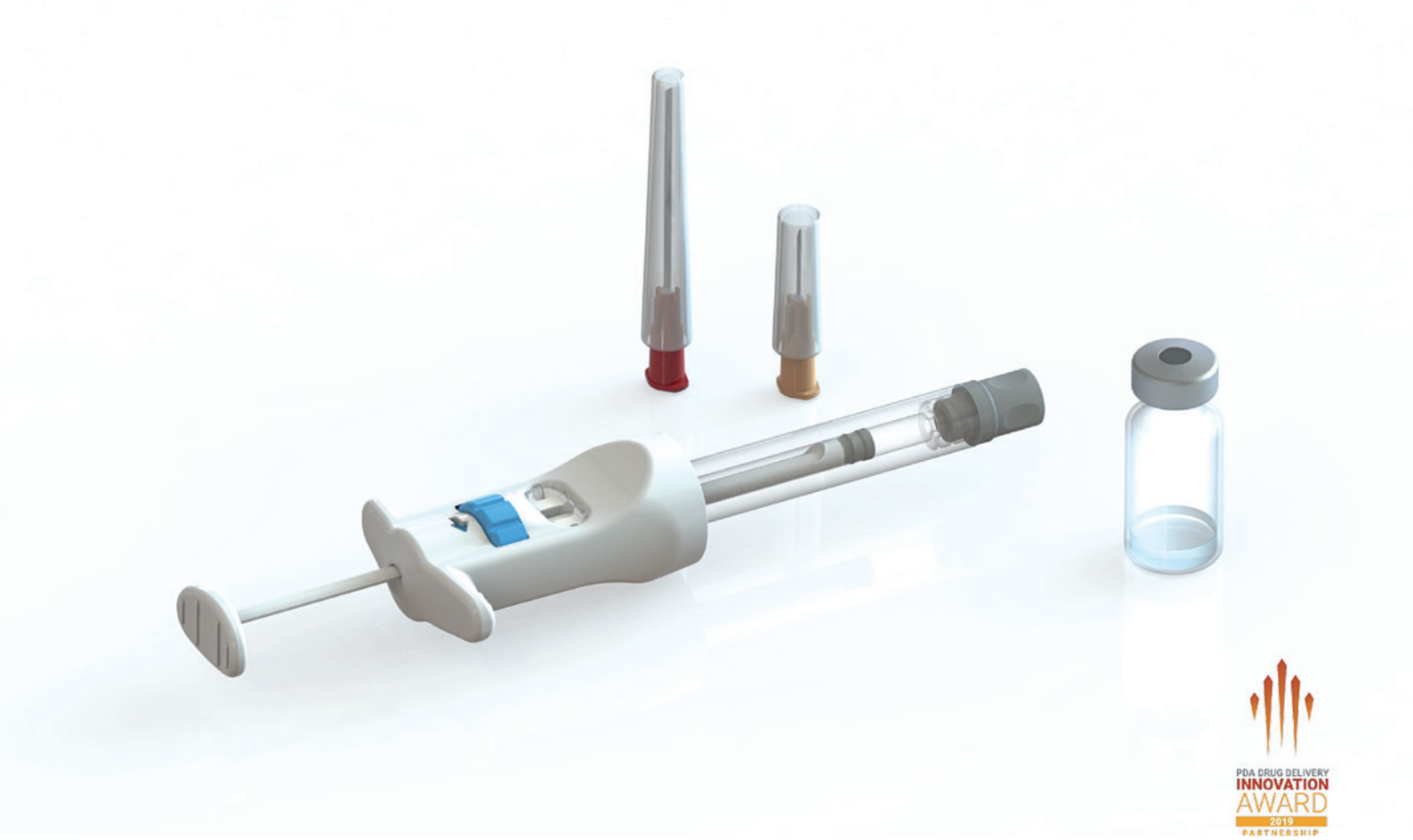


PDA DRUG DELIVERY INNOVATION AWARD 2019 PARTNERSHIP

510(k) CLEARED, USER-FILLED MICRODOSING DEVICE FOR OPHTHALMIC AND OTHER APPLICATIONS

CONGRUENCE MEDICAL SOLUTIONS, LLC

Gautam Shetty of **Congruence Medical Solutions** discusses unmet drug delivery needs in applications requiring accurate and precise microlitre-scale doses, going on to detail how the company's recently cleared Microliter Dosing Syringe can bring the benefits of advanced syringe materials and performance to these applications.

Parenteral injections typically involve millilitre-scale volumes. However, since the approval and launch of Macugen® (pegaptanib, OSI Pharmaceuticals) in 2004 and Lucentis® (ranibizumab, Genentech) in 2006, more than 20 million[1] microlitre intravitreal injections are estimated to take place every year, with more than 7 million[2] injections in the US alone. Since then, other drugs targeting other diseases of the eye, such as geographic atrophy, and those involving microlitre injections have also been launched.

Outside of oncology, immunology and, more recently, obesity and metabolic disorders, ophthalmology is a key area of interest and investment for pharmaceutical companies. Beyond ophthalmology, applications such as local organ delivery for cell and gene therapy, intratumoural delivery and preclinical testing also involve injection of microlitre-scale doses.

AN UNMET NEED: USER-FILLED MICRODOSING DEVICE

Some approved ophthalmic drugs are currently available in a prefilled syringe format. While these meet the need for accuracy and precision, several drugs that are currently in clinical development or those drugs that cannot be prefilled even after approval, such as for cell therapies, have some or all of the following unmet needs.

Accuracy and Precision

Currently marketed syringes developed for the injection of millilitre volumes have been repurposed for injection of microliter volumes and are therefore inherently

Figure 1: Congruence's MDS.

inaccurate and imprecise.[3] These syringes have printed dose marks for reference; however, the accuracy of these markings does not impute delivery of an accurate dose volume – this is a common misunderstanding. Accuracy of dose delivery is limited by human capacity for axial manipulation of the plunger rod at the start and end of dose.

Overcome Dose-Marking Resolution

The resolution of a non-prefilled syringe with the lowest nominal volume approved for clinical use is 10 µL. Finer resolution is limited by the resolution of printing the dose marks by pad, screen or laser printing. Therefore, applications involving volumes that are not multiples of 10 µL cannot avail of off-the-shelf syringes.

High-Quality Drug Contact Materials

In certain sensitive applications, such as ophthalmology and neurology, conventional hypodermic syringes are unsuitable because of lubricants, unacceptable endotoxin content and/or other leachables. Some hypodermic syringe manufacturers have even issued a field safety notice asking users not to use their syringes for intravitreal injections due to the risk of leachable silicone. Additionally, hypodermic syringes may not conform to regulatory requirements for endotoxin content in sensitive applications. Futhermore, some silicone-free syringes have lubricants to replace silicone;[4] therefore, not all silicone-free syringes are also lubricant-free. Also, the potential presence of perfluoroalkyl substances (PFASs) in contact with the drug should be avoided in light of REACH regulation in Europe and a recent lawsuit filed in the US by the state of Maryland involving PFASs.

Enabling Applications with High Injection Forces

Viscous formulations, fine injection needles, long delivery conduits or any combination thereof results in high injection forces. With currently available hypodermic syringes, there is a need to enable a comfortable injection. Two-piece syringes – syringes with no elastomeric plunger stopper – are known to leak past the plunger rod when attempting to inject viscous formulations.

MICROLITER DOSING SYRINGE: A USER-FILLED MICRODOSING DEVICE

The US FDA recently cleared Congruence's Microliter Dosing Syringe (MDS) that aims to address these unmet needs for non-prefilled drugs (Figure 1). This 510(k)-cleared device (K243149) is the first of its kind to incorporate a prefillable syringe for use with drugs that are filled in a vial and is indicated for intravitreal injections.

> "THE BENEFITS OF HIGH-QUALITY SYRINGE AND PLUNGER STOPPER MATERIALS DEVELOPED FOR PREFILLED DRUGS ARE NOW AVAILABLE FOR DRUGS THAT NEED TO BE USER-FILLED AT THE POINT OF INJECTION."

This means that the benefits of high-quality syringe and plunger stopper materials developed for prefilled drugs are now available for drugs that need to be user-filled at the point of injection (Table 1). This includes a silicone-free and lubricant-free syringe that conforms to USP <789> and whose extractables have been evaluated to be safe for intravitreal injections. The MDS meets stringent requirements to be classified as an ophthalmic syringe.

Indication	Use in intravitreal injections
Intended Use	Inject fluid into or withdraw fluid from the body
Models	9, 20, 25, 37.5, 50 and 100 µL models cleared
Dose Accuracy	±3 µL for all models (95% confidence levels and reliability)
Usage	Single dose; disposable
Dosage Type	Fixed (one device configured to set and inject preset dose)
Needle Attachment	Luer lock (user-selectable needle)
Sub-visible Particulates	Conforms to USP <789>, USP <788>
Endotoxin	≤ 0.2EU/mL
Biocompatibility	ISO 10993-1 compliant Tested for ocular irritation, intravitreal irritation
Sterilisation	Irradiation; provided sterile
Syringe Lubrication	None (silicone-free, lubricant-free)

Table 1: MDS 510(k) Summary excerpt.

Each model of the MDS is configured to deliver a preset dose within 3 µL of the target volume. While few models, each with a different target injection volume, have been FDA cleared, additional models could be cleared using the current platform. Accuracy and precision of dose delivery for four different models are summarised in Figure 2. As shown, MDS models include target doses that are not possible with conventional user-filled hypodermic syringes – 9, 25 and 37.5 µL. Data from retina specialist users show accurate, precise microlitre injections when using the MDS technology.

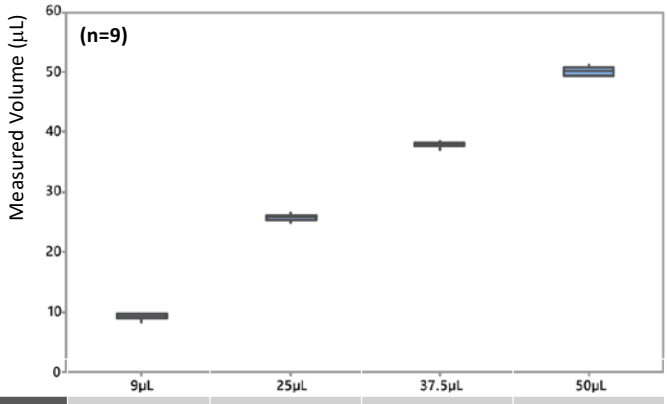
Intravitreal injections involve fine-gauge needles – ideally 30G or finer to minimise pain and maximise patient comfort. Using a needle this fine increases the injection force, which is compounded by the increasing viscosity of drug formulations. Congruence's MDS has been shown to inject formulations as viscous as 100 cP using a 30G ½" long needle. The MDS technology attenuates the injection force experienced by the user due to inherent mechanical advantage in its design and a further reduction in injection force experienced by the user from a reduction in flow rate, even when maintaining the same plunger rod speed. Figure 3 shows a comparison with and without the MDS when injecting a 50 cP formulation using a 30G ½" needle for the same plunger rod speed.

MAKING ANY SYRINGE A MICROLITER DOSING SYRINGE

The MDS technology is essentially a dose-metering plunger rod. This device architecture could make any syringe equivalent to a MDS, including prefillable syringes (Figure 4). The availability of a 510(k)-cleared embodiment could facilitate faster development and introduction of a prefilled device. Any such development can now leverage the market experience and usability data of the user-filled, 510(k)-cleared version.

CONCLUSION

Congruence's MDS is a high-performing, high-quality, user-filled microdosing device that is now available for drugs, including for intravitreal injection, that are currently



	9µL	25µL	37.5µL	50µL
Mean Measured Volume (µL)	9.3	25.9	38.0	50.2
Standard Deviation (µL)	0.5	0.5	0.5	0.7
Co-efficient of Variation	5.4%	1.9%	1.2%	1.5%
Minimum (µL)	8.3	25.0	37.1	49.2
Maximum (µL)	9.9	26.5	38.6	51.2

Figure 2: Accuracy and precision of MDS (9, 25, 37.5 and 50 µL models).

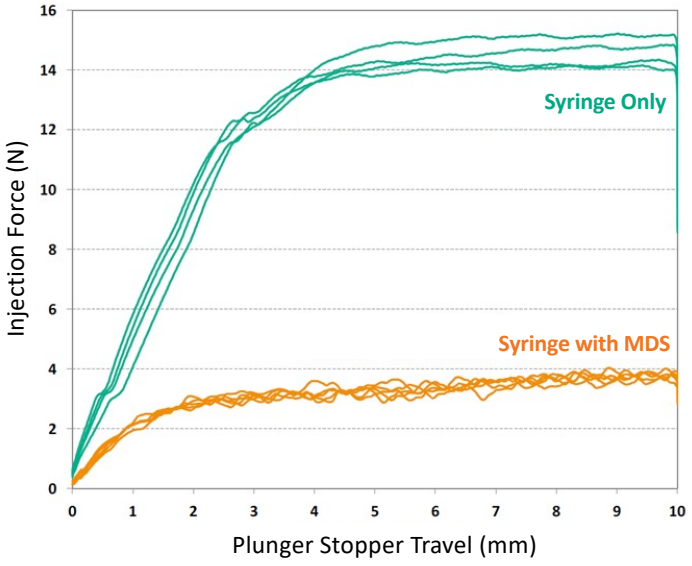


Figure 3: Attenuation of injection force.

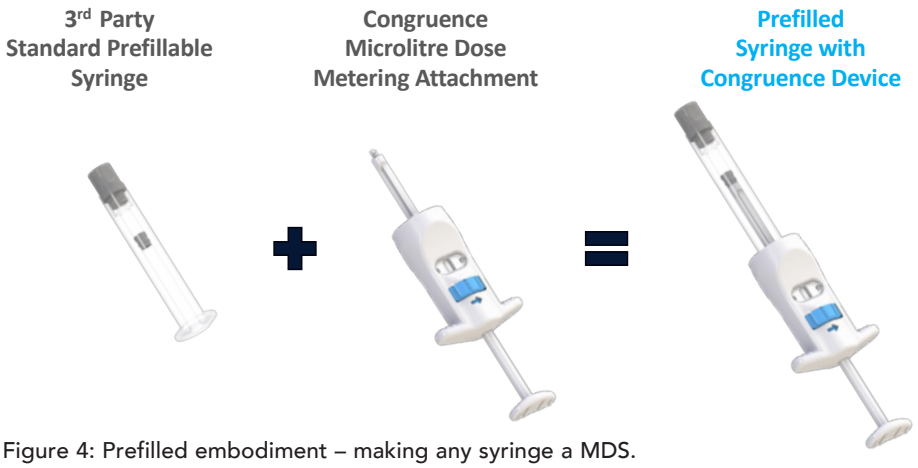


Figure 4: Prefilled embodiment – making any syringe a MDS.

not prefilled in a syringe or those that cannot be prefilled in a syringe. The MDS has been shown to deliver accurate, precise injection volumes as low as 9 µL and has demonstrated the ability to inject viscous formulations with a fine-gauge needle. The MDS incorporates high-quality drug contact materials that were previously available only for prefilled drugs, opening them up to drugs that are (or have to be) user-filled, thereby also making it ideal for sensitive applications

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Dr Gautam Shetty

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EMPOWERING PHARMA WITH INNOVATIVE INFUSION TECHNOLOGIES AMID US POLICY CHANGES

eitan medical
care & beyond™

Mindy Katz and **Michael Ratigan** of **Eitan Medical** outline the implications for pharmaceutical manufacturers of recent US policy changes – and highlight how Eitan Medical's portfolio of infusion solutions can offer support.

The dynamic intersection of regulatory policy and pharmaceutical innovation has once again taken centre stage as the US undergoes administration changes, while simultaneously working through the evolution and effects of the Inflation Reduction Act (IRA) and the Recovering Excessive Funds for Unused and Needless Drugs (REFUND) Act. Understanding the implications of these Acts for pharmaceutical manufacturers (Figure 1), both in the US and abroad, demands rigorous examination, while embracing a level of uncertainty in light of the presidential administration transition.

This evolving landscape underscores the potential for drug delivery partnerships to successfully address the complexities of modern healthcare trends. Eitan Medical's expertise in infusion technology, together with its commercial product experience, global presence, flexibility in pharmaceutical partnerships and robust portfolio of connected, infusion solutions – including the Sapphire™ and Avoset™ infusion pump platforms and the Eitan Insights™ digital health platform – position it as a pivotal partner of the pharmaceutical industry as it navigates these challenges.

LEGISLATIVE CONTEXT: IRA AND REFUND ACT

The IRA, signed into law in 2022, fundamentally shifts the dynamics of drug pricing policies in the US market. Key provisions include the ability for Medicare to negotiate prices for several

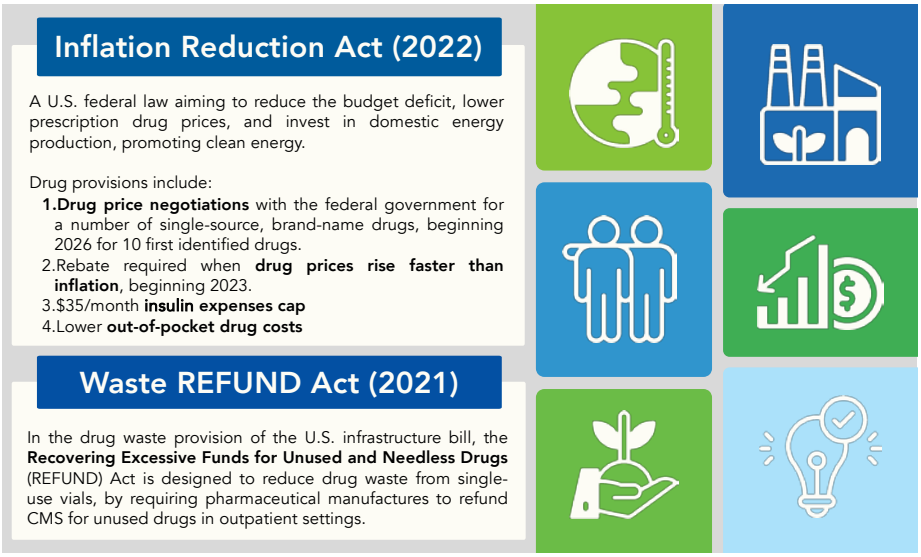

Figure 1: US legislation implications for pharmaceutical manufacturers.

recently identified high-cost drugs, penalties for price increases that outpace inflation, and caps on insulin supplies and out-of-pocket expenses for beneficiaries. While this aims to promote affordability and patient access across the nation, it also introduces challenges for pharmaceutical manufacturers, as expensive drugs and biologics eligible for direct price negotiations with Medicare may experience significant price cuts, unplanned for at this stage of their lifecycle.

Similarly, the REFUND Act, signed in 2021 and in effect since 2023, targets inefficiencies in the healthcare system, specifically focusing on reducing drug waste associated with single-dose vials. By mandating refunds for discarded medication exceeding threshold amounts in outpatient settings, the Act pressures manufacturers to rethink packaging and delivery formats to minimise waste and associated costs.

IMPLICATIONS FOR PHARMACEUTICAL MANUFACTURERS

Both the IRA and the REFUND Act demand a paradigm shift in how pharmaceutical companies approach product development, packaging, pricing and market strategies. These policies incentivise innovations that enhance cost efficiency and demonstrate clear value to payers and providers. To address the REFUND Act, a pharmaceutical manufacturer may consider transitioning to a different vial format, potentially minimising drug waste, or allowing multiple vial configurations to optimise for weight-based dosing.

While these actions may lead to reduced drug waste and accordingly decreased penalties under the REFUND Act, they are generally considered both lengthy and costly endeavours for a pharmaceutical manufacturer to undertake, and accordingly are not initiated easily. Choosing the right primary container and drug delivery device for a drug product and, specifically, considerations for choosing the right infusion pump and digital health platform, can play a critical role in meeting policy requirements and avoiding negative financial implications.

PRICING PRESSURE AND DURABLE INFUSION PUMPS

With the introduction of penalties and price negotiations across a variety of drugs leading to increased pricing pressure and lower margins, drug manufacturers may choose to invest in cost-efficient drug delivery products, with lower costs per dose, shifting away from single-use, fully disposable devices and prioritising reusable systems. Infusion pumps, generally considered durable systems with disposable administration tubing sets, address this pricing challenge, allowing homecare providers and out-patient institutions to use a single robust infusion pump for multiple years, across a variety of therapies.

> "THESE POLICIES INCENTIVISE INNOVATIONS THAT ENHANCE COST EFFICIENCY AND DEMONSTRATE CLEAR VALUE TO PAYERS AND PROVIDERS."

EITAN MEDICAL: SUPPORTING PHARMA IN A NEW REGULATORY ERA

Eitan Medical's portfolio of infusion solutions can support pharmaceutical manufacturers as they align with the priorities established by the IRA and REFUND Act.

Sapphire

The Sapphire™ infusion pump platform is the solution of choice for infusion therapy devices across the continuum of care, from pre-acute to hospital and to home. Designed with patient safety in mind, and aiming to improve the daily lives of patients, built-in safety mechanisms are included, along with a simple and intuitive, full-colour touchscreen for fast operation. Smart technology helps infusion providers reduce dosage errors and false alarms. With Sapphire Connect, Sapphire pumps are within reach, transmitting data to the cloud through universal plug-and-play cellular technology. And comprehensive service and support provided by a global network of authorised service centres ensures the infusion providers and patients are at the centre of care.

Avoset

The connected Avoset™ infusion pump transforms specialty pharmacy and home infusions with a compact and simplified technology that enhances the user experience. Remote visibility of infusion data and access to data analytics can help healthcare professionals and infusion providers monitor compliance and identify trends for better care planning. The solution may increase patient access to home infusion and improve quality of life by making home

infusion delivery safe, with the potential to allow more patients to receive therapy in the comfort of their own home. The Avoset pump is easy to set up and simple to operate, reducing risk of error with minimal set-up steps, an easily clicked-in administration set and web-based PC programming. Finally, the pump is designed to deliver from a variety of medication containers, including bags, rigid containers and syringes, with further configurations in development.

Eitan Insights

Eitan Insights™, the company's cloud-based software platform designed to transform infusion management, launched in 2023 and has since won the 2024 National Home Infusion Association innovation award. The platform provides remote visibility to treatment data, along with geolocation of the Sapphire and Avoset pumps, supporting infusion providers in care planning and adherence monitoring. The data presented in the platform eliminate subjectivity, which can help avoid anxiety-provoking troubleshooting, thus helping to improve both patient and caregiver experience. Eitan Insights is built on cutting-edge cloud architecture that uses the latest security features and best practices with state-of-the-art encryption and multi-factor authentication – and it is HIPAA and GDPR compliant (Figure 2).

Figure 2: Eitan Insights, the cloud-based digital health platform.

TAILORED INFUSION SOLUTIONS

Eitan Medical's software-based pumps are engineered to support accurate infusion therapy, aimed at reducing variability and enhancing outcomes. In parallel, its digital health capabilities provide access to robust evidence of increased operational efficiency, cost effectiveness, proof of treatment and patient adherence. In addition to its commercially available products, Eitan Medical partners directly with pharmaceutical manufacturers, tailoring infusion pumps, sets, accessories and software to meet the needs and challenges of specific drug products, patient populations, geographies and care environments. This can include customised administration sets to meet the specifications of unique primary containers, software and labelling translations to allow introduction into new markets, and complex infusion protocols supported by pump software.

Eitan Medical's tailored approach also includes aligning pumps and sets to therapy needs, reducing drug transfer steps to minimise wastage and optimising software configurations for specific treatment protocols. The company's commitment to innovation ensures its solutions not only comply with regulatory requirements but also deliver measurable value to pharmaceutical partners, addressing demands for cost-effective, patient-centric solutions.

INFUSION DATA AND INSIGHTS

Eitan Medical's connected pumps collect infusion data, not only informing the company as a manufacturer on how its pumps are used – helping to optimise technology, investigate complaints and better support users – but also having the potential to offer pharmaceutical manufacturers real-world evidence on how their drugs are being administered. Access to this data throughout clinical studies can support research efforts and provide aggregated, drug-specific insights. These insights have the potential to serve as never-before-seen

Figure 3: Connected infusion pumps, enabling care at home.

"WHILE THE IRA AND REFUND ACT ARE US-CENTRIC POLICIES, THE RIPPLE EFFECTS ARE EXPECTED TO EXTEND TO EUROPEAN PHARMACEUTICAL MANUFACTURERS AND BEYOND."

evidence for pharmaceutical companies for optimisation of drug product protocols, enhancing patient support programmes and improving adherence strategies.

ENABLING HOME CARE AND DECENTRALISED TRIALS

The shift towards home care and decentralised clinical trials is a significant trend in global healthcare, with pharmaceutical innovators using digital technologies to address the limitations of traditional site-based clinical trials[1] and commercialising their drug products in outpatient settings. These models not only reduce costs to the healthcare system as a whole but also improve patient outcomes by providing care in the comfort of a patient's own home, while significantly reducing the risk of hospital-acquired infections.

With a primary gap of the adoption of both decentralised clinical trials and home-based therapies being the risk of non-adherence to prescribed medications, Eitan Medical's products are at the forefront of this transformation, with the Avoset and Sapphire pumps designed to support remote monitoring and flexible care delivery, making them ideal to address these challenges. Eitan Insights plays a crucial role in these settings as well, providing remote visibility to treatment data, supporting healthcare providers in the shift towards care at home (Figure 3).

ADDRESSING GLOBAL IMPLICATIONS

While the IRA and REFUND Act are US-centric policies, the ripple effects are expected to extend to European pharmaceutical manufacturers and beyond. Companies operating internationally must adapt to these regulatory shifts, especially as similar trends in drug pricing and waste reduction are expected to emerge in other regions. Eitan Medical's infusion solutions, with a global distribution presence in over 40 countries, provide a universal framework for compliance and efficiency, ensuring pharmaceutical partners remain competitive across markets.

THE ROAD AHEAD

As the pharmaceutical industry navigates the challenges of drug pricing reforms and regulatory changes, the role of advanced drug delivery technologies and partnerships becomes increasingly critical. Companies must adapt to a regulatory environment that prioritises affordability and efficiency, while continuing to innovate for patient-centric care. Eitan Medical's proven commercial track record, global presence and comprehensive product offering position it as a trusted partner in this evolving landscape. By using Eitan Medical's infusion solutions and digital health tools, pharmaceutical manufacturers can strive to not only achieve compliance but also drive innovation, sustainability and efficiency in patient-centred drug delivery.

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ten23 health is a pharmaceutical CDMO that supports its clients in developing differentiated, stable, usable and safe injectable treatment options for patients. The company combines the latest scientific findings with proven industry and regulatory expertise to forge new paths for its clients' needs. ten23 health provides its innovative services in a fair and sustainable manner.

To learn more, see **Page 66**

tip-top.com

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tip-top specialise in the design and development of Proprietary sharps protection technology for out-licensing to the medical and pharmaceutical sectors and has amassed a large portfolio of patents relating to standalone safety needles and integrated needlestick protection systems for prefillable syringes.

See **Page 05**

Zwick / Roell

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ZwickRoell is a materials testing system developer and manufacturer. The company develops and manufactures both the load frames and all main components itself. With 15 product groups and testing solutions for more than 20 industries, as well as support from the company's approximately 1,900 employees representing over 50 countries, ZwickRoell is an expert partner in the field of materials testing.

To learn more, see **Page 86**

More Spotlights overleaf






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Haselmeier, the drug delivery device business of medmix, designs, develops and manufactures advanced drug delivery systems. The company has a broad portfolio of technologies and services, delivering user-friendly injection systems that enable patients to self-administer their medication reliably and accurately, with more than 100 years of expertise, nearly 250 experts and more than 200 granted patents.

To learn more, see **Page 50**

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Instron manufactures and services a wide range of mechanical testing equipment used in the design and production of drug delivery devices. A strategic partner to global companies of all sizes, Instron helps its partners investigate new technologies and ensure product quality while maintaining the highest levels of data integrity and security.

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MicroMED is a Taipei-based medtech company that designs and manufactures micro-electromechanical systems (MEMS)-enabled drug delivery actuation systems. The company has developed a novel MEMS pneumatic actuator/gas micropump to address emerging trends and unmet needs in subcutaneous and specialised drug delivery. MicroMED welcomes partnerships across the value chain, including biopharmaceutical companies, device developers and payers, through product sales, co-development or technology licensing.

To learn more, see **Page 77**

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Nipro Pharma Packaging is specialised in developing and manufacturing advanced pharma packaging products and complete packaging solutions for early development drugs or the enhancement of packaging solutions for existing drugs.

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PCI Pharma Services is a global contract development and manufacturing organisation that provides integrated end-to-end drug development, manufacturing and packaging solutions to increase product speed to market and opportunities for commercial success. PCI's experience includes more than 90 successful product launches each year and over five decades in the delivery of supply chain healthcare services.

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Phillips Medisize, a Molex company, helps clients get from concept to care quickly while reducing the inherent risks of any new product journey. The company acts as a singular resource for its clients, offering robust end-to-end capabilities, including drug delivery device platforms. For over 60 years, pharma, diagnostic and medtech companies have trusted Phillips Medisize to deliver quality products to these key industries.

To learn more, see **Page 90**

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Shaily specialises in the design and manufacturing of high-quality pen injectors, autoinjectors and drug delivery devices for the pharmaceutical and medical device sectors. With a commitment to innovation and precision, Shaily provides advanced drug delivery solutions that enhance patient care and meet the stringent requirements of the global healthcare industry.

See **Page 134**

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STÜKEN is a supplier of precision deep-drawn metal parts, stampings, plastic injection-moulded components and assemblies. The company supplies the automotive, medical technology and electronics industries, among others. The family-owned company produces in the USA, the Czech Republic and China, a plant in India is underway. STÜKEN employs around 1,250 people.

To learn more, see **Page 100**

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BAUMANN Group, headquartered in Switzerland and employing around 1,400 people across nine countries, manufactures over 4.8 billion springs, stampings and bendings annually – approximately 152 per second. Baumann Medical, an independent division within the group, provides tailor-made solutions and services in medical devices at ISO 13485 certified sites, addressing the specific needs of the medical and pharmaceutical industries.

To learn more, see **Page 106**

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Cambridge Consultants develops breakthrough products and services, creates intellectual property and provides business consultancy in technology-critical issues. With over 800 staff, including engineers, scientists, mathematicians and designers, and offices in Cambridge (UK), Boston, Tokyo and Singapore, Cambridge Consultants offers solutions in healthcare, digital health, medical technology, biotech and multiple other industries.

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Congruence Medical designs, develops and supplies innovative, flexible drug delivery device platforms to optimise injectable drug delivery. The company provides solutions that address compelling needs in microlitre-scale dosing, injection of viscous formulations and minimising drug waste at the point of injection.

To learn more, see **Page 120**

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DCA is a product design consultancy with a wealth of experience developing leading drug delivery devices for global markets, including all types of injection, infusion, inhalation, intranasal, oral and topical devices. DCA provides comprehensive, expert support for device design and development, including strategy, usability, connectivity, engineering, electronics, medical device software and industrialisation.

See **Page 02**

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Credence MedSystems is an innovator in drug delivery devices, solving emerging challenges in parenteral drug delivery. Credence's philosophy of Innovation Without Change results in products that impress and protect end users while preserving pharma's existing processes, sourcing strategies and preferred primary package components.

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For over a decade, **Eitan Medical** has provided safe, intuitive and flexible solutions that meet evolving drug delivery needs. Product lines include the Sapphire™ infusion platform, connected infusion therapy systems in hospital and ambulatory settings; the Avoset™ connected infusion system, focusing on the specialty infusion market; and Eitan Insights™, a digital health platform.

To learn more, see **Page 124**

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Fischer Söhne AG is a pharmaceutical packaging provider. With its Tub & Nest solutions, the company is committed to innovation, quality and sustainability in the pharmaceutical packaging sector. As the market for prefilled syringes and injection devices continues to grow, the company remains a trusted partner for pharmaceutical manufacturers worldwide.

To learn more, see **Page 112**

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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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With over 40 years of experience, **Ypsomed**'s comprehensive drug delivery device platforms consist of autoinjectors for prefilled syringes, disposable pens, reusable pen injectors, ready to-use prefilled wearable patch injectors and injection devices for drugs in dual chamber cartridges. Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services.

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To learn more, see **Page 10**

SG Stevanato Group

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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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To learn more, see **Page 22**

TERUMO
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As Part of **Terumo Medical Care Solutions**, the Pharmaceutical Solutions Division develops patient-oriented parenteral delivery solutions for therapeutic performance and safety. Terumo's expert teams lead the industry in developing and manufacturing advanced, high-performing infusion and injection technologies, including contract development and manufacturing organisation services for all parenteral applications.

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To learn more, see **Page 26**

altek MED

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Altek Biotechnology Corporation designs, develops and manufactures medical devices, providing solutions and services with a proven record of product development and manufacturing across a global footprint. Altek specialises in electromechanical design with a combination of mechanical, electronics, optics and software expertise. The company's key products include endoscopes and smart injection devices.

To learn more, see **Page 60**

Aptar pharma

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Aptar Pharma offers proven drug delivery solutions and services that support pharmaceutical companies worldwide to develop safe, efficient and compliant medicines. Aptar Pharma's drug delivery systems, components and active material solutions serve the widest range of delivery routes, Aptar's digital healthcare solutions help improve patient adherence and Aptar Pharma Services helps accelerate and derisk development.

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