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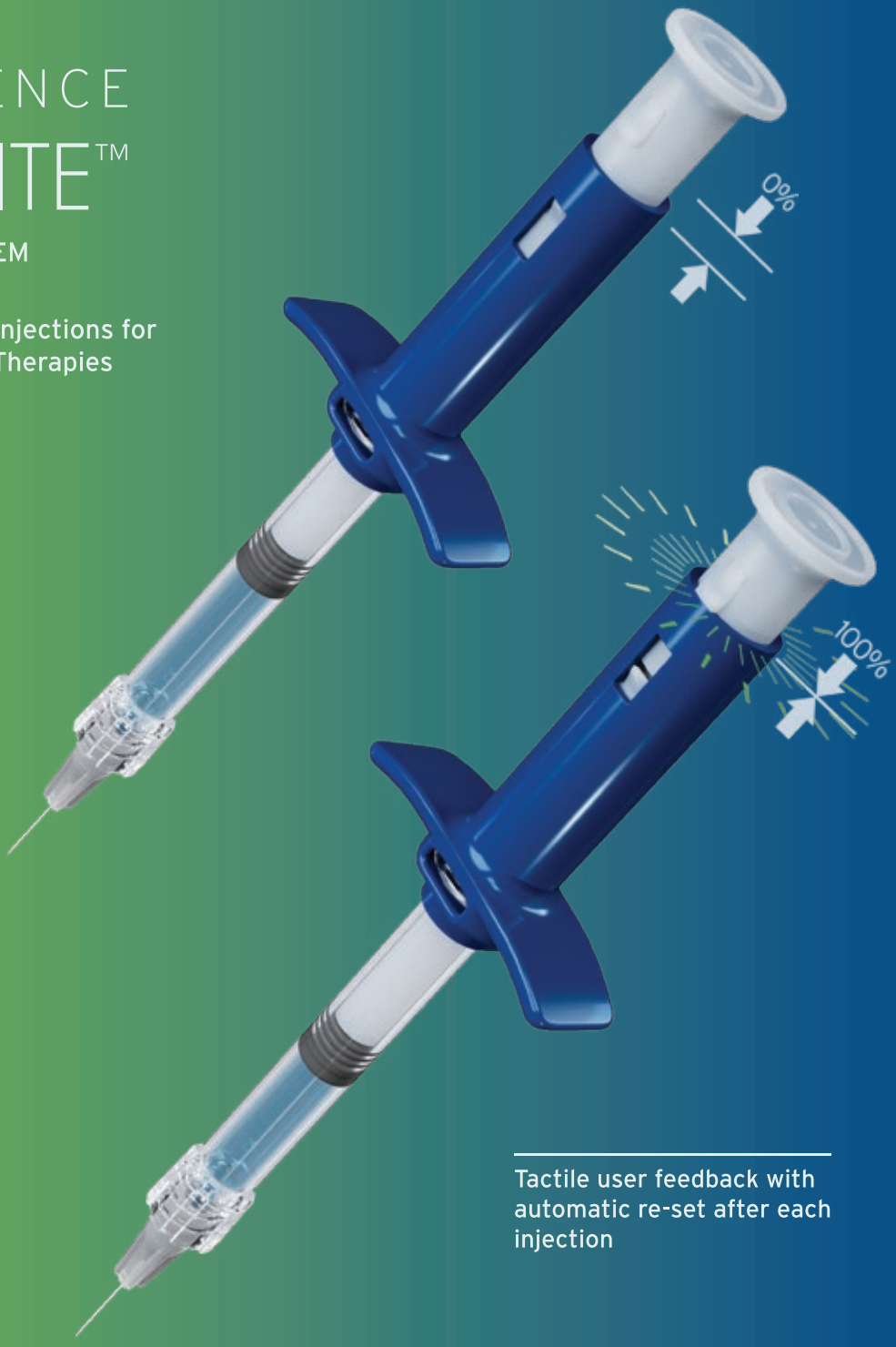

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ONdrugDelivery Issue N° 156, January 22nd, 2024

PREFILLED SYRINGES & INJECTION DEVICES

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

EDITORIAL CALENDAR 2024/25

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Apr	Pulmonary & Nasal Drug Delivery
Apr/May	Drug Delivery & Environmental Sustainability
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HOW *DIABESITY* IS SHAPING THE WORLD OF SELF-INJECTION DEVICES

In this piece, Ian Thompson, Vice-President of Account & Business Development at Ypsomed, takes us through the recent history of diabetes and obesity therapeutics, the innovative peptide hormone molecules that have reached the market over the past decades and the equally innovative devices developed to deliver them. He addresses the growing challenge of diabesity, and shows that diabetes and obesity will continue to influence self-injection device development substantially.

THE EMERGENCE OF "DIABESITY"

For people of all ages, the risk of Type 2 diabetes rises with increasing body weight and, in rich and developing countries, the prevalence of both obesity and Type 2 diabetes has increased continuously since the 1980s. No more so than in the US, where 35% of the population is obese, while rates in Europe range between 10-25% depending on the country (Figure 1). Today, the number of people with Type 2 diabetes is ~500 million globally, and approximately one billion people are obese. While around 50 million people, or 10%, of Type 2 diabetics are insulin dependent and peak diagnosis of Type 2 diabetes is established at around 50 years of age (Figure 2), there is a 15-30% overlap between the Type 2 diabetes and obesity populations, depending on the country. This means that there are many obese people who will potentially develop insulin dependency as they grow older.

Considering these numbers, there is a huge opportunity to treat obesity and thereby significantly reduce further growth in the number of people developing Type 2 diabetes, as well as other life-threatening conditions. Obesity is now recognised as a disease that increases the likelihood of comorbidities such as heart disease, hyperlipidaemia, hypertension, dementia,

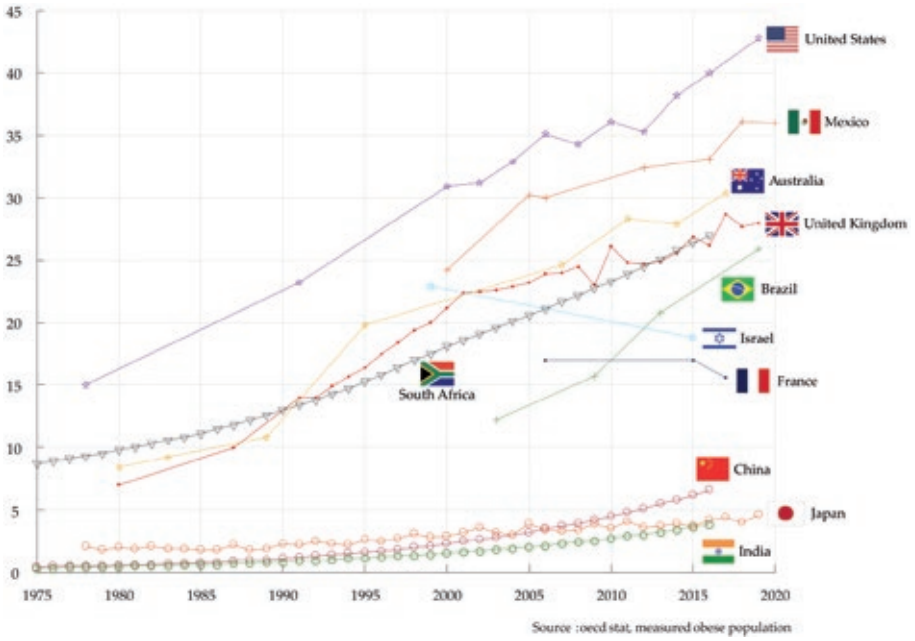

Figure 1: Obese population (BMI >30) in selected OECD countries (% of total population).

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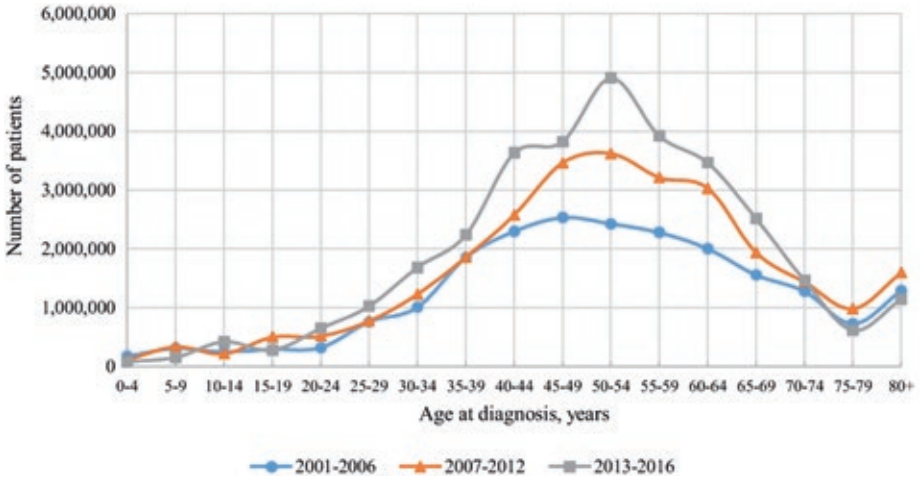

Figure 2: Number of US adults with diabetes by age of diagnosis.[3]

cancer and liver disease, as well as Type 2 diabetes. The overall costs to healthcare systems of treating these conditions is significant and there is a huge potential to reduce healthcare costs by reducing overall levels of obesity and Type 2 diabetes. The term diabesity is used to describe the combined adverse health effects of obesity and Type 2 diabetes / diabetes *mellitus*, and was coined in 1970s by Sims *et al*[1] to describe the very strong pathophysiological link between diabetes and excess body weight. Visceral adiposity, which leads to insulin resistance, is the putative mechanism in the development of diabesity, leading to insulin dependent Type 2 diabetes.[2]

THE RISE OF GLP-1 AGONISTS (INCRETIN MIMETICS)

Along with newer classes of oral drugs for treating Type 2 diabetes such as DPP-IV (dipeptidyl peptidase-4) inhibitors and SGLT-2 (sodium-glucose co-transporter-2) inhibitors, the GLP-1 (glucagon-like peptide-1) receptor agonist drug class is being prescribed to combat Type 2 diabetes and to slow patient progression towards insulin dependency.

The commercialisation of GLP-1 receptor agonists ("GLP-1s"), also known as incretin mimetics, that enhance the response of the GLP-1 receptor, began nearly 20 years ago in 2005, with the launch of twice-daily injections of AstraZeneca's Byetta (exenatide), followed by daily injections in 2010, with the launch of liraglutide (Victoza) from Novo Nordisk. The weekly formulations were launched around 10 years ago, but it was the launches of liquid-stable weekly formulations, such as Eli Lilly's Trulicity (dulaglutide) in 2014, Novo Nordisk's Ozempic (semaglutide) in 2017, and Mounjaro (tirzepatide), again from Lilly, in 2022, that is transforming the treatment of Type 2 diabetes today.

> "The GLP-1 journey did not stop at treating Type 2 diabetes alone but has moved on to treating obesity, typically using higher dosing."

The GLP-1 journey did not stop at treating Type 2 diabetes alone but has moved on to treating obesity, typically using higher dosing. Following the approval of daily injected liraglutide by Novo Nordisk in 2014, branded as Saxenda for treating obesity in selected patient populations, the two leading GLP-1s semaglutide, launched as Wegovy for obesity in 2021, and tirzepatide as Zepbound in obesity in 2023, are now set to transform the treatment of obesity. Table 1 (next page) summarises the major product launches from 2010 to 2023.

Today there are around 15 million Type 2 diabetics and obese patients already being treated with GLP-1s and this is likely to increase to more than 60 million patients within 10 years. This number is therefore greater than the current patient population of around 50 million insulin-dependent Type 2 diabetes.

IMPACT ON SELF-INJECTION DEVICE DESIGN

The development of pens for self-injection, which are essentially "cartridge-based" variable dosing, multi-dosing syringes, coincided with the development of peptide hormones and their frequent daily injections, namely insulin, human growth hormone (hGH), follicle-stimulating hormone (FSH) and parathyroid hormone (PTH), and their use for the administering GLP-1s followed.

Reusable pens, introduced in the 1980s, evolved to more convenient prefilled pens in the 2000s and most pen demand today serves the diabetes market: insulin for Type 1 and Type 2 diabetes as well as the growing demand for GLP-1-based injectable drugs. Today more than 12 million reusable pens and more than 1.7 billion prefilled pens are sold annually, with the majority still sold to deliver insulin. GLP-1s are now responsible for the additional growth in demand for pens.

Peptide hormones have a low molecular weight, just 3–30 kDa, and are generally preserved formulations for use in multidose pens. Based on daily injections, the shelf-life of most peptide hormones like insulin and hGH is up to 28 days. With the development of long-acting peptide hormones like GLP-1 and hGH, soon to be joined by long-acting insulin, which are injected on a weekly basis, the shelf-life has been extended to up to 56 days. The fact that some GLP-1 receptor agonists like semaglutide can be formulated in a preserved way means that pens are an option for GLP-1s.

TWO-STEP AUTOINJECTORS: ANTIBODY THERAPIES & GLP-1S

Autoinjectors, as their name implies, automatically insert the needle, and perform the injection. They are typically spring driven and usually designed for use with staked-needle prefilled syringes. Ideally the drug is liquid-stable, and the full dose is injected.

Autoinjectors were introduced in the 1970s for military and emergency use, and reusable autoinjectors were introduced for frequently injected peptide-based interferons for treating MS (multiple sclerosis) in the 1990s.

In 2006 weekly and biweekly antibody-based therapies, such as the TNF (tumour necrosis factor)-inhibitors Humira (adalimumab from Abbott, now AbbVie) and Enbrel (etanercept from Amgen and Pfizer), were introduced for the treatment of rheumatoid arthritis. It was with these launches that the market for prefilled autoinjectors was born.

Pharma	Generic Name	Brand	Frequency	Indication	Launch Year	Device
Novo Nordisk	liraglutide	Victoza	Daily	T2D	2010	
Novo Nordisk	liraglutide	Saxenda	Daily	Obesity	2014	
Eli Lilly	dulaglutide	Trulicity	Weekly	T2D	2014	
Novo Nordisk	semaglutide	Ozempic	Weekly	T2D	2017	
Novo Nordisk	semaglutide	Wegovy	Weekly	Obesity	2021	
Eli Lilly	tirzepatide	Mounjaro	Weekly	T2D	2022	
Eli Lilly	tirzepatide	Zepbound	Weekly	Obesity	2023	

Table 1: Launches of key GLP-1 related injectables by year (2010-2023).

Today's two-step manual-needle-insertion autoinjectors were subsequently launched 10 years later in 2016. They are buttonless, smaller and less complex than first-generation autoinjector devices. Today there are over 70 different drugs available in prefilled autoinjectors on the market totalling >450 million units annually.

Over the last seven years, more than 30 new devices have been launched and almost all are two-step push-on-skin devices.

The largest proportion of the marketed autoinjectors are already being sold for a handful of GLP-1 therapies dominated and controlled by the two market leaders, Novo Nordisk and Eli Lilly. Eli Lilly is the largest supplier of autoinjectors today, for Trulicity. With annual sales of US$7 billion (£5.5 billion), Trulicity is supplied exclusively in Lilly's three-step autoinjector presentation.

EASY-TO-USE PENS & AUTOINJECTORS: SIGNIFICANT DEMAND

As previously discussed, some of the new GLP-1 injected drugs like semaglutide, which are simple peptides, can be formulated to be administered from a pen or from an autoinjector, while others like dulaglutide, which consists of GLP-1 covalently linked to the Fc region (fragment crystallizable region) of human IgG4 (immunoglobulin G4), are not available in a preserved formulation suitable for a pen. It is worth noting that monoclonal antibody (mAb) therapies as typically used for the treatment of autoimmune diseases can only be formulated for single-use for delivery from an autoinjector.

> "Peptide hormone targets that are in development as part of dual and triple agonist molecules include glucagon, amylin or islet amyloid polypeptide (IAPP) and calcitonin."

The future growth of the pen and autoinjector market is largely dependent on the relative success of current- and next-generation GLP-1 drugs. Even though autoinjectors are more convenient for weekly injections, far fewer pen injectors are needed annually per patient. For example, based on a pen containing four once-weekly injections, a patient would only require 13 pens annually compared to 52 autoinjectors. For every 10 million patients this equates to 130 million pens compared with 520 million autoinjectors annually!

CONTINUED DEVELOPMENT OF INCRETINS AND OTHER PEPTIDE HORMONES: DUAL AND TRIPLE AGONISTS

The dynamic market for GLP-1s for Type 2 diabetes and obesity is growing exponentially and will be even more exciting in future as there are ever more molecules in development from a broad range of pharma companies.

Explaining one of the key ways in which this market will develop first requires some more detail about the incretins group of metabolic hormones, which stimulate a decrease in blood glucose levels. Incretins are released after eating and augment the secretion of insulin released from pancreatic beta cells of the islets of Langerhans by a blood-glucose-dependent mechanism.

The main incretins are GLP-1 and gastric inhibitory polypeptide (GIP). Whereas the first incretin agonists targeted just GLP-1, both GLP-1 and GIP are the active targets of some of the new dual agonists such as tirzepatide. Other peptide hormone targets that are in development as part of dual and triple agonist molecules include glucagon, amylin or islet amyloid polypeptide (IAPP) and calcitonin.

Novo Nordisk and Eli Lilly, clearly have a dominant position and economy of scale for drugs to treat Type 2 diabetes and obesity, and both companies have new dual and triple incretin agonists in their pipelines. Other companies have dual and triple incretin agonists in their pipelines and are looking to enter the market.

Daily oral drugs will enter the market to join Novo Nordisk's oral semaglutide, Rybelsus, in a few years' time, including a new group of oral GLP-1s that includes Pfizer's danuglipron and Eli Lilly's orforglipron (collectively known and the "gliprons"), with approvals likely from 2027. The new glipron class is a non-peptide GLP-1 receptor agonist which is easier to manufacture than GLP-1s currently on the market, and is expected to be cheaper. How these oral products will impact the use of injectables is unclear.

Figure 3: Ypsomed's key platform products for delivery of GLP-1 based therapeutics: UnoPen and YpsoMate.

"Ypsomed's comprehensive pen and autoinjector platform portfolio, including UnoPen and YpsoMate, is ideally positioned to support the burgeoning demand for peptide hormones for treating Type 2 diabetes and obesity."

YPSOMED PERFECTLY POSITIONED: BROADEST SELF-INJECTION PLATFORM PORTFOLIO

Ypsomed's comprehensive pen and autoinjector platform portfolio, including UnoPen and YpsoMate (Figure 3), is ideally positioned to support the burgeoning demand for peptide hormones for treating Type 2 diabetes and obesity.

Ypsomed is building its global manufacturing footprint in Switzerland, Germany and China and manufacturing options in US are currently being assessed. In addition, Ypsomed has ongoing development projects with a range of companies active in the peptide hormone space and is developing next generation devices to better serve the needs of Type 2 diabetes and obesity patients.

ABOUT THE COMPANY

Ypsomed's comprehensive self-injection device platforms consist of autoinjectors for prefilled syringes in 1 mL and 2.25 mL formats, disposable pens for 3 mL and 1.5 mL cartridges, reusable pen injectors and ready-to-use prefilled wearable patch injectors.

Since 1984, Ypsomed has focused on the development and manufacture of innovative injection systems. Ypsomed is well equipped to tackle digital healthcare challenges and has invested strategically in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed has moved beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases and integrating these insights with third-party digital ecosystems.

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

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ABOUT THE AUTHOR

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

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DRUG DELIVERY TRENDS FOR 2024

In this article, Tom Oakley, Vice-President Design and Development, and Kamaal de Silva, Principal Engineer, both of Springboard, consider how keeping abreast of the latest trends can help the industry predict and prepare for the future and, commenting from the company's privileged position at the centre of many of the drug delivery sector's most exciting developments, discuss the top trends to look out for in 2024.

THE BOOMING MARKET FOR WEIGHT MANAGEMENT DRUGS

Delivery devices for weight management drugs such as GLP-1s are, unsurprisingly, attracting huge development interest and funding. Originally developed to treat Type 2 diabetes, several GLP-1s have been approved for weight management and weight loss since Saxenda (liraglutide, Novo Nordisk) was approved in December 2014 (Table 1).[1]

The GLP-1 market is forecast to increase at 6.1% compound annual growth rate from 2021 to 2028, from a starting point of US$12.7 billion (£10.0 billion) in annual sales.[2] This projection may be conservative if GLP-1s are approved for additional indications, such as reduction of cardiovascular disease.

Most GLP-1 drugs need to be injected, but some oral GLP-1s are coming to market, for example, Rybelsus (semaglutide, Novo Nordisk), which was approved by the US FDA in September 2019, and by the EMA in April 2020.[3]

The first GLP-1s to come to market used repurposed insulin pens, or adaptations of existing autoinjector platforms. With the new GLP-1s in development, and the biosimilars coming to market, there is substantial opportunity (and funding) to develop better delivery devices.

> "With the new GLP-1s in development, and the biosimilars coming to market, there is substantial opportunity (and funding) to develop better delivery devices."

CLOSED-LOOP INSULIN SYSTEMS (ARTIFICIAL PANCREAS)

Since the FDA approved the MiniMed 670G in 2016, there have been several new hybrid artificial pancreas systems approved by regulators for the treatment of Type 1 diabetes (Table 2). The essential components of such a system are a continuous glucose monitor (CGM), an insulin pump and an algorithm, where the latter can be

	Dosing frequency			Brand name for each indication		
Drug	Twice daily	Daily	Weekly	Type 2 diabetes	Weight loss	Company
Exenatide	X			Byetta		AstraZeneca
Liraglutide		X		Victoza	Saxenda	Novo Nordisk
Lixisenatide		X		Lyxumia		Sanofi
Semaglutide (tablet)		X		Rybelsus		Novo Nordisk
Semaglutide			X	Ozempic	Wegovy	Novo Nordisk
Tirzepatide			X	Mounjaro	Zepbound	Eli Lilly
Exenatide			X	Bydureon		AstraZeneca
Dulaglutide			X	Trulicity		Eli Lilly

Table 1: Example GLP-1s and their brand names for diabetes and weight management indications.

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Medtronic MiniMed 670G/770G Tandem t:slim X2 pump with Control-IQ technology	

Table 2: Hybrid closed-loop systems approved for Type 1 diabetes in Europe and the US.[4]

implemented in the pump itself or on a separate device such as a mobile phone.

The time taken to develop, validate and launch these systems has prompted some people to adapt or develop their own DIY closed-loop systems, an example being the Nightscout project, which uses the tagline #WeAreNotWaiting.[5] The risks of using systems that have not been through regulatory approval are being addressed by initiatives such as Tidepool, which achieved FDA clearance for Tidepool Loop in January 2023.

High costs are also a large factor in driving users to DIY systems.[6] However, approved systems will be provided by an increasing number of public health providers, such as the UK NHS, over the next few years.[7] This increase in user base should lead to increased interest and investment in 2024.

The significant market for diabetes management has fuelled significant innovation in closed-loop delivery systems, but similar technologies are expected to be applied to a range of indications outside of diabetes where self-monitoring and self-administration can bring benefits for patients and payers.

LARGE-VOLUME INJECTION

Large-volume injection continues to be a hot topic due to the formulation requirements of some new biologics and the preference to move some therapies from intravenous infusion to subcutaneous injection. There are two main categories of delivery devices for large-volume subcutaneous injection:

- On-body delivery systems, also called patch pumps, bolus injectors and other names
- Large-volume autoinjectors.

Relatively recent approvals of on-body delivery systems include Alexion's (MA, US) Ultomiris® (ravulizumab-cwvz) in the West (PA, US) SmartDose platform in September 2022,[8] and Apellis Pharmacueticals' (MA, US) Empaveli® (pegcetacoplan) in the Enable (OH, US) enFuse platform in September 2023.[9] There are many other on-body delivery systems in development, with some on the market.[10]

The biggest change in the past year, and the biggest question for 2024, is the emergence of large-volume autoinjector platforms. Most autoinjector platforms are based on a 1 mL staked needle and, in recent years, 2.25 mL syringes have started to be supported. The increasing capability for larger volumes has been extended to 3 mL in cartridge-based autoinjectors, such as Gerresheimer's (Düsseldorf, Germany) Inbeneo or SHL Medical's (Zug, Switzerland) Maggie platforms.

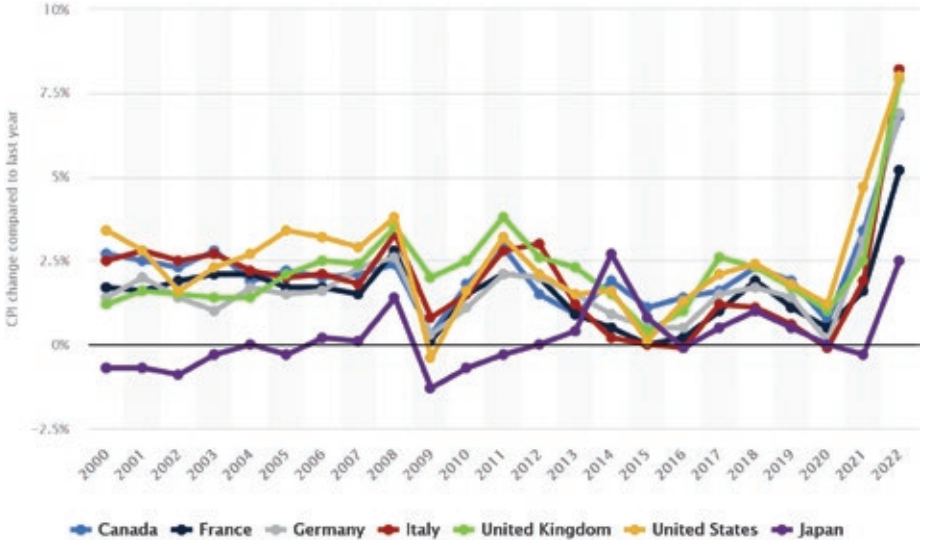

Figure 1: Annual inflation rates in G7 countries from 2000 to 2022.[14]

In the past year or so, several autoinjector families have been extended to 5.5 mL, such as Ypsomed's (Burgdorf, Switzerland) YpsoMate 5.5 (based on a syringe)[11] and Maggie 5.0 (based on a cartridge).[12] The question is how much these 3 mL and 5 mL autoinjectors will eat into the market for on-body injectors.

OPHTHALMIC INJECTIONS

Ophthalmic injections have specific requirements that mean that standard injection systems are often inappropriate, such as:

- Very low particulate limits
- No suction
- Minimal increase in intraocular pressure
- Difficult access and targeting
- Small dose volumes and strict dose accuracy.

The ophthalmic drugs in development, and the new solutions that they require, have created a steady stream of device innovation over recent years that is expected to continue, or even increase, in 2024.

The ophthalmic drug delivery market is split roughly equally between topical applications and injections, so it is important to remember the innovation opportunities for topical applications such as eyedroppers or, more recently, spray devices. The usability of preservative-free eyedroppers could be improved, for example, by reducing their squeeze force, reducing the chance of multiple drops and assisting alignment with the eye.

NEW DEVELOPMENT BUDGETS FOR 2024

Every annual cycle comes with its changes to budgets, so why raise the subject for 2024? The reason is that the healthcare industry went through a substantial boom from mid-2020 through to late 2021, or perhaps even mid-2022 (coined the "covid dividend"),[13] and a market correction since then.

The healthcare industry has faced significant headwinds since the middle of 2022, including:

- The full-scale Russian invasion of Ukraine leading to shocks in financial markets and some supply chains
- Energy prices increasing substantially
- High inflation pushing up wages and other costs (Figure 1)

- The sales of various covid-19 mitigations reducing substantially, such as vaccines, other covid-related drugs, personal protective equipment, certain diagnostics, critical care equipment and so on.

These headwinds led to waves of redundancies and budget cuts through 2023. With inflation reducing in leading economies (Figure 2) and the industry having made corrections for the other adverse factors, there is cautious optimism that 2024 will return to increased investment in R&D and innovation.

Some companies are displaying corporate agility and moving back towards investment for 2024. Fast-forwarding to the end of 2024, it can be expected that those agile companies will have a competitive advantage over those that continue to restrict investment in R&D.

> "Fast-forwarding to the end of 2024, it can be expected that those agile companies will have a competitive advantage over those that continue to restrict investment in R&D."

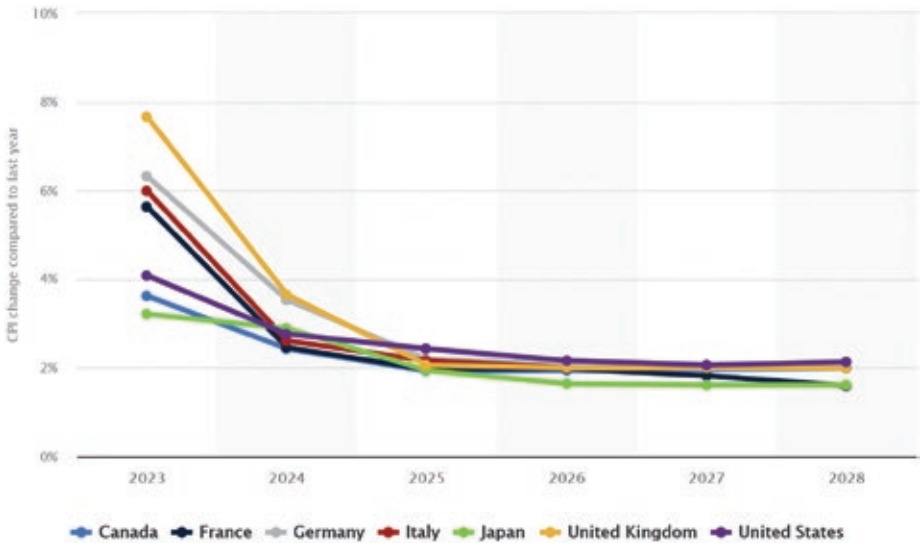

Figure 2: Forecast of annual inflation rates in G7 countries from 2023 to 2028.[15]

SUMMARY

Sales of GLP-1s are predicted to increase and the trend is expected to accelerate if new indications, such as reducing cardiovascular disease, are approved. This means there will be greater funding and demand for improved GLP-1 delivery devices.

Closed-loop diagnostic-and-delivery systems are maturing for diabetes. The principles involved could be applied to many other indications, perhaps with new devices and algorithms tailored to the different user needs and technical requirements.

New on-body large-volume delivery systems continue to gain regulatory approvals and face competition from large-volume autoinjectors. Meanwhile, ophthalmic drug delivery is an area ripe for innovation in 2024, for both injection and topical devices.

Finally, 2024 promises to be a year of increased investment in drug delivery devices as companies emerge from the post-covid correction in healthcare sales and economists predict reductions from uncharacteristically high energy prices and inflation. It remains to be seen which companies are most agile in adapting to the new opportunities in drug delivery.

If you have questions or would like to discuss any points, please do not hesitate to contact the authors.

ABOUT THE AUTHORS

Tom Oakley leads engineering and scientific teams developing new injection devices, pumps and inhalers. He has been the named inventor on dozens of patents throughout his 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).

Kamaal de Silva is an experienced engineer who has led design and development projects at Springboard on a range of drug delivery devices, including infusion pumps, on-body delivery systems, autoinjectors, pen injectors and soft mist inhalers. He is committed to developing innovative hardware and software-based solutions that enhance user experiences, improve healthcare outcomes and satisfy key business requirements. Mr de Silva studied Mechanical Engineering at Imperial College London (UK). The knowledge he has accrued throughout his career has led to a comprehensive understanding of design, manufacturing and scientific principles that he can leverage to create robust, risk averse designs.

ABOUT THE COMPANY

Springboard is a technology and design consultancy, and forms Sanner Group's Design Centre of Excellence. Springboard creates and develops new products and technology, including products in the field of medtech and drug delivery devices, assisting companies in resolving technical challenges and decreasing time to market.

Sanner GmbH was founded in 1894. Headquartered in Germany and with best-in-class manufacturing facilities across Germany, France, Hungary and China, Sanner has successively developed from a global market leader for desiccant closures and effervescent tablet packaging into a sought-after provider of customised solutions in the areas of medical devices, diagnostics, pharmaceuticals and consumer healthcare. Today, Sanner supplies its products to more than 150 countries globally and has over 600 employees.

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A SYMBIOTIC RELATIONSHIP BETWEEN DRUG DELIVERY DEVICE SYSTEMS AND PHARMA

In this interview, Troels Keldmann, PhD, DDS Device Consultant and Adviser, discusses the significance of the drug delivery industry, its relationship to pharma, the challenges it faces and how the pharma industry is shaping the drug delivery device field.

DR TROELS KELDMANN, KELDMANN HEALTHCARE

Troels Keldmann, PhD, MBA, has spent 25 years in DDS devices and the medical devices industry, working cross-functionally across development, technology sourcing, innovation, IPR-strategy, business development, external innovation, partnering and technology commercialisation. As Interim Technical Lead on Injection Devices at LEO Pharma A/S, Dr Keldmann headed the identification, evaluation and selection of subcutaneous injection devices. His earlier DDS experience includes co-founding and heading innovative DDS technology start-ups up to industry sale exit and working as a consultant in DDS devices for pulmonary, nasal, subcutaneous (both needle-based and needle-free) and intramuscular delivery. Dr Keldmann has been appointed as Business Coach by the European Innovation Council EIC and Industry Fellow at the Technical University of Denmark. He holds a BSc, MSc and PhD in Mechanical Engineering & Innovation and an MBA.

Q Why is the drug delivery device industry an important industry?

A To me, drug delivery device systems (DDSs) are where the drug meets the patient and the healthcare professional (HCP). Identifying the correct drug dosing and delivery route ensure that efficacy and safety are realised for the patient. However, there is more to it. When we are successful in this industry, the DDSs are accurate and convenient, resulting in compliance and adherence to therapy. We get the intended therapeutic outcome for patients and the best commercial outcome for the pharma company. So, I see both a technical and commercial side to why our industry is important.

> "When we are successful in this industry, then the delivery systems are accurate and convenient, resulting in compliance and adherence to therapy."

A DDS can be the technological "enabler" for a drug, but it can also be the element that differentiates "similar drugs". These two aspects drive the need for innovation. Often, device development and manufacturing are not internal competencies within pharma companies. This creates a need for external innovation and manufacturing. The drug delivery device industry fulfils that need.

Our industry has become significant. Alone, the global injectable drug delivery device market size was estimated at a value of more than US$15 billion (£11.8 billion) in 2022. And, more broadly, if you include inhalation and transdermal delivery devices, for example, the global market size is estimated to be over $39 billion. In my view, the industry is attractive due to the market size, unmet needs in new therapeutics and improvement opportunities for acute and chronic patients.

Q Please describe how you became involved in this sector?

A My way in was a bit different to others I have met in our industry. I did not go directly into injectable drug delivery, but had an entry in inhaled delivery, coming from the role of an innovator.

I grew up in a family of innovators and entrepreneurs, so spotting unmet needs and addressing them was a part of daily life. My family responded with interest when a distant family member directed our attention to unmet needs in asthma inhalers. At that time, I was studying engineering at university. At first, it was a spare-time project , and stayed that way for several years, but it evolved into a spin-out company from the family business. After completing my PhD in Product Innovation, I committed myself to lead the spin-out. So, at a young age, I became an innovator in this industry. We created a unique, patented device technology platform for pulmonary and nasal delivery. Thirteen years later, we completed an industry sale exit to a North American specialty pharma company.

During those years, we matured the two device technologies and advanced a portfolio of three generic asthma drugs into clinical trials in a pharma partnership. I learned how to blend hands-on DDS technology maturation with strategic commercial thinking on applications and intellectual property rights (IPR)-based commercialisation in pharma deals.

After the industry sale, I directed my attention to DDSs for injection. This has included consulting tasks on device commercialisation and a management role in a venture capital-backed injection device start-up. Later, I took up longer-term

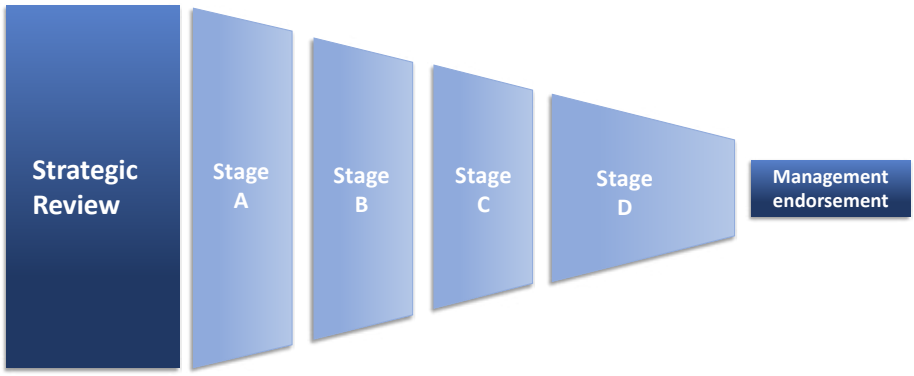

Figure 1: Strategic review to endorsement in six steps.

consultant roles in corporate pharma with a focus on strategic review and selection of injection devices and suppliers (Figure 1). On top of that, I am a Business Coach for technology innovators in the EIC Accelerator programme under EISMEA. In that role, I have coached injection device innovators.

I am experienced on both sides – innovator and corporate. I bridge technical and commercial perspectives, and I work at cross-functional and cross-management levels. My experience enables me to work hands-on with an executive's mindset.

Q What do you see as the two to three main current or emerging trends in pharma, and healthcare more broadly, that are going to shape the injectable drug delivery space over the coming years?

A In the general picture, I have noticed that biological treatments are increasing and current pharma R&D pipelines indicate that a continued rise in the number of available treatments is likely. These therapies are costly, which will be challenging for healthcare systems that are already affected by increasing costs. So, paying attention to value-based healthcare is logical – from the initial drug–patient match to any later follow-up on actual outcomes. In my view, the new opportunities in digital tools and artificial intelligence will be important enablers, but will still require approval, endorsement and adoption among HCPs and patients. The general societal awareness of environmental sustainability will also have an impact on the DDS sector.

Specifically for the injectable drug delivery space, biologicals have clearly influenced DDS R&D, especially in the development of large-volume injectors. Significant attention is being directed towards larger-volume injectors and the liquid properties of biologics, notably their higher viscosity, which is even higher under cold storage temperatures. All this leads to longer injection times. So, the concept of on-body and wearable injectors has spread.

We have not yet seen wide implementation of these device solutions to the extent expected a few years back. In my view, part of the explanation may be that, in many indications, marketed biologics are first or second in class. The drug itself is a strong differentiator. This means that the pharma companies prioritise the earliest possible product launch to capitalise on their drug asset to the greatest extent possible. I believe that this explains why prefilled syringes and autoinjectors are preferred by pharma. This may change when differentiation of the drug efficacy and safety becomes insufficient by itself. In that case, both lifecycle management of successful drugs and new drug launches of "similars" will focus on product differentiation by the DDS. In my opinion, that could bring renewed opportunity for alternatives to the currently used injectable delivery systems.

Biologic therapies are costly for healthcare systems, so the focus on patient outcomes, compliance and adherence will increase. The availability of digital tools is an important enabler, which will likely impact the injection systems. Either these digital solutions will be applied for data capture in clinical trials or tools will be added for general use with the launched drug product. It is logical to consider the ways in which these tools can be integrated or combined with the DDSs. Digital tools and innovation are still considered "external innovation" by pharma companies. So, in my view, the DDS industry has the opportunity to take the "integrator role" when linking digital tools and the delivery device in clinical and commercial use cases.

> "The availability of digital tools is an important enabler, which will likely impact the injection systems."

The environmental sustainability agenda will also influence the industry, if not by direct regulation, then by pharma and device companies applying their own environmental policies to their operations. If you attend conferences, then many insights are being shared through lifecycle analysis (LCA) of injectable delivery systems. I know from dialogue with LCA specialists that the challenge is how you frame your analysis – either as a specific part of the product lifecycle or the "largest picture". Currently, attention is on energy and materials (recycled, reusable, recoverable). From an environmental perspective, there are different implications with injectors using different types of power source: mechanical spring, gas container, battery and electro mechanical, osmotic force, etc. In my view, choosing device solutions with a significantly high environmental impact may soon require explainable justification.

Q In your experience, how well does pharma communicate its DDS requirements to the devices sectors? Likewise, how well is the DDS industry aligned to pharma's requirements?

A My experience is that most pharma companies are able to state what they are looking for when you ask them. Especially when you are in close dialogue with the central people in R&D or Commercial. It may be necessary to communicate under a non-disclosure agreement (NDA), the reason being that key device specifications may mirror confidential characteristics of the drugs in development or the company's confidential strategic priorities on device technology. Mostly, I find that pharma companies prefer that device companies share device characteristics, performance intervals and customisation dimensions. On that basis, pharma companies will consider the relevance of requesting test samples for their own evaluation, or they may request specific feasibility tests to be performed by the device company. The scope is two-fold on the pharma side – searching for technology with specific characteristics and scouting for novel and potentially future-relevant device technologies.

Regarding alignment with pharma needs, my opinion is that a wide range of DDS technologies with different performance and use characteristics are available. However, besides the device performance parameters, there are additional aspects such as technology maturity, IPR and freedom to operate, fit with preferred primary packaging, a supplier's track record and supply cost. The ideal device solution from an application perspective for the pharma company may not readily meet the additional key criteria. Consequently, the matching of pharma needs with device technology may be a longer process.

Q What challenges do you see for device innovators when selling to pharma, and how can device companies overcome these challenges?

A Generally speaking, it is challenging to be an innovator. Access to the right people in the targeted pharma company is key. The Commercial or R&D departments are often the preferred contact points, although Business Development is a reasonable alternative. Having had prior contact at conferences or on other occasions is a significant advantage that can ease the process. Here, the long-established device companies – with a track record of prior contact and approved and marketed innovations – often face less of a challenge.

> "The deeper your dialogue with pharma, the more internal stakeholders will be involved in the evaluation of your innovation."

The perceived relevance and uniqueness of your innovation will determine the attention you receive. Your value proposition has to be clear and quantified. You need to reveal enough about your innovation to establish sufficient interest and demonstrate willingness to enter an NDA.

You will benefit from having a visualisation of your ideal use cases where all the unique characteristics of your innovation are impactful. Explain the difference between your innovation and the current reference solutions and back it up with data. Novelty requires high attention to communication.

The deeper your dialogue with pharma, the more internal stakeholders will be involved in the evaluation of your innovation. The range may include R&D (e.g. device, formulation, primary packaging, human factors engineering, drug programme), commercial (e.g. marketing, sales), regulatory affairs, quality assurance, manufacture (e.g. MSAT), procurement and IPR. The challenge is that gaining support from all stakeholders is important. So, the most convincing approach is to craft information packages for each type of stakeholder. Ideally, these packages should be both convincing and self-explanatory, which can be a serious challenge. You will be assigned a key contact person, who, ideally, will be championing your innovation inside the pharma company. With self-explanatory packages, the internal review will be less dependent on the expertise and availability of your key internal contact.

Pharma companies often prefer to engage with device innovators with a proven track record, including for device manufacturing capacity. For smaller and younger innovator companies, I would recommend teaming up with an established contract development and manufacturing organisation. This will strengthen your credibility in any dialogue with pharma.

As I've already stated, access to the right people is important, but timing is also very important – matching up with an R&D pipeline, prioritised disease areas, product lifecycle management and the pharma company's general competitive situation. These are challenging factors that are out of your control. So, it is essential to establish contact and remain in contact with pharma, even over longer periods. At some point, the timing may become right for your innovation.

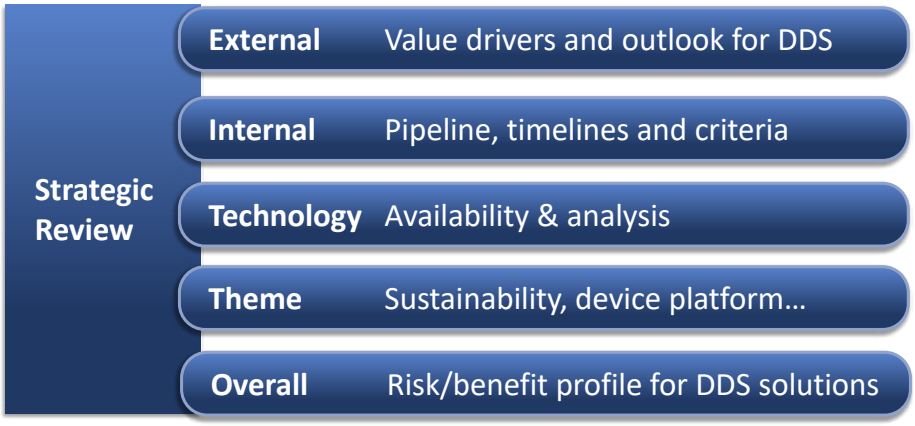

Figure 2: Five work streams in strategic review.

Also related to timing, it is important that you make your innovation visible and findable for those who perform technology searches. Industry publications, conferences and online platforms are ideal for showcasing your innovation. ONdrugDelivery has been instrumental in my work on commercialising drug delivery technology.

Q What challenges do you see for pharma companies deciding on injection devices and how can they overcome these challenges?

A Device selection may appear to be a straightforward task. But, when you dig into the implications of device selection, it is clearly a strategic decision. Even more so if you intend multiple drugs to share a single device platform. Matching the device's technical performance parameters with the drug's dosing and liquid characteristics is a basic exercise, but any need for device development and adaptation may impact overall drug programme-related timelines and risk. The device may have compatibility issues with specific primary packaging, as well as with the preferred fill-finish lines (either internal or with a contract manufacturing organisation). Obviously, the device is central in the user experience for patients and HCPs, so usability and human factors are key elements – especially if the device is to be used by different patient categories. Finally, the device is likely to be used for a significant period of the drug's time on the market. So, the device selection also means entering into a supplier–development relationship that is expected to last for long time – ideally, a productive and robust partnership based on trust, collaboration, competence and capacity. This aggregate set of aspects is complex and has long-term impact, so you need these decisions to align with broader corporate goals and long-term strategies. In my view, this requires a structured and systematic approach to device selection.

> "Obviously, the device is central in the user experience for patients and HCPs, so the usability and human factors are key elements – especially if the device is to be used by different patient categories."

In my experience, there is value in any prior internal work on device selection. So, build upon existing knowledge and expertise – such as from your collection of information, analysis and prior decisions. If the right strategic clarifications are in place and all device selection criteria are defined, then you can move into a funnel of steps where device alternatives are evaluated. If these aspects are not in place, then you need a device strategy process where cross-functional teams collect and extract information for strategic analysis. Generally, there will be an internal analysis, external analysis and technology analysis (Figure 2). The technology analysis should include availability and trends, IPR situation, timelines for device development and adaptation, costs and risks; the external analysis should focus on user preferences, regulatory requirements, competition and future trends; and the internal analysis should include pipeline, timelines, competences, resources and necessary alignment with business strategy.

Internal stakeholder involvement and management is key in both the strategy process and the later funnel of device-selection steps, so cross-functional involvement is critical. I use visualisation tools and diagrams to ease the understanding of the most complex issues, which are also useful when sharing and discussing across management levels up to C-suite. Be diligent on taking minutes in meetings – it will help you keep momentum during the process of reaching a final selection and recommendation to management.

This brings me back to the earlier question of the importance of the DDS industry. When we pair the right drug with the right device, then it results in both the intended therapeutic outcome of drugs for patients and the best commercial outcome for the pharma company. This is key to my motivation for my consulting work with device innovators and suppliers and with pharma on DDS projects.

ABOUT THE COMPANY

Keldmann Healthcare A/S is a family-owned DDS innovation and business development consultancy. The company is experienced with various drug delivery routes and offers its services as a team member or lead in client projects on:

- Drug delivery device search
- Device strategy and selection
- Concept development and IPR strategy
- Partnering and commercialisation
- Industry sale exit.

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KEY CONSIDERATIONS FOR SUCCESSFUL COMMERCIALISATION OF DRUG-DEVICE COMBINATION PRODUCTS

In this article, Bill Welch, Executive Director of Services, PCI Pharma Services, delves into the key considerations that stakeholders must address to ensure the successful commercialisation of drug-device combination products.

In the rapidly evolving landscape of patient-centred healthcare, the intersection of drug product and medical devices has given rise to a unique drug delivery category of products known as drug-device combination products. The emergence of drug-device combination products, where a large- or small-molecule drug product is integrated with a medical device, has paved the way for novel therapeutic solutions.

Driven by the growing prevalence of chronic disease, such as diabetes, respiratory disease and cancer, advancements in the drug-device combination product market are expected to have a significant impact on the healthcare sector over the coming years. According to a recent report by insightSLICE, the global drug-device combination products market, which was valued at US$109.17 billion (£86.4 billion) in 2022, is estimated to be $236.36 billion by 2033, with an estimated compound annual growth rate of 7.2% between 2024 and 2033.[1]

These innovative drug delivery solutions offer the promise of enhanced therapeutic outcomes by seamlessly integrating drug products and delivery devices, but their development and commercialisation come with a set of intricate challenges.

REGULATORY LANDSCAPE

Navigating the regulatory landscape is arguably the most critical aspect of developing and commercialising drug-device combination products. Regulatory agencies, such as the US FDA and the EMA, have established specific guidelines to ensure the safety and efficacy of these complex products.

First, companies must determine the regulatory pathway applicable to their product. Understanding the regulatory classification of a drug-device combination product is essential and depends on its principal mode of action. This will dictate whether the product will be regulated as a medical device, a drug or a combination product. This determination influences the type of regulatory submission required and the specific requirements for demonstrating safety and efficacy.

> "Navigating the regulatory landscape is arguably the most critical aspect of developing and commercialising drug-device combination products."

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HUMAN FACTORS AND USER EXPERIENCE

Human factors engineering is a critical aspect of drug-device combination product development. With a patient-centric focus, interaction between users and the product as-received is paramount. Understanding how patients and healthcare professionals interact with the packaging, instructions for use and the device itself is vital for optimising usability, minimising user errors, and enhancing overall safety, efficacy and adherence to gain improved outcomes.

Conducting usability studies and incorporating human factors considerations early in the design process can help to identify potential issues and inform design modifications. Human factors and usability engineering is an integral component of regulatory submissions and essential for demonstrating the product's usability and user comprehension.

DESIGN CONTROL AND DEVELOPMENT CHALLENGES

The successful integration of a drug and a device requires meticulous design control to address the unique challenges posed by combination products. The compatibility of the drug product and the device, as well as the potential impact on the product's stability and performance, must be thoroughly assessed during the development phase.

Additionally, establishing a robust risk management plan is crucial to identify and mitigate potential issues that may arise during product development. This includes addressing concerns related to drug stability, device functionality and any possible interactions between the two components.

Whether internally at the biopharmaceutical company or the company's preferred partnering contract development and manufacturing organisation (CDMO), it is imperative that multidisciplinary teams work together across drug product development and packaging design to ensure compatibility.

QUALITY AND MANUFACTURING CONSIDERATIONS

Ensuring the quality and consistency of drug-device combination products is paramount. Manufacturers – whether the biopharmaceutical company or their partnering CDMO – must adhere to good manufacturing practices to guarantee the reproducibility and reliability of the product. This involves implementing rigorous quality control measures at every stage of production, from raw material sourcing and sterile filling of the drug product into the primary container to final drug-device combination product assembly, labelling and packaging.

Validating robust, scalable manufacturing processes and controls is essential to produce combination products with consistent quality and performance throughout the drug-device combination product lifecycle, from clinical trials to commercial market supply.

CLINICAL DEVELOPMENT

The generation of robust clinical evidence is paramount for the successful commercialisation of drug-device combination products. Companies must design and conduct clinical trials that not only demonstrate the product's safety and efficacy but also provide meaningful real-world data on the interaction between the drug and the device.

FIVE TRENDS IN DRUG-DEVICE COMBINATION PRODUCT FINAL ASSEMBLY

1. **Preference of top-opening cartons to hold multiple devices simultaneously:** Not only do top-opening cartons provide the benefits of immediate presentation of entire contents for users, superior integration of disparate elements, such as additional needles and small vials, more evident tamper protection and ease of reclosure but, more importantly, they provide ease of access for the patient and aid patient compliance.
2. **Convergence of packaging engineering and human factors:** The convergence of packaging engineering and human factors is propelled by the need to create packaging solutions that prioritise the user experience, safety and usability. This interdisciplinary approach ensures that packaging not only serves its primary function of protecting products but also enhances the overall patient experience, contributing to product success in the market.
3. **Earlier adoption of devices within the clinical lifecycle:** Early adaption is driven by a combination of factors, including a focus on patient centricity, improved clinical data accuracy, safety monitoring, real-world simulation, competitive positioning and regulatory considerations. As the pharmaceutical industry continues to prioritise patient experience and adherence, the use of drug-device combination products in early clinical trials will remain a prominent and strategic choice for many companies.
4. **Multiple formats for regional presentations:** Companies are increasingly bringing different injectable formats to different geographical territories. Often driven by cost and reimbursement, for example, some may commercialise vials with syringes for Eastern European markets but may look to more advanced prefilled syringes (PFSs) with safety devices or autoinjectors or even on-body injectors for the US or Western Europe.
5. **Testing, testing, testing:** Once a secondary consideration with developing a drug-device combination product, testing is now front and centre. Presentation and batch size will shape testing requirements and level of automation.

The design of clinical studies should align with regulatory requirements and consider the unique challenges posed by drug device combination products. Well-designed clinical trials should consider patient populations and clinical endpoints. Collecting data on both the drug and device components individually, as well as their combined effects, is essential for building a comprehensive body of evidence to support regulatory submissions.

DEVICE STRATEGY – INTELLECTUAL PROPERTY PROTECTION

Forming part of the device strategy, securing intellectual property (IP) rights is a critical consideration in the competitive landscape of drug-device combination products. Companies must navigate patent landscapes carefully to protect their device innovations and establish a strong IP position. This includes considering both the drug and device components, as well as any novel aspects of their combination.

"Ensuring a robust and secure supply chain is vital for the commercial success of drug-device combination products."

SUPPLY CHAIN MANAGEMENT

Ensuring a robust and secure supply chain is vital for the commercial success of drug-device combination products. Companies should establish strong relationships with suppliers and partnering CDMOs, implement risk mitigation strategies and have contingency plans in place to address potential disruptions. This is particularly important given the interconnected nature of the drug and device components, each with its own set of manufacturing and sourcing considerations.

ADVANCED DRUG DELIVERY SOLUTIONS AT PCI PHARMA SERVICES

The increasing use of biologics, which often require specialised delivery systems, has contributed to the growth of drug-device combination products and the need for technically advanced sterile manufacturing and specialised advanced drug delivery assembly, testing and packaging support. Committed to being a market leader in the packaging of biologic drug products for its global clients, PCI Pharma Services' goal is to support its customers in safely and efficiently bringing their novel therapies to patients.

Driven by innovation and patient centricity, the company's design and development expertise, combined with its device assembly and advanced drug delivery packaging capabilities, offers flexible solutions for a diverse portfolio of conventional and specialty injectable drug-device combination products (Figure 1). PCI has the scalability to handle dynamic volumes, large or small, from niche personalised medicines to large-volume treatments.

EXPERT ADVICE FROM DEVICE STRATEGY TO PACKAGING DESIGN

With a global network of experts with extensive experience in advanced drug delivery, PCI provides guidance at critical milestones to assist its clients in developing an optimum patient-centric drug-device combination product.

The company's deep industry experience can help to determine the best device strategy for clients' patients and drug products, from the use of established, well-accepted platforms that have previously received regulatory approval as part of a drug-device combination product – which may be deemed lower risk – to, alternatively, developing a more innovative device approach that may be more attractive for specific patient populations compared with that of more readily available platforms.

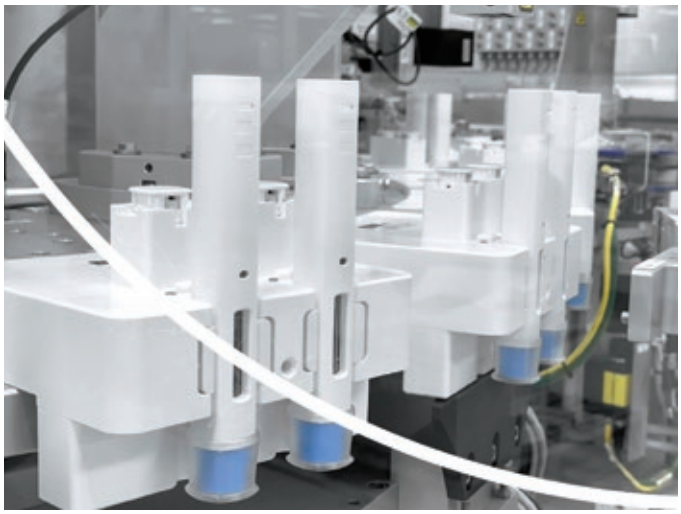

Figure 1: PCI provides specialised advanced drug delivery assembly, testing and packaging support.

PCI's pharmaceutical packaging design department provides an innovative and value-added service. The company's in-house team of specialists delivers insightful packaging design and practical knowledge to deliver differentiated and cost-effective packaging solutions (Figure 2). Working with client partners as early as possible during their drug products clinical phases, PCI's design team – together with a cross-functional network of experts in sterile drug product manufacturing, engineering, operations and approved vendors – develop expert design processes focused on human-factors engineering and technical functionality to deliver patient-centric designs optimised for manufacturability, scalability and automation. This seamless solution ensures that key considerations are addressed at the right time, leading to both cost and time efficiencies and, ultimately, ensuring speed to market.

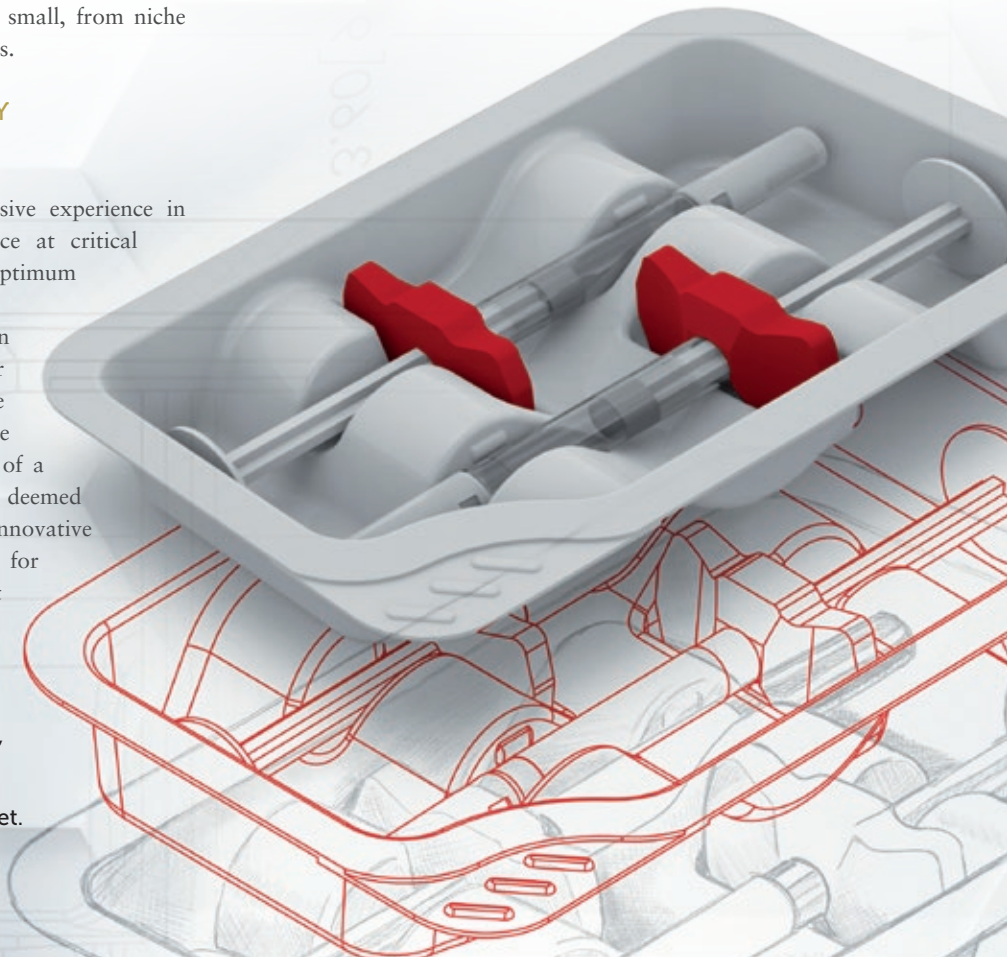

Figure 2: PCI's expert packaging design team, using three-dimensional modelling can facilitate rapid prototype design and an expedited response to enable speed-to-market.

Figure 3: PCI is investing to expand its Rockford (IL, US) site to meet the growing biologic market need for specialised assembly and packaging of injectable drug-device combination products.

EXPANSION OF DRUG-DEVICE COMBINATION PRODUCT CAPABILITIES AND CAPACITIES

Complementing the continued growth and investment across PCI's sterile manufacturing network, the company continues to expand its European, North American and UK Centers of Excellence for clinical and commercial packaging. These state-of-the-art facilities are equipped with advanced drug delivery packaging technologies for the assembly and labelling of vials, cartridges, standard PFSs, advanced safety syringes, autoinjectors and pen devices complete with integrated top-load cartoning and serialisation.

Most recently PCI announced an investment of $150 million in a new 200,000 sq ft facility at its Rockford (IL, US) site to meet the growing biologic market need of specialised assembly and packaging for injectable drug-device combination products. With over 20 dedicated suites, the new facility will support the assembly and packaging of vials, PFSs, autoinjectors, on-body injectors and pen cartridges, such as those for glucagon-like peptide 1 agonists for the treatment of diabetes and obesity, as well as those needed for oncology treatment and autoimmune diseases (Figure 3).

FLEXIBLE, SCALABLE AUTOINJECTOR ASSEMBLY

As a leading global CDMO, PCI Pharma Services provides highly flexible, reliable advanced drug delivery packaging solutions to meet the dynamic needs of its clients. Meeting the exponential growth in the development and use of autoinjectors, PCI continues to invest in innovative scalable autoinjector assembly, labelling and packing technologies.

Although many autoinjectors have similar components, their design varies in terms of size, material and shape. With true customer focus and flexibility at the core of the company's injectable packaging service offering, its technologies can adapt to the unique requirements of each global market from concept to commercialisation.

> "Providing integrated scalable solutions, PCI's larger-scale technologies can also accommodate various autoinjector types to support product launches and commercial market supply."

For example, PCI's small-to-mid-scale autoinjector assembly lines provide multi-platform autoinjector solutions, including Ypsomed's Ypsomate, SHL's Molly and BD's Physioject, alongside other platform devices. They also have the capability to assemble and label needle safety device platforms, such as BD's Ultrasfe/Plus and Nemera's Safe & Sound, making them ideal for development studies, clinical trials and niche orphan drugs.

Providing integrated scalable solutions, PCI's larger-scale technologies can also accommodate various autoinjector types to support product launches and commercial market supply. Providing true customisation, its larger-scale lines can easily and cost-effectively be retooled for future new autoinjector types, allowing the company to respond quickly and efficiently to technological changes and future innovation.

SEAMLESS MANUFACTURING, PACKAGING AND TESTING SOLUTIONS

At PCI, ensuring life-changing medicines reach those who need it most is the highest priority. As a truly integrated global CDMO, the company is an expert in manufacturing, packaging and supply chain, harnessing its experience and expertise to deliver seamless solutions with the ultimate aim of improving the lives of patients.

Providing expert sterile fill-finish and lyophilisation solutions from development to commercialisation, together with integrated custom assembly and packaging solutions for sterile injectables, allows for ultimate knowledge sharing and communication between teams to ensure the drug product packaging is optimised for the product, patient and production.

With in-house laboratories, PCI provides a range of packaging and analytical services to support clients' development, clinical and commercial supply of medicines globally. From product identity testing, method transfer, release and stability testing to autoinjector system testing with ISO 11608 functional tests, such as cap removal force, activation force, extended needle length, dose accuracy, injection time and lockout force, the company ensures that clients' life-changing therapy meets regulatory guidelines and is safe for patient use (Figure 4).

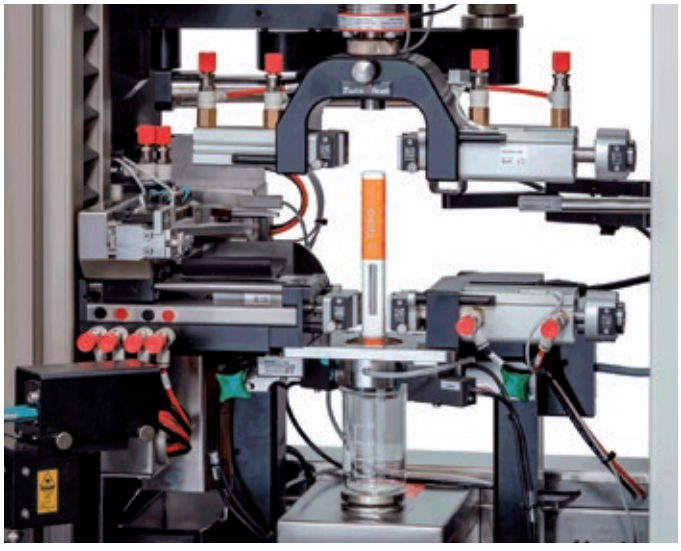

Figure 4: PCI provides a range of onsite device functional testing for drug-device combination products, according to ISO 11608, ISO 11040 and ISO 7886. Image courtesy of PCI's partner ZwickRoell.

CONCLUSION

Successful commercialisation of drug-device combination products requires a multidisciplinary holistic approach, combining expertise in drug product and medical devices. By addressing the key considerations outlined above and when needed, partnering with an expert CDMO, such as PCI Pharma Services, manufacturers can navigate the challenges along the journey to commercialisation, ensuring the successful integration of drug and device components and, ultimately, delivering life-changing therapies to patients.

ABOUT THE COMPANY

PCI Pharma Services is a leading global CDMO, providing integrated end-to-end drug development, manufacturing and packaging solutions to increase product speed to market and opportunities for commercial success. PCI Pharma brings the proven experience that comes with more than 90 successful product launches each year and over five decades in the delivery of supply-chain healthcare services. With 30 sites across Australia, Canada, North America, the UK and Europe and over 5,500 dedicated employees, the company's mission is to bring life-changing therapies to patients. Leading technology and continued investment enable PCI to deliver development to commercialisation solutions throughout the product lifecycle, collaborating with its clients to improve the lives of patients globally.

REFERENCES

1. *"Providing expert sterile fill-finish and lyophilisation solutions from development to commercialisation, together with integrated custom assembly and packaging solutions for sterile injectables, allows for ultimate knowledge sharing and communication between teams to ensure the drug product packaging is optimised for the product, patient and production". insightSLICE, Aug 2023.*

ABOUT THE AUTHOR

Bill Welch is Executive Director of Services for PCI Pharma Services' advanced drug delivery business segment, with a focus on injectable drug-device combination products. Mr Welch has over 30 years of contract development and manufacturing experience, with over 20 years in drug delivery devices and combination products. Prior to joining PCI, he served as Chief Technology Officer at Phillips-Medisize, leading a 900-person global innovation, development and new product introduction service segment. Mr Welch holds a BS in Industrial Engineering from the University of Minnesota Duluth (MN, US).

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INTERVIEW

In this interview with ONdrugDelivery's Guy Furness, Alexandre Fontayne discusses Unither Pharmaceutical's EuroJect® injection device, based on the company's extensive experience with blow-fill-seal technology. Mr Fontayne covers the advantages of EuroJect® compared with traditional glass syringes and multidose vials, as well as touching on where Unither sees EuroJect® having an impact in the market

ALEXANDRE FONTAYNE, UNITHER PHARMACEUTICALS

Alexandre Fontayne received his PhD in Biological Science at the University of Paris Sud (France). He has 20 years of experience in R&D, including 13 years in the pharmaceutical industry working around drug design and the production of biologics, including ublituximab. Mr Fontayne is the co-author of 28 scientific articles and inventor of 12 patents. He contributes to the training of students and employees in drug design, chemistry manufacturing and control activities and subcontracting. Since 2021, Mr Fontayne has worked for Unither Pharmaceuticals as Chief Scientific Officer for biological products, and is deeply involved in the development of the Euroject® device.

Q To begin with, can you explain how the EuroJect® device leverages blow-fill-seal technology and what makes it an innovative solution for single-dose injection of therapeutics?

A Unither has extensive experience in blow-fill-seal (BFS) technology. In fact, as a world leader in this aseptic and fully automatic technology, we celebrated our 30th anniversary in 2023, so we were ideally positioned to apply BFS to EuroJect's design. The device combines a BFS ampoule with a connector and needle, and can be adapted for various injection types, including intramuscular, subcutaneous and intradermal, by attaching different cannulas. It's a single-use system, where you detach the dose, open it, screw on the connector and it's ready for injection (Figure 1).

We see EuroJect® as a potential replacement for traditional multidose glass vials – it's ready to use with minimal preparation, reducing the risk of errors during delivery and cross-contamination. Compared with prefilled syringes, EuroJect® has a much simpler mono-material design, using only low-density polyethylene (LDPE), a well-characterised and accepted material for primary containers, including for biologics. The BFS process (Figure 2) is fully automated, minimising the risk of contamination during filling compared with multidose glass vials or prefilled syringes. The device is lightweight, unbreakable and there's essentially no risk of raw material shortage, unlike with glass vials or prefilled syringes.

Additionally, BFS is recognised by regulators as an alternative primary container process for injectables.

"We see EuroJect® as a potential replacement for traditional multidose glass vials – it's ready to use with minimal preparation, reducing the risk of errors during delivery and cross-contamination."

Q Could you provide more details on the production scale and cost-effectiveness of solutions for vaccines and biologics?

A The BFS process is fully automated, not requiring any manual input (Figure 3). We feed LDPE pellets into the production machine and the product is manufactured automatically in an aseptic environment. In terms of scale, we can produce about 200 million doses a year on a single machine, which is a significantly higher capacity than we see with glass vials or prefilled syringes.

We are currently building a new workshop in our facility in Amiens (France), with five lines in a BSL-2 environment – a capacity of a billion doses per year – with

Figure 1: EuroJect® – Unither's novel injection device made using BFS technology.

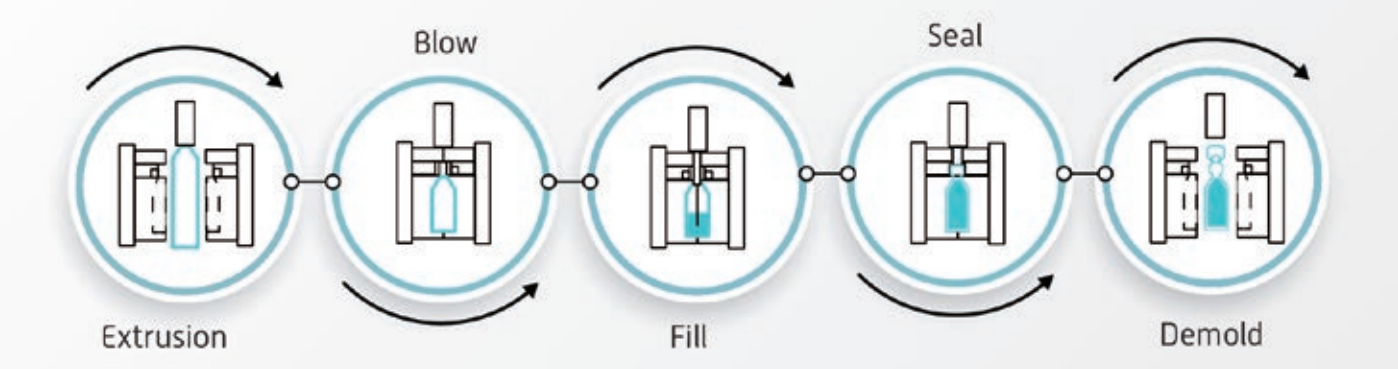

Figure 2: The BFS process.

the first line to be installed by the end of 2024 and qualify for GMP production by the beginning of 2025 (Figure 4). The equipment we use is all standardised. The core of the system is a machine from Rommelag (Sulzbach-Laufen, Germany), which is equipped with various options to maintain the product and system temperature, ensuring that it is compatible with biologics.

In terms of size and weight, Euroject® is generally smaller and lighter compared with traditional primary containers, giving it a smaller logistical footprint, therefore making it cheaper to transport. Coupling that with the fill/finish being comparable to glass vials, we firmly believe that EuroJect® is well positioned to be competitive in the market, and is particularly suited to low- and middle-income countries. EuroJect® has all the advantages of prefilled solutions, but the price point of a multidose vial.

We also have an advantage in dosing accuracy compared with multidose vials. As our doses are prefilled, there's no risk of administering a lower or higher dose. Unlike multidose glass vials, where unused doses might be discarded, the EuroJect® system ensures that no dose is wasted.

Q **Let's talk about ease of use – is EuroJect® easier for healthcare professionals to use compared with traditional syringe-based injection methods?**

A We conducted a study concerning this with healthcare professionals in January 2023. We gave healthcare professionals in the UK the opportunity to try EuroJect® and most of them approved of it, saying that they found it easy to prepare and use. They had no difficulty attaching the connector and found it straightforward for all types of injection.

Even those who were initially unconvinced became more comfortable

Figure 3: Fully automated BFS production at Unither's Amiens facility.

Figure 4: Unither's (A) present and (B) future facilities in Amiens, France.

"It's applicable for vaccines, monoclonal antibodies, coagulation factors, insulin and GLP-1 agonists."

with the device after a few uses. This wasn't unexpected because EuroJect® changes the traditional way of injecting – instead of pushing a plunger, users gently squeeze the flexible primary container to deliver the dose. While the injection method is different, requiring some practice perhaps, it's straightforward. For example, the angle of injection is more vertical than horizontal, as for classical intramuscular injections, but the end result is completely equivalent. Overall, we found the response very convincing and it suggests that EuroJect® will receive a positive reception amongst healthcare providers.

Q Could you elaborate on the main therapeutic applications you're targeting with EuroJect®?

A EuroJect® is primarily targeted towards biologics, with routes of administration including intramuscular, intradermal and subcutaneous, and we're also considering the potential to use the system for intraocular and intratumoral administration. It's applicable for vaccines, monoclonal antibodies, coagulation factors, insulin and GLP-1 agonists. Looking further into the future, we could even extend it to gene and cell therapies, which are currently generating significant interest in the industry.

Q In the autoinjector space, we've seen devices with a variety of delivery volumes – up to 5 mL – what is the upper volume limit for EuroJect®?

A The capacity is 4 mL but, for injection, we consider the upper dose limit to be around 1.5 mL, as we need some air to push the product during delivery. Alternatively, the ampoule can be used as a primary container to aspirate the full volume for transfer or reconstitution.

Q How do you manage the quality and safety of therapeutics during the filling process for EuroJect®, for example, how do you manage temperature during the BFS process for sensitive biologics?

A The BFS technology melts the polymer to form the primary container, which, as you can imagine, requires high temperatures. However, we use machine options to cool down the drug product and limit the heat it experiences. During experiments using a thermochrome indicator, we've validated that, for a minimum of 90% of the product, the temperature never exceeds 40°C during filling, even for a few seconds. We've conducted experiments and tests with biologics, proteins and live attenuated viruses that have confirmed no loss in biochemical and functional activity.

Considering safety and quality more broadly, we have several controls throughout the filling process, including automatic visual and leakage inspections. Another challenge is detecting particles, given the machine's speed. Regarding extractables, Unither has 30 years of experience with this technology, so we have comprehensive data on the extractables from LDPE. For leachables, it depends on the product, and we conduct trials to evaluate them.

Q Speaking of extractables and leachables, how does EuroJect® compare with glass on that front?

A EuroJect® has a significant advantage for extractables and leachables, which is that it only has one component, LDPE, whereas glass is often coated and may add other molecules, complicating its extractables and leachables profile. Our system is simpler as we don't have these additional components. Adding compounds increases the complexity of potential interactions with different products. A common example is silicone coating, which is often used as a lubricant in glass syringes – with EuroJect®, we don't have to worry about any of that.

Q Is there anything else you'd like to add or any points you'd like to make that we haven't covered?

A As I've mentioned, EuroJect® is a monomaterial LDPE device, which makes it highly recyclable. We already recycle leftover LDPE from the production process, and we're planning to organise the collection and recycling of used doses. LDPE is easy to sort for waste management and, in terms of raw material, we receive LDPE in bulk, reducing packaging waste. During melting, LDPE is sterilised, eliminating waste. EuroJect® is beginning to be recognised for its sustainability advantages compared with traditional packaging methods for biologics and injectables.

ABOUT THE COMPANY

Unither Pharmaceuticals is a pharmaceutical subcontractor specialising in the development and manufacturing of single-dose liquid formulations, including eye drops, saline solutions and asthma medications in BFS single doses and liquid stick-packs, for originator pharmaceutical companies and generics manufacturers. Currently employing more than 2,000 people in eight manufacturing plants in France, the US, Brazil and China, Unither Pharmaceuticals recorded sales of €371 million (£320 million) in 2022.

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"EuroJect® has a significant advantage for extractables and leachables, which is that it only has one component, LDPE, whereas glass is often coated and may add other molecules, complicating its extractables and leachables profile."

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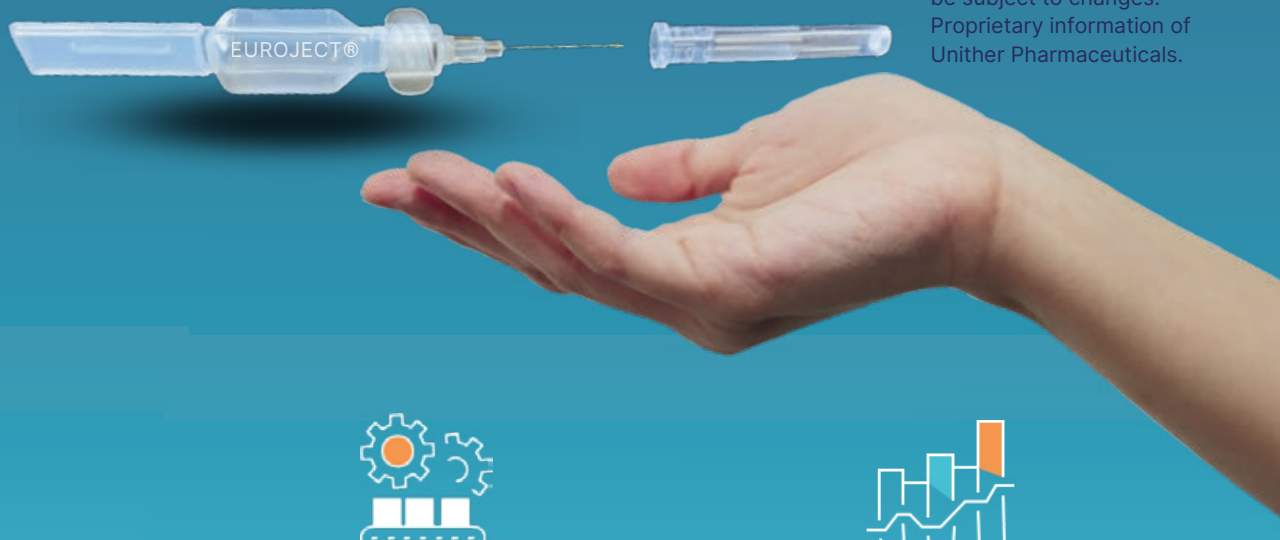
Approved by top health authorities

Introducing a new way to inject therapeutics

EUROJECT®



This prototype device might be subject to changes. Proprietary information of Unither Pharmaceuticals.

- Open system, **free of royalties**
- Adaptable to any type of needle
- Different routes of administration for injection

- Dedicated BSL2* building in our Amiens facility
- Very large capacity: up to 1 billion doses/year
- No risk of shortage in components and capacities

- Competitive pricing
- Opportunity for new markets (LMIC*)

*Biosafety level

*Low middle income countries

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SMC® Ltd.

AN ENABLING AUTOINJECTOR TECHNOLOGY FOR DELIVERY OF LONG-ACTING INJECTABLES

Here, Asmita Khanolkar, Senior Director, and Susanna White, Mechanical Engineer, both at SMC Ltd, explain why the Vita autoinjector with resuspension technology provides a potential solution for the delivery challenges of long-acting injectables.

Long-acting injectables (LAIs) provide patients with a higher compliance solution for chronic diseases. However, the current parenteral formulations for LAIs are pushing the limits of traditional drug delivery device technologies. LAIs typically have high molecular weight carriers that increase viscosity and can also lead to non-Newtonian behaviour and increased sensitivity to environmental conditions. Additionally, suspension formulations can settle out during storage. Some LAIs are presented as an "*in-situ* forming depot" (ISFD) where the bolus shape and size can impact the controlled release and pharmacokinetics (PK). Consistent dose delivery and consistent PK are essential for a successful therapeutic outcome.

Given these technically challenging delivery needs for LAIs, and the drive towards at-home administration, it is evident that there is a need for an enabling drug delivery technology platform that can be customised to the patient and technical needs of the application. The Vita autoinjector with resuspension technology for delivering intramuscular injections provides a potential solution for these types of challenging applications.

High Viscosity	Non-Newtonian	Suspension	Stability
• LAIs are formulated in a delivery matrix to provide extended release over time • Delivery matrix for such formulations typically involve high molecular weight vehicles • Increased viscosity and sensitivity to environmental conditions • Where an injected drug forms a bolus, size and shape can affect the release	• Non-Newtonian behavior can be either shear-thickening or shear-thinning in nature • Shear-thinning (pseudoplastic) formulations pose the biggest challenge for injection • They heighten any mechanical variation in the device, which subsequently effects delivery consistency	• Two phase systems • Delivery can be complicated due to characteristics such as phase separation, particle separation, settlement, particle agglomeration and needle clogging • Requirement for high-pressure systems to overcome these challenges • Onus on device to manage and optimise delivery	• Compatibility with container materials • Moisture loss • Oxygen ingress • Effect of temperature, age, batch-to-batch consistency • Settling can be exacerbated by storage time, temperature and transit vibration • Some suspensions can experience particle size change during storage

Table 1: LAI delivery challenges.

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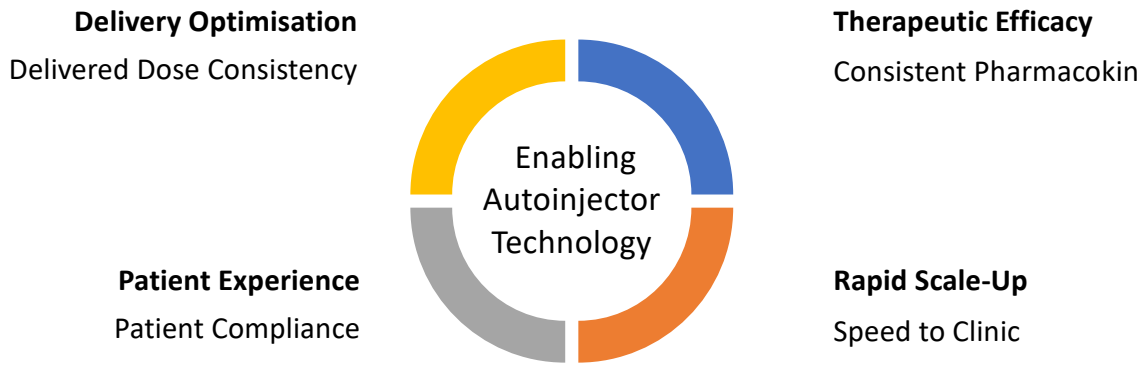

Figure 1: Key drivers for an enabling autoinjector technology.

"An enabling autoinjector technology can help address the delivery challenges presented by LAIs for successful outcomes."

LAI FORMULATIONS

Delivery of LAIs faces multiple challenges (Table 1). Understanding the formulation is key to optimisation of filling, storage and delivery. LAIs are formulated in a delivery matrix to provide extended release over time. Depending on the formulation technology used – such as oil solutions, water insoluble suspensions or crystalline polymeric barriers – the formulations can exhibit high viscosity, non-Newtonian behaviour or phase separation in storage. This, in turn, can cause inconsistencies in delivery.

NEED FOR AN ENABLING DELIVERY DEVICE TECHNOLOGY

An enabling autoinjector technology can help address the delivery challenges presented by LAIs for successful outcomes. Delivery optimisation, therapeutic efficacy, patient experience and rapid scale-up are some of the key considerations when developing an autoinjector solution (Figure 1):

1) **Consistency of Delivered Dose:** Where the LAI drug is a suspension that can "settle out" during storage, an autoinjector can be designed to help "resuspend" the formulation during delivery:

- This can increase dose accuracy and homogeneity of the formulation.
- It can be particularly valuable when a suspension is opaque, such that it is difficult for the user to judge whether the formulation has been fully resuspended by shaking.
- Formulations in prefilled syringes and autoinjectors can be harder to mix by shaking than those in vials because there is a smaller amount of gas alongside the drug in the primary container.
- Shaking can cause foaming or result in a reduced therapeutic effect if any air bubble in the formulation is small.

2) **Consistency of PK Profile:** Where a drug forms a slow-release ISFD in a patient's body tissues, a more consistent bolus shape can be formed by an autoinjector than by manual delivery. This matters if the rate of drug release is proportional to the surface area of the bolus:

- An autoinjector can provide a consistent PK profile by consistent mixing of the solid and liquid phases of the formulation.
- Non-Newtonian formulations can suffer from variable "jetting" effects that affect bolus size and shape.
- Optimisation of delivery speed can help in overcoming some of these effects.

3) **Patient Experience:** Smaller needle sizes can support compliance and prescribing preference:

- When delivering suspensions, smaller needles can be more susceptible to clogging.
- Autoinjectors can provide more force to clear clogs than a human hand.
- High-pressure container closure system is required to be able to manage smaller needle sizes.
- Needle depth optimisation for specific patient groups, considering their BMI and physiology differences.

4) **Rapid Scale-up:**

- Integrated iterative studies are required throughout the development cycle to optimise LAI delivery, adjusting formulation parameters to optimise release and PK performance.
- Test method development and implementation is also an integral part of development for LAIs to characterise the formulation's behaviour in delivery.
- Early studies with an autoinjector solution for early-stage development are required for optimising delivery.

APPROACH TO LAI DELIVERY

SMC has developed some specific mechanisms to aid in the understanding of the nuances of an LAI formulation via a range of analyses, as well as potentially eliminate development challenges through careful design to facilitate resuspension of a formulation during autoinjector delivery. The approach to optimising LAI delivery involves focus on three areas: dose preparation, dose delivery and slow-release optimisation (Figure 2).

Dose Preparation

The first step involves defining what constitutes a good delivery. Delivered dose, delivery rate and particle size can be used as parameters to specify good delivery.

"The approach to optimising LAI delivery involves focus on three areas: dose preparation, dose delivery and slow-release optimisation."

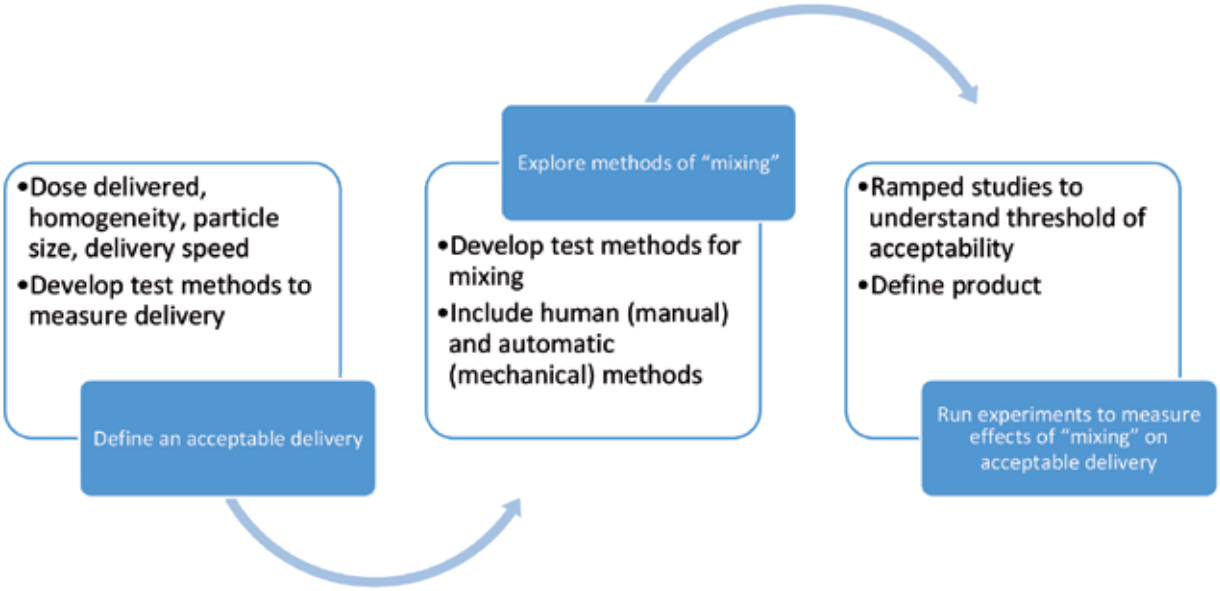

Figure 2: How to approach LAI delivery.

The acceptable dose variability through delivery can be defined as the total dose delivered or as maximum and minimum concentrations.

Simultaneously, a worst case "settled" state specification can be defined for the formulation based on observations of stability samples, accelerated ageing and vibration testing. Samples for worst case "settled" states can be prepared through centrifuging, vibration and temperature exposure.

To investigate the concentration of drug at different stages of delivery via an autoinjector, SMC has developed an evacuation rig for segmented delivery. With a three-beaker set-up, the dose can be divided into three equal portions, as shown in Figure 3. The beakers can be weighed pre- and post-fill to ascertain weight. Using methods such as high-performance liquid chromatography (HPLC), the API content and concentration can be measured during the different stages of delivery to make sure the overall concentration meets the specification. Particle size analysis and directional light imaging techniques can be used to understand if the separation is within the acceptable level. Different formulations and batches can then be tested to understand the level of separation.

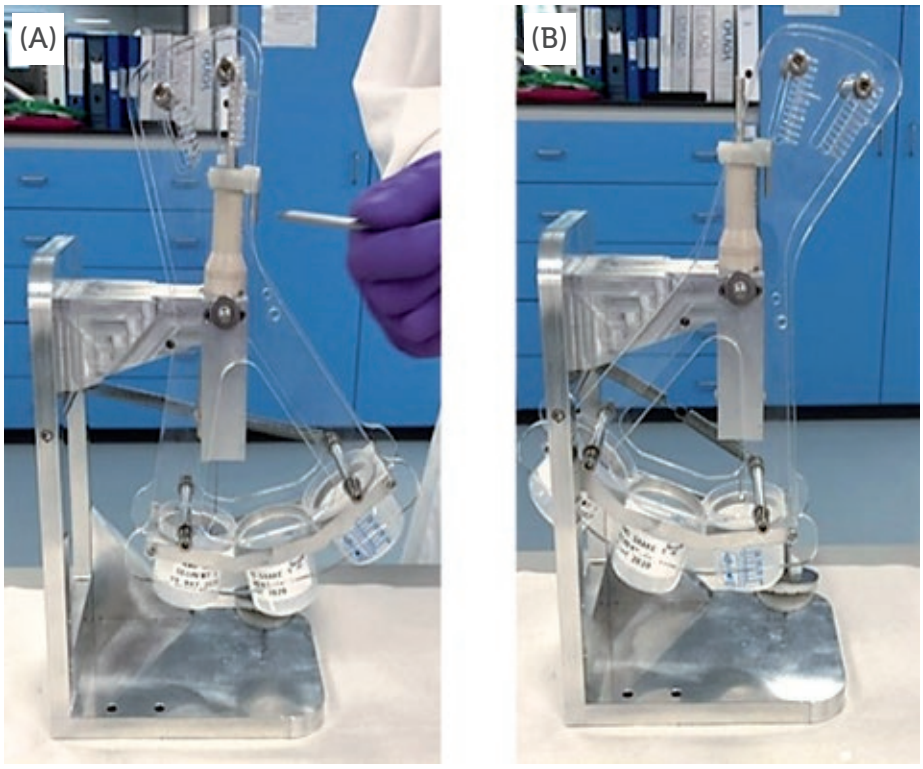

Figure 3: Segmented delivery with the evacuation rig showing (A) start and (B) end of delivery.

Dose Delivery

Suspensions are vulnerable to settling during storage. Unless this is addressed (e.g. through device agitation as an additional user step), it will result in a two–phase suspension with two distinct viscosities and a two-stage delivery. At the start of delivery, the plunger moves slowly as it delivers the settled sediment. However, beyond this, delivery of the remaining fluid takes place much more quickly. To combat this, an increase in the overall amount of force being used in the device allows the whole system to become less sensitive to this variation in viscosity. This approach is only possible if the container closure system can withstand the pressures required for such delivery.

SMC's injection characterisation system (ICS) tests the flow rate of a fluid through a known needle size. A spring is placed behind the syringe plunger and used to expel the formulation while three sensors record the spring load, plunger position and container pressure throughout injection. This data is then analysed to understand the viscosity and flow characteristics of the fluid. Figure 4 shows an example of a representative two-stage delivery flow behaviour of a suspension.

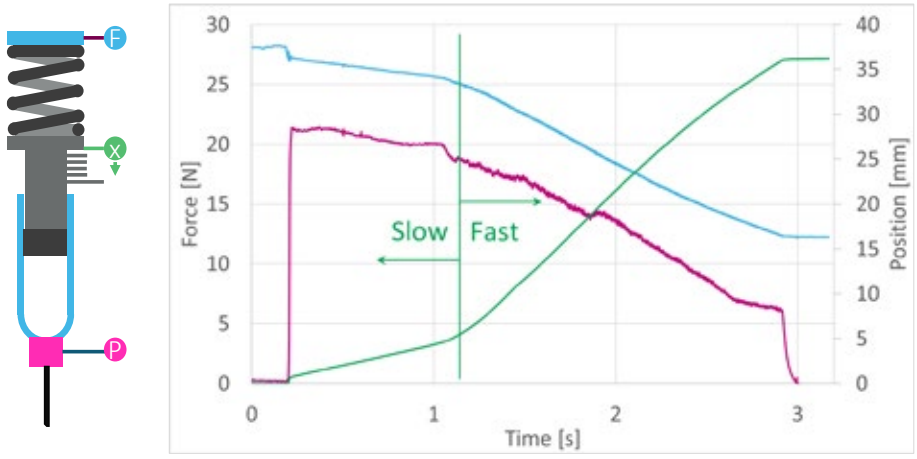

Figure 4: Optimising delivery for a suspension formulation.

"The Vita device is a powerful autoinjector for deep intramuscular delivery that offers repeatable and reliable performance in an intuitive, patient-friendly design that is suitable for both chronic and crisis applications."

Using the ICS, the delivery performance and resuspension of a "settled" formulation can be tested for delivery performance in "mixed" and "settled" states across a range of parameters. The parameters can include temperature, delivery rate, shear, needle bore and clogging effects. A mathematical model can be generated from the empirical data to enable prediction of formulation performance. SMC has developed a "mix on delivery" technology for resuspension and its effects can be studied using both SMC's "mix on delivery" technology and user interactions.

Slow-Release Optimisation

LAI formulations are all unique and will behave differently when injected, so it is important to assess bolus formation for each individual formulation. The bolus size and shape may be affected significantly by the surrounding tissue. High-speed injections have been seen to cause "jetting", effectively elongating the bolus, and creating a higher surface-to-volume ratio. To capture and assess the physical shape of the bolus, *in vitro* 3D scanning is necessary – as an example, a CT scan image of an intramuscular injection is shown in Figure 5. Where appropriate, the shape, size and position can then be quantified and compared across a range of injection parameters (needle gauge, delivery time, etc).

It is also important to carry out *in vivo* studies to fully understand the effect that the delivery system has on drug release and, therefore, the PK profile. To facilitate these studies, SMC has designed an *in vivo* injection rig – an autoinjector simulator (AIS). This is a modular system that allows injections using off-the-shelf syringes in combination with a range of springs and needles to replicate the final autoinjector. As well as imitating the final delivery system, this rig is instrumented such that it is possible to acquire data on the injection force and speed of delivery for each injection. This allows a direct correlation to be drawn between PK and the injection characteristics of each individual injection.

"LAI formulations are all unique and will behave differently when injected, so it is important to assess bolus formation for each individual formulation."

VITA DEVICE

The Vita device (Figure 6) is a powerful autoinjector for deep intramuscular delivery that offers repeatable and reliable performance in an intuitive, patient-friendly design that is suitable for both chronic and crisis applications.

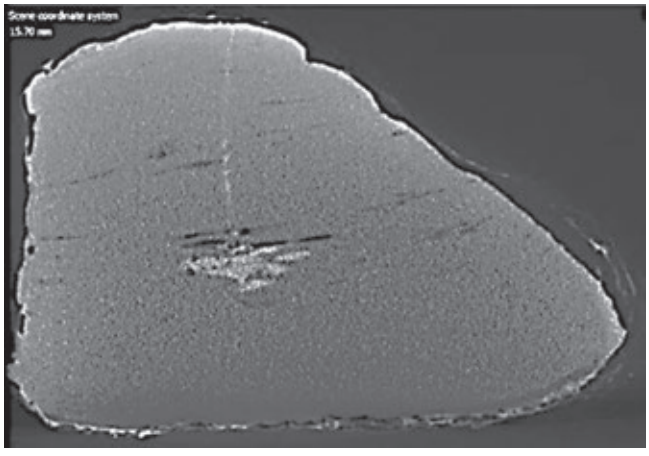

Figure 5: CT scan for bolus shape and size.

Figure 6: The Vita autoinjector.

The Vita device can handle volumes up to 2 mL with viscosities of up to 100 cP and a variety of needle sizes ranging from 21G–25G with an exposed length of between 12.5 mm and 40 mm, depending on the patient population (Figure 7). The device incorporates a proprietary mechanism that facilitates consistent delivery of non-Newtonian formulations or drugs held in suspension, which may pose a risk of separation over shelf life. The device also features a large viewing window with visual delivery indication and both a start and end-of-dose audible indication (Figure 8).

In summary, the Vita autoinjector platform can offer some solutions to the delivery challenges of LAIs. With a high-pressure container system, resuspension mechanism and patient-centric design , the Vita's features provide a unique offering. In addition, specific *in vitro* and *in vivo* mechanisms have been developed that can aid in understanding and characterising the formulation in terms of dose preparation, dose delivery and slow-release optimisation. These include the segmented delivery evacuation rig, the ICS and the AIS. Coupled with other techniques, such as HPLC, particle size analysis and 3D imaging techniques, a holistic approach fosters a greater understanding of the formulation and delivery needs in applications involving LAIs.

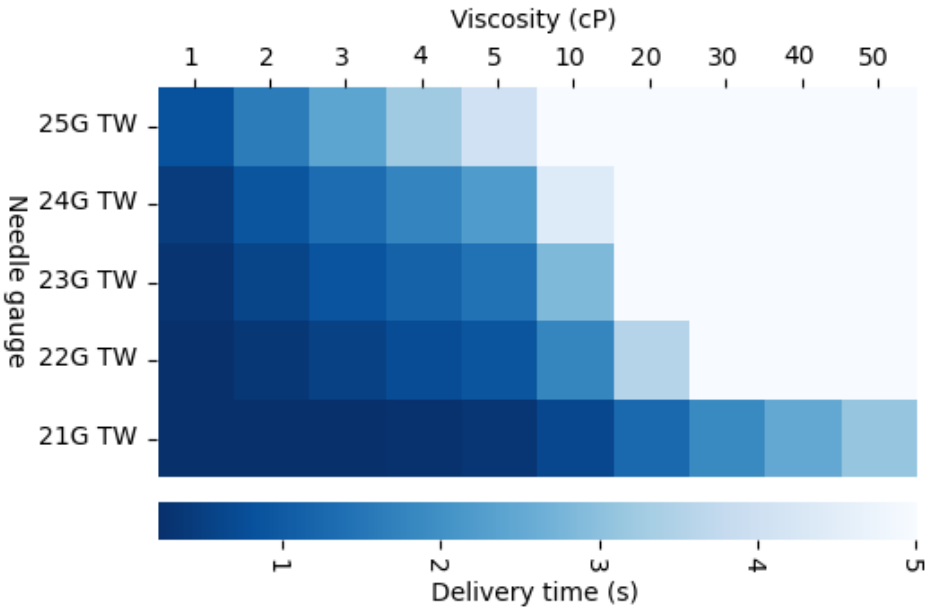

Figure 7: Vita performance.

ABOUT THE COMPANY

SMC Ltd brings more than 35 years of experience and provides end-to-end integrated services for clinical and commercial manufacturing of combination products for drug delivery that span contract manufacturing services and pharmaceutical services, as well as patient-centric autoinjector technologies.

SMC's autoinjector platforms are designed to meet the most challenging requirements arising from diverse patient groups and novel drug formulations and can be customised to deliver a wide range of drug formulations, including fragile molecules and biologics for both subcutaneous and intramuscular injection with high viscosities and large volumes.

SMC Pharma Services specialises in analytical services and sterile fill/finish batches for a range of presentations including syringes, cartridges and vials

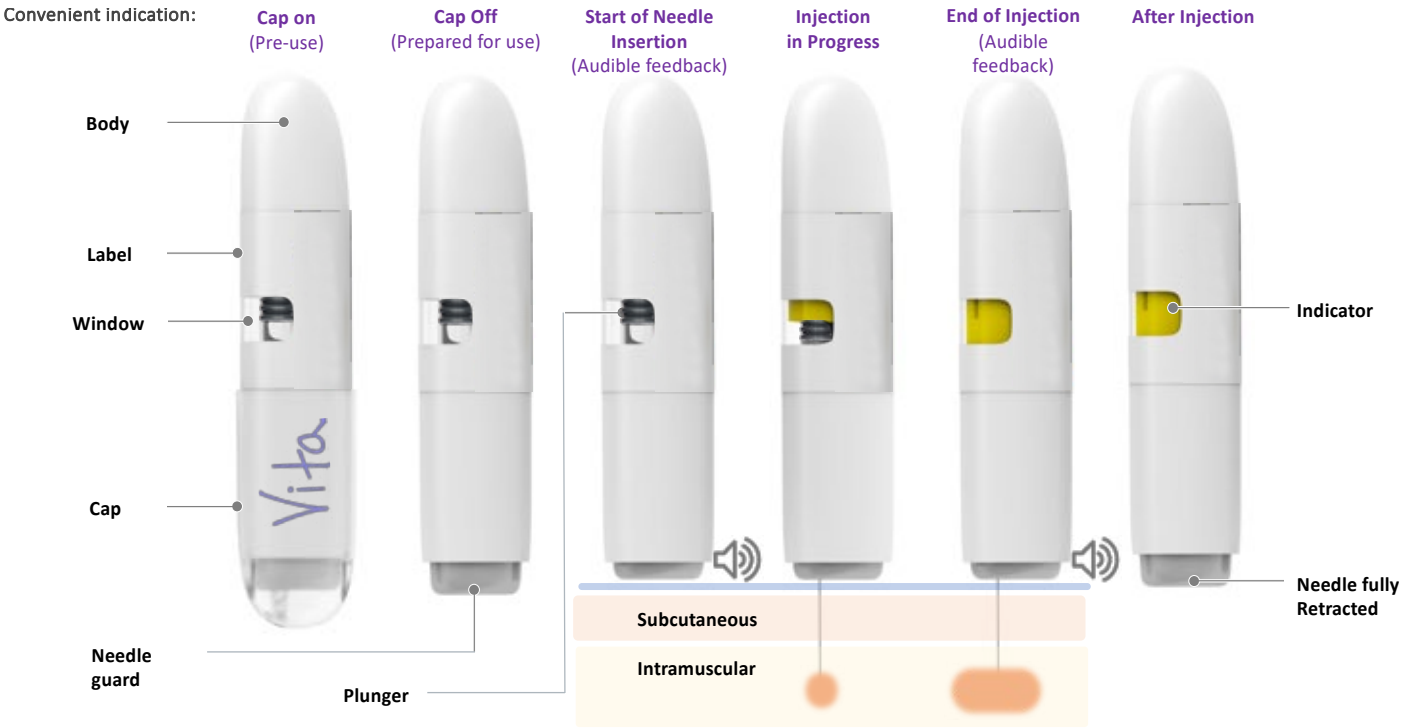

Figure 8: Vita's sequence of injection.

with the highest standard of quality to ensure sterility assurance. It can work with a wide variety of formulations including small molecules, proteins, peptides and biologics. SMC offers clients development of the fill-finish process including container closure integrity method development and testing, analytical methods for quality control release and stability testing.

SMC provides contract manufacturing services for every phase needed – from initial concept through to assembly and final packaged device, including programme management, design and development, product manufacturing, clinical/commercial manufacturing, electronics integration and global supply chain management. SMC has global GMP manufacturing sites in the US, the UK, Costa Rica and India.

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Asmita Khanolkar has a master's degree in Materials Science & Engineering from Worcester Polytechnic Institute in Worcester (MA, US). With more than 25 years of manufacturing experience, specialising in the medical device and pharmaceutical industry, she has managed various device projects from concept to commercial launch. Her product portfolio includes single-use, wearable and implantable devices, drug-device and device-biologic combination products for drug delivery, biotech, biotherapeutics and pharmaceutical applications. Ms Khanolkar has held various engineering and management roles in new product development, manufacturing engineering, advanced quality planning, operations, supply chain and product lifecycle management.

Susanna White is a Mechanical Engineer at SMC, with over a decade of experience in the design and test programmes for SMC's innovative autoinjector technology platforms. Much of her work has focused on the study of highly viscous and non-Newtonian drug formulations – using numerical modelling techniques in combination with experimental investigation to achieve the most appropriate delivery system for challenging formulations. Ms White graduated from the University of Cambridge (UK) with a master's degree in Engineering for the Life Sciences.

BEYOND THE POINT: NAVIGATING THE IMPACT OF NEEDLES ON PAIN, ANXIETY AND THE PATIENT EXPERIENCE

Here, Omar Rahman, PharmD, Medical Director, and Mehul Desai, PharmD, Vice-President of Medical Affairs, both at Enable Injections, and Keith Candiotti, MD, Professor and Chairman of the Department of Anesthesiology, Perioperative Medicine and Pain Management at the University of Miami, Miller School of Medicine, discuss the role that needle size plays in the pain and anxiety patients experience during injections and how smaller, hidden needles (30G), such as those employed by Enable's enFuse large-volume injector, may minimise patient discomfort and maximise subcutaneous injection efficiency.

Over the last decade, the subcutaneous (SC) administration of therapeutics has experienced significant growth, emerging as a widely accepted option for drug delivery. The shift from intravenous (IV) infusions to SC injections has not only reduced the drug administration burden on the healthcare system, but is also generally preferred by patients and healthcare practitioners (HCPs).[1–4] This positive impact has led to intensified research aimed at understanding the key elements of the SC administration process, such as the impact of needle size, needle phobia and environment, on the overall patient experience.

The choice of needle size can significantly influence the patient experience, particularly when larger diameters are employed. Larger needle diameters have been associated with heightened levels of pain and anxiety in patients, casting a shadow across the overall quality of care. The discomfort induced by needles not only amplifies the immediate physical sensations, but also contributes to long-lasting psychological repercussions, potentially leading to or exacerbating needle phobia.

Needle phobia, characterised by an intense fear and anxiety of needles, is a prevalent concern that further complicates the patient experience. The widespread prevalence became evident in a recent global survey conducted among a general adult population (N = 2,098), where 63% of participants reported experiencing needle phobia.[5] Individuals afflicted by needle phobia may exhibit heightened anxiety, increased heart rate and even avoidance behaviours. Aversion to needles not only poses challenges for HCPs but also jeopardises the overall wellbeing of patients, as essential treatment may be delayed or avoided altogether.

> "Aversion to needles not only poses challenges for HCPs but also jeopardises the overall wellbeing of patients, as essential treatment may be delayed or avoided altogether."

When delving into the impact of larger needle diameters, needle phobia and the environment on the patient experience, it becomes imperative to explore strategies and innovations that mitigate these adverse effects. By understanding the psychological

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"63% of insertions with 23G needles caused pain, compared with 53% with 27G needles and 31% with 32G – the thinnest needle."

and physiological dimensions of needle-related distress, HCPs and injection-system manufacturers can begin to tailor interventions to minimise pain, alleviate anxiety and enhance the overall SC administration experience for patients.

NEEDLE SIZE AND PAIN

The impact of needle size on pain during SC administration is a critical consideration, as highlighted in research by Arendt-Nielsen *et al* and Præstmark *et al*.[6,7] These studies emphasise the significant correlation between the outer needle diameter and the frequency of pain, shedding light on the direct relationship between needle characteristics and the patient experience.

The study conducted by Arendt-Nielsen *et al* specifically looked at the association between the outer needle diameter and the frequency of insertion pain during SC administration among healthy volunteers.[6] The results revealed a positive and statistically significant correlation, underscoring the influence of needle size on pain perception. Notably, the study demonstrated that larger needle diameters were associated with a higher frequency of insertion pain. For instance, 63% of insertions with 23G needles caused pain, compared with 53% with 27G needles and 31% with 32G – the thinnest needle. This clear trend emphasises the importance of considering needle diameter as a crucial factor in predicting and managing pain during SC administration.

Examining the data in detail reveals a more significant reduction in pain perception when transitioning from a 27G to a 32G needle size (22%) compared with the difference observed from a 23G to a 27G needle (10%). This finding prompts the intriguing consideration of a potential threshold effect, indicating that pain becomes notably more apparent at the 27G mark. Another study, conducted by Præstmark *et al*, lends support to the existence of another threshold effect, suggesting that the 30G needle size represents the point with the least impact on pain.[7] Beyond this threshold, going to needle sizes smaller than 30G does not seem to yield any noticeable impact on pain perception. This conclusion is based on observations where there was no significant difference in pain scores or the increase in skin blood perfusion (SBP) between a 32G and 30G needle.

To reinforce this argument, Yomtoob *et al* conducted a study specifically addressing periocular injections, a notably sensitive area around the eyes.[8] The findings revealed no noticeable distinction in pain scores between the use of a 32G needle and a 30G needle. The lack of distinction in pain perception when going beyond 30G could be attributed to the subjects' limited ability to differentiate between needles when they fall below a certain size. This finding strongly suggests that the 30G needle size represents a point at which the impact on pain is notably minimal, potentially serving as a threshold for optimising patient comfort during SC administrations.

Præstmark *et al* also explored the relationship between needle diameter and both penetration force (PF) and SBP.[7] The study revealed positive correlations between needle diameter and both PF and SBP, indicating that larger needles require more force for penetration and are associated with higher levels of local tissue trauma. Additionally, the findings indicated a positive trend in relation to pain, further highlighting the impact of needle diameter on pain perception during SC administrations.

The research findings collectively suggest that thinner needles are associated with less pain during SC injections. Reduced needle thickness not only results in diminished pain but also requires a lower PF. This aligns with the broader understanding that minimising tissue trauma and nerve stimulation via less force contributes to a more favourable patient experience. Both studies' positive correlations between outer needle diameter and insertion pain frequency emphasise the need for thoughtful consideration of needle characteristics in injection-system development and clinical practice.

NEEDLE PHOBIA

The impact of needle phobia associated with drug administration via needle is a multifaceted challenge with far-reaching implications for patient wellbeing and healthcare delivery. The study by Albrooks *et al* sheds light on the prevalent reasons behind needle fear, highlighting the intricate relationship between general anxiety, pain and the complex aetiology of needle phobia.[5] Among the participants experiencing needle phobia, general anxiety (96.1%) and pain (95.5%) emerged as the most common reasons for their fear of needles. This emphasises the pervasive nature of anxiety in the context of needle-related procedures and underscores the need to better understand the factors contributing to anxiety and, ultimately, needle phobia.

Albrooks *et al* examined various factors that positively correlate with needle phobia.[5] Notably, "non-needle-related medical fears" was the highest positively correlated independent variable with needle phobia, which suggests a broader context of anxieties associated with the wider administration process and healthcare system. Coupled with the common selection of "distractions" and "relaxation techniques" as top non-device-related strategies to cope with needle phobia, this aligns with the overarching argument that visibility of the administration process plays a pivotal role in shaping a patient's level of anxiety, which has direct implications for comfort and compliance.

Another crucial aspect highlighted in the study was the identification of potential device-related solutions to alleviate fear, which included "non-invasive alternatives" (94.1%) and the use of "smaller needles" (91.1%) as the most commonly suggested strategies. Another study by Jaber *et al* adds further weight to this argument, demonstrating that injections using needles with thermoplastic elastomer shield material were consistently perceived as less painful than those with rubber needle shields, irrespective of variations in needle

"Recognising and addressing visible aspects of the administration process is crucial for HCPs to implement strategies that enhance the overall patient experience and alleviate anxiety and pain."

diameter.[9] This reinforces the link between the visibility of different administration aspects, the perceived level of anxiety and, ultimately, pain.

Collectively, these findings validate the pivotal role of a patient's level of anxiety and pain triggered by the visibility of the administration experience and interaction with the wider healthcare system. Recognising and addressing visible aspects of the administration process is crucial for HCPs to implement strategies that enhance the overall patient experience and alleviate anxiety and pain.

SAFETY

The relationship between smaller needle sizes and fewer safety events is underscored by compelling data, as indicated in the study by Jaber *et al*.[9] Specifically, when patients self-administered interferon beta-1a using a 29G needle compared with a 27G, not only was there a notable reduction in reported pain, but patients also experienced fewer safety events. The survey revealed a significant decrease in bruising, burning, stinging and injection-site reactions associated with the use of the smaller 29G needle.

These data support the notion that the adoption of smaller needle sizes in SC drug delivery addresses patient comfort by minimising pain, but also contributes to a more favourable safety profile. These results are consistent with prior evidence by Præstmark *et al*, demonstrating that smaller needles lead to reduced tissue trauma and provoke gentler physiological responses, which are crucial elements in the overall development of injection-site reactions.[7] Therefore, incorporating smaller needles in SC drug delivery has the potential to enhance patient comfort and concurrently promote safety.

ENFUSE TECHNOLOGY

Enable Injections' novel enFuse® drug delivery system delivers high-volume therapeutics through SC administration, offering a more flexible alternative to IV administration and other currently available SC options, such as infusion pumps. Among its numerous advantages, the enFuse system features a remarkably small, 30- to 31-gauge ultra-thin-walled and hidden needle (30G for discussion in this article), directly addressing patient needs regarding the pain and anxiety associated with the administration process (Figure 1).

A cross-over study comparing enFuse with the Crono Pump (Canè Medical Technology, Turin, Italy) among patients with primary immunodeficiency vividly illustrates the real-world impact of using smaller, hidden needles. For SC administration of immunoglobulin G with the enFuse (30G needle), the incidence of most injection site reactions was notably lower than with the Crono Pump (26G needle). Specifically, the percentage of any injection-site reaction for all infusions was 3.4% for the enFuse and 6.7% for the Crono Pump. A parallel safety trend was observed in a separate study involving the enFuse, demonstrating excellent local tolerability with only seven injection site reactions out of 404 administrations (1.7%) – all of which were Grade 1.[10]

In terms of pain perception, the cross-over study involved patients listing their reasons for preferring the enFuse over the Crono Pump. Nearly 50% of patients chose "causes less pain at the injection site" as one of their top reasons – a direct testament to the positive impact of enFuse's smaller and hidden needle feature on patient comfort and pain.[10] The advantages of the hidden needle feature extend beyond patients to include payers, who recognise a distinct link between the hidden needle and potential improvements in treatment adherence. Notably, in a preference study for the enFuse, payers ranked the hidden needle among the primary advantages of the wearable system.[4] The enFuse technology also stands out with its unique constant-pressure design, employing elastomeric technology rather than a constant-flow design via an electromechanical pump. This distinctive approach enables the enFuse system to dynamically adjust to the back pressure at the injection site, potentially reducing pain even further in conjunction with its small, hidden needle.

In the elastomeric constant-pressure design, the needle serves as the flow restrictor, allowing for the adjustment of various flow rates by modifying needle features, such as diameter and length. The distinctive design of the enFuse flow restrictor has enabled minimal alteration to the needle outer diameter,

> "These data support the notion that the adoption of smaller needle sizes in SC drug delivery addresses patient comfort by minimising pain, but also contributes to a more favourable safety profile."

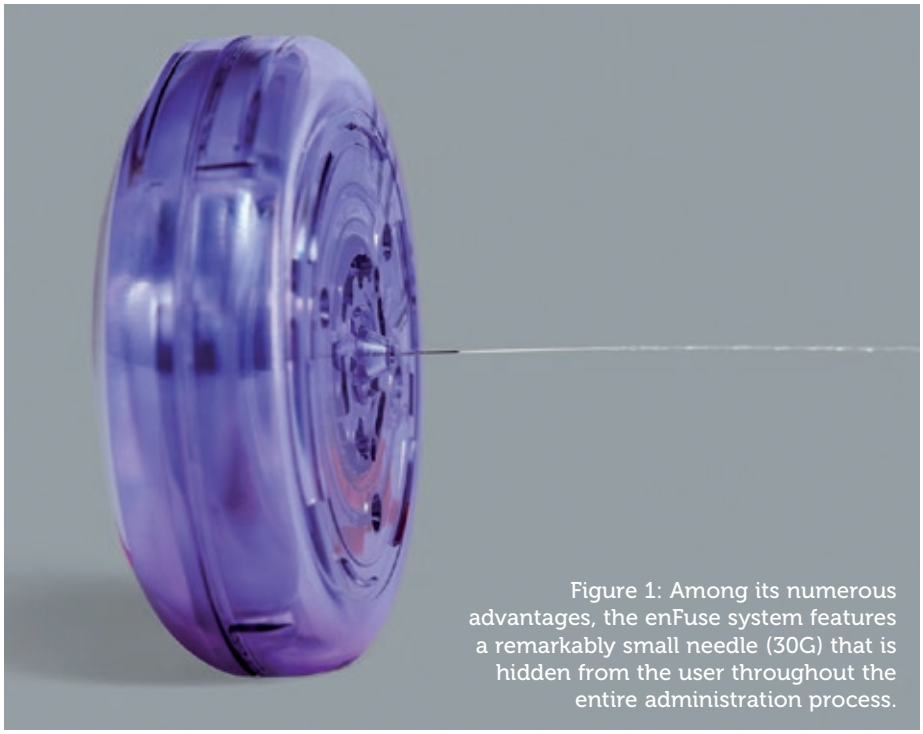

Figure 1: Among its numerous advantages, the enFuse system features a remarkably small needle (30G) that is hidden from the user throughout the entire administration process.

> "In the pursuit of expediting delivery times, the reliance on larger needles in large-volume SC delivery has inadvertently compromised the overall patient experience."

maintaining it at or around a conventional 30G, while adjusting the inner diameter to meet the desired delivery time. This adaptability emphasises the versatility and accuracy of the enFuse technology, giving partners the tools to tailor drug delivery and address the unique requirements of specific patient groups.

In the pursuit of expediting delivery times, the reliance on larger needles in large-volume SC delivery has inadvertently compromised the overall patient experience. The emphasis on faster administration, without due consideration for the associated discomfort, underscores the need for a paradigm shift towards prioritising patient comfort in SC administration. Moving forward, a re-evaluation of needle size choices is imperative to align SC drug delivery with a more patient-centric approach, ensuring that advancements in delivery speed do not come at the expense of the patient's wellbeing. By fostering a balance between efficiency and patient experience, the enFuse can pave the way for more comfortable and effective healthcare practices in large-volume SC drug delivery.

ABOUT THE COMPANY

Enable Injections is a global healthcare innovation company that develops and manufactures drug delivery systems designed to improve the patient experience.

ABOUT THE AUTHORS

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Mehul Desai, PharmD, MBA, serves as Vice-President of Medical Affairs at Enable Injections. His experience includes development and execution of tactical plans, driving strategic direction through key opinion leader insights, supporting clinical trial execution and contributing to business development activities across various therapeutic areas. His background includes being the Associate Medical Director for the haematology franchise at argenx. Prior to this, his experience included field medical assignments in rare disease for haematology at argenx, haematology/nephrology at Alexion and nephrology/neurology at Mallinckrodt Pharmaceuticals. Dr Desai holds a Bachelor's degree in Biochemistry and Business Foundations from Indiana University (IN, US); a PharmD from Purdue University (IN, US); and an MBA in Pharmaceutical and Healthcare Business from the University of the Sciences (PA, US).

Keith A Candiotti, MD, is the Professor and Chairman of the Department of Anesthesiology, Perioperative Medicine and Pain Management at the University of Miami, Miller School of Medicine. In this role, he oversees the largest anaesthesia training programme in the US. In tandem, the department manages the prestigious UM/JMH Center for Patient Safety, which is dedicated to reducing patient harm. With over 130 peer-reviewed publications and numerous invited lectures, Dr Candiotti is noted for his contributions to healthcare research. He has also provided consulting services to a large number of healthcare and pharmaceutical companies. He has conducted numerous clinical trials, including US FDA studies in post-operative nausea and vomiting, pain and various clinical areas. Dr Candiotti is a graduate of the University of Miami School of Medicine.

Enable's body-worn enFuse® device delivers high-volume pharmaceutical and biologic therapeutics via SC administration, with the aim of improving convenience, supporting superior outcomes and advancing healthcare system economics.

Approved in the United States in combination with a specific drug, more information: https://enableinjections.com/our-products.

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windgapmedical

DESIGNING FOR SUCCESS: CHOOSING THE RIGHT PRIMARY DRUG CONTAINER FOR PREFILLED DELIVERY DEVICES

In this article, Brent Buchine, PhD, Chief Business Officer, and Jason Durkin, Vice President Supply Chain, both at Windgap Medical, reflect on the motivations and lessons from Windgap's journey to design patient-centric, prefilled autoinjectors around custom and standard primary drug containers.

As a company founded to simplify, automate and accelerate the administration of complex drug therapies, Windgap often finds itself asking an important question when approaching a new development programme:

Do we innovate around a standard primary drug container (PDC) with all its existing benefits and limitations – or do we create a novel solution to better address the needs of the target patient population?

The answer, of course, is almost as complex as the drugs themselves. In this article, Windgap shares the possibilities – and problems – associated with each approach and sheds light on new opportunities that are forming the frontier of pharma.

A SHIFTING DECISION MATRIX

When initiating a programme to design and develop an injection device for drug delivery, one of the first major decisions is the selection of the PDC. Various standard options are available, including the prefilled syringe (PFS), cartridge and vial, as well as the mated plungers, cannulas, sterility barriers, seals and other accessories that make up the complete PDC system.

Several considerations drive the decisions behind these options – device type (e.g. pen injector, autoinjector, on-body wearable, etc), whether the device will be disposable or reusable, and how it interacts with the drug product. In the past, these considerations alone could lead to a clear decision, especially as indications often have a preferred PDC format with widespread industry adoption.

With today's injectable therapies, however, increasingly complex molecules and value chains require additional evaluation. Taking the disposable autoinjector as an example, therapy trends that preclude the conventional use of a standard 1 or 2.25 mL PFS include:

- The use of lyophilisation to enhance stability, particularly for high-value monoclonal antibodies and biologics
- Long-acting injectables, formulated as a nanoparticle suspension, require separation from the liquid vehicle until mixing and administration
- Co-administration of two drugs with formulation and storage incompatibilities.

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"In some cases, the standard primary drug container is perfectly suitable; in others, it must be completely reimagined to support a combination product that suits the needs of the patient, the drug requirements and the market demands."

The administration challenges of these drug products are compounded further when also incorporating the needs of human factors, high-viscosity and large-volume dosage requirements, and a strong desire to stay as close to the conventional "two-step" autoinjector as possible. In some cases, the standard primary drug container is perfectly suitable; in others, it must be completely reimagined to support a combination product that suits the needs of the patient, the drug requirements and the market demands.

As a company known for its focus on "injecting simplicity" into complex drug delivery, Windgap faced this dilemma when developing each of its current product platforms. Its large-volume, dual-chamber (LVDC) device relies on proven cartridges, while the ANDI® device was intentionally developed around a completely custom PDC design. With each development journey, Windgap established a deep understanding of the risks and benefits of either pathway, giving the company an intimate appreciation of when and why to do either.

SETTING THE STAGE: STANDARD VERSUS CUSTOM

From supply constraints to added capital costs, standard and custom approaches each bring pros and cons that must be carefully assessed before beginning the long journey of product design and development. These considerations are described below and summarised in Table 1.

The "Standard" Scenario

A standard primary container typically consists of a glass syringe with a cannula and elastomer plunger or a glass cartridge with an elastomer seal and plunger; less commonly, cyclo-olefin polymer or copolymer (COP/COC) may be used in place of glass. Several world-class suppliers of these components have become the norm for injection systems over time. Today, off-the-shelf components provide a low-risk, cost-effective option with a long history of manufacturing optimisation and use on common filling lines.

While mature and known, the manufacturing of standard glass primary containers has recently been plagued by demand spikes, supply constraints and long lead times. In addition, standard containers are nearly always coated with silicone to reduce glide forces and PFSs may contain traces of tungsten from the fluid path-forming process – both of which can lead to stability and particulate issues for the contained drug.[1]

"Custom" Considerations

COP is often the material of choice for a custom development project. Custom injection-moulded primary containers offer the benefit of bespoke shapes and sizes alongside additional functionality, for example, assembly features or an insert-moulded cannula. In some cases, the use of silicone can be avoided for drugs with which it is not compatible. This is due to the reduced friction between a plunger and polymeric barrel as compared with glass or the use of dry film lubricants.[2]

Despite the advantages of polymeric materials and custom manufacturing, these custom containers introduce new challenges not typically seen with standard PDCs. Multiple suppliers must be identified and managed for product design. A custom filling line may be required, surface-drug interactions must be characterised to ensure drug compatibility and non-glass containers may threaten drug stability due to increased gas permeation. Properly addressing such risks may result in a longer development cycle and require significant capital investment.

	Standard PDC	Custom PDC
Benefits	• Lower risk with a long history of compatibility and rigor • Can be cost-effective and readily available • Compatible with common filling lines	• Bespoke shapes and sizes • Custom assembly features or insert moulded cannula • Silicone-free options • Additional design functionality connecting device mechanisms directly to container function and performance
Challenges	• Demand fluctuation and supply constraints • Long lead times and supply interruptions • Concerns around silicone coatings and tungsten residuals	• May require a unique filling process with significant initial capital investment • May introduce a level of risk related to drug stability and compatibility • Longer development cycle due to the need for custom design and a manufacturing process

Table 1: Summary analysis of standard versus custom PDC decision matrix.

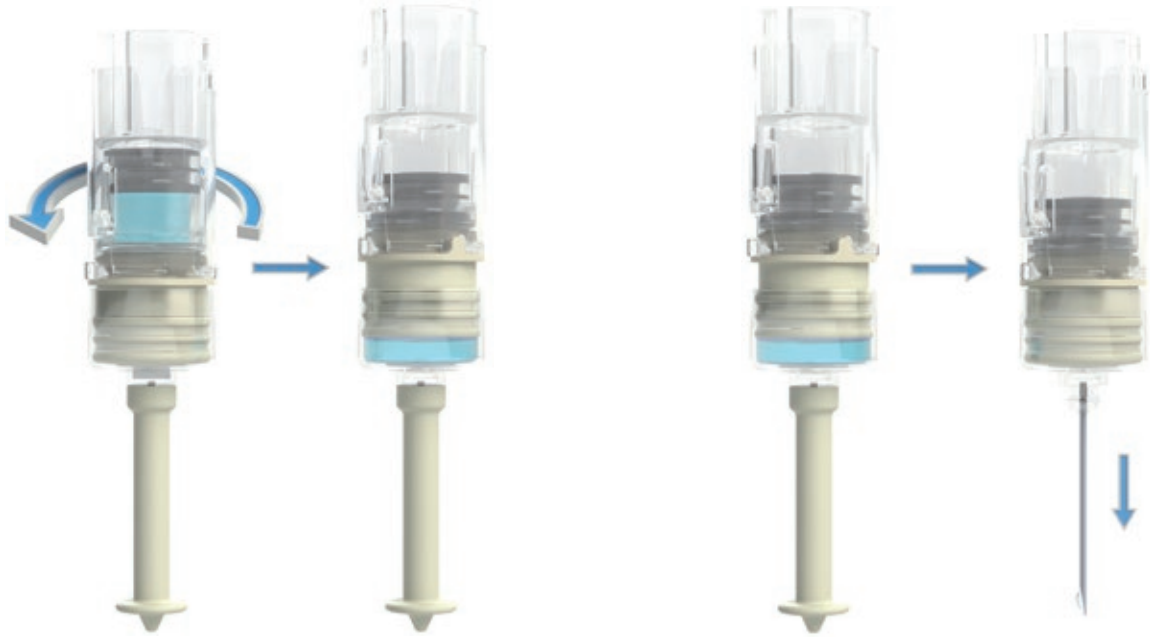
THE JOURNEY TO DESIGNING A FULLY CUSTOM PDC

Early in Windgap's development programme for emergency injections with its ANDI® device, the company found the widely available standardised systems forced it to sacrifice the patient experience and depart from its ideal target product profile. Windgap faced constant trade-offs between device form factor, usability, performance and other attributes. To satisfy all user needs, the company began to explore design options relying on a novel PDC architecture that would resolve these dilemmas.

The final design (Figure 1) achieved the integration of all critical functions while maintaining a compact, portable form factor.

The Advantages of Innovative Design

Windgap takes "injecting simplicity" seriously – the mixing mechanism for the ANDI® device is driven mechanically by the user, who simply twists the cap for removal. This action automatically rehydrates the powdered drug in just a few seconds, thanks to design-controlled fluidics – no shaking or swirling necessary.



STEP 1: TWIST	STEP 2: INJECT
The two channels on either side of the rotational face seal are intentionally misaligned while the device is in its stowed state. Upon twisting the cap, the channels are rotated into alignment to establish a fluid pathway between the chambers. Continued rotation releases a spring to force the liquid diluent into the powder chamber. The powder chamber recedes in the axial direction, creating an optimal environment for API/solvent interaction and complete dissolution.	To deliver the drug, the user presses the needle shield against the skin to trigger the injection of the mixed medication. The needle shield locks out upon removal from the skin to provide complete needle protection.

Figure 1: The ANDI® device, a revolutionary "twist" on emergency autoinjectors, administers injections in just two steps thanks to its custom PDC design.

The key component of the custom PDC design is a rotating face seal between the powder and liquid chambers and how the twisting user input is connected to it. Windgap was unable to identify anything "off the shelf" that would have been able to achieve the level of simplicity that this device offers while still being small enough to carry comfortably.

Unexpected Challenges – and Custom Solutions

The implications of Windgap's decision to move forward with a custom PDC affected both budget and timeline. Given the novelty of the PDC, the company had to develop a compatible filling method rather than relying on existing standard equipment and processes. It also had to ensure the entire supply chain and overarching quality management system complied with 21 CFR 210 and 211 requirements for drug-device combination product manufacturers and included all systems required for properly managing drug handling. On the design side, Windgap balanced its sterilisation strategy with efforts to achieve acceptable container closure integrity and seal integrity.

> "Leveraging a proprietary needle hub and regulated gas power, this platform uses two single-chamber cartridges to administer therapies requiring reconstitution, liquid/liquid mixing or sequential delivery."

Despite the array of challenges, the decision to pursue a fully customised PDC remained appropriate as it offered several significant benefits along the way:

- Windgap could hold tight tolerances on critical parts specific to its design
- Given its control over the filling process, the company eliminated the risk of variable lead times with contract manufacturers as it scheduled filling runs
- Windgap was able to navigate the covid-19-related supply chain disruptions in glass sourcing and ongoing capacity constraints from the rise of GLP-1 volumes, thanks to its independently managed network of component suppliers
- The company maintained best-in-class performance requirements to deliver effective and efficient product attributes to patients.

LEVERAGING STANDARD PDCs IN A NEW WAY

With ANDI® well positioned for commercial development through a product partnership with ALK-Abelló (Hørsholm, Denmark),[3] Windgap set out to develop another device platform around a new set of requirements inspired by continued customer engagement. One requirement was compatibility with readily available, proven glass cartridges.

The resulting LVDC platform reimagines the dual-chamber drug delivery system

by maintaining the usability and aesthetics of a conventional, single-chamber autoinjector. Leveraging a proprietary needle hub and regulated gas power, this platform uses two single-chamber cartridges to administer therapies requiring reconstitution, liquid/liquid mixing or sequential delivery. This innovative arrangement of off-the-shelf PDCs substantially streamlines the administration process for these complex formulations to just three steps, as shown in Figure 2.

Elevating the Standard Solution with the Patient in Mind

The LVDC's nested PDC architecture accommodates the use of two readily available, ISO-compliant cartridges (from 1 to 5 mL) compatible with industry-standard fill-finish processes while maintaining a compact, easy-to-handle form factor.

LVDC products are gas powered to enhance functionality when managing both high-viscosity and large-volume injections. For reconstitution or liquid/liquid mixing applications, this removes the need to shake or swirl, substantially reducing the steps required for prep and administration. Users can activate and regulate the mixing and administration of complex *and* combined drug therapies with a press of a single button.

When the mixing device variant is in its fully automatic configuration, treatment may be delivered in just three steps – initiate mixing, remove cap, inject – to minimise user effort and required training.

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

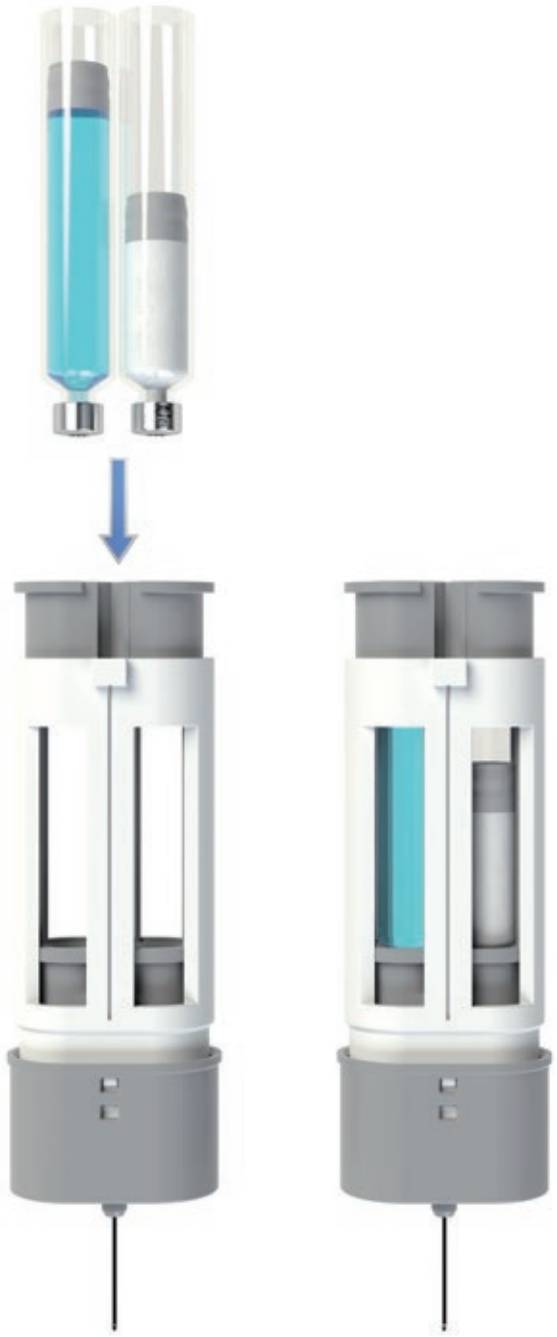
TURNING NOVELTY INTO THE NEW NARRATIVE

Windgap has accumulated experience developing injectable combination products with both custom and standard, off-the shelf PDCs and as part of a novel combination product. This knowledge is used to inform the company's collaborations with biopharmaceutical partners to bring together device and drug or biologic into a robust combination product.

Windgap encourages its fellow device innovators and pharmaceutical counterparts to consider the following:

- If combination product requirements can be met with a standard off-the-shelf PDC system, this option should be prioritised, especially if the intention is to develop an injector platform that would be supplied to other pharmaceutical companies, which are historically risk-averse.
- If developing a full combination product in-house, there is more latitude and innovation freedom for custom designs to improve performance. Such customisation brings increased risk, investment and development time. However, if companies are willing and able to accept the challenge of developing and integrating non-standard aspects of the supply chain, such as drug handling and drug filling, the rewards can be substantial.

Windgap believes that the strongest and most critical innovations align the requirements of the drug, the needs of the patient, and the ability of the surrounding science and supply chains to meet both.



STEP 1	Push-button device activation causes needles to puncture both cartridge septums simultaneously. This dual puncture creates a closed fluidic connection between the two chambers. The device automatically regulates the release of stored gas to transfer the liquid to the powdered drug cartridge for initial mixing and then reciprocates the drug product back and forth between the two cartridges.
STEP 2	Remove the cap once the number of reciprocated cycles reaches the validated endpoint for mixing completion.
STEP 3	To deliver the drug, the user presses the needle shield against the skin to trigger the injection of the mixed medication. The needle shield locks out upon removal from the skin to provide complete needle protection.

Figure 2: Putting standard cartridges to work in new ways with Windgap's LVDC side-by-side dual-chamber architecture, in this example for the reconstitution products.

Some statements are forward-looking. Unless specifically stated, these devices are not approved for sale in the US or the EU.

ABOUT THE COMPANY

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

ABOUT THE AUTHORS

Brent Buchine, PhD, has worked in advanced R&D and innovation for over 20 years. In addition to being a serial entrepreneur, he has authored multiple peer-reviewed publications, received over 150 citations and filed over 100 patents based on his inventions. As Chief Business Officer of Windgap Medical, Dr Buchine oversees business development, corporate partnerships and pipeline strategy. He received his PhD in Materials Science & Engineering from Georgia Tech (US).

Jason Durkin has nearly 30 years of experience in the combination products industry across a variety of injection and inhalation technologies. Over his career, he has worked on several innovative inhalation products, implemented new drug handling capabilities and managed commercial injection programmes. As Windgap's Vice President Supply Chain, Mr Durkin continues to leverage his expertise in building and deepening supplier relationships for both device and drug products. He holds a Bachelor of Science in Business Administration from Boston University (MA, US) and a Mechanical Engineering degree from Wentworth Institute of Technology (MA, US).

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CAPA VALVE'S PATENTED TECHNOLOGY TRANSFORMS ANY SYRINGE INTO A DCD

In this article, Phil Green, PhD, Technical Director, Dale Charlton, PhD, Chief Scientific Officer, and Kevin Abbott, Managing Director, all of Capa Valve, introduce the company's novel valve system for converting standard syringes into prefilled dual-chamber devices, capable of simplifying and improving the delivery of liquid-liquid and liquid-powder drug products, including reconstitution of lyophilised powders.

DUAL-CHAMBER DEVICES MADE EASY

Dual-chamber devices (DCDs) are combination products that typically contain a freeze-dried drug and a diluent in two separate chambers of the device. In particular, they are designed to provide stability and convenience for biopharmaceuticals that require reconstitution before administration. They can also significantly reduce the number of handling steps and therefore the potential for preparation errors by the patient or caregiver. DCDs are of growing interest in large part due to self-administration trends and needs but their wider adoption, even after several decades of availability, is, arguably, still quite limited, most likely due to challenges in manufacturability, product formulation and costs.

> "The Capa Valve DCD was developed to address many of the issues around the current limitations of DCDs and overcome some of the challenges in the manufacture and economics of their use."

The Capa Valve DCD was developed to address many of the issues around the current limitations of DCDs and overcome some of the challenges in the manufacture and economics of their use. The patent protected technology is a simple and cost-effective way to realise a DCD for injection, be it for reconstitution within a prefilled syringe (PFS), such as for a lyophilised drug, or a liquid-solid powder for injection (PI). The additional parts needed can be sized for any standard syringe suitable for prefilled applications. To date, the Capa Valve technology has been tested for suitability from standard 1 mL PFSs up to larger 60 mL infusion syringes.

> "The valves within the syringe barrel have excellent inherent container closure integrity, so seal each chamber fully until such times as the valve is activated."

The multi-chamber Capa Valve PFS device, when compared with the current methods of reconstitution for lyophilised drugs for injection, reduces risk to the patient, reduces packaging, transport and logistics costs, and drastically reduces the time required to reconstitute prior to injection, as well as addressing some of the limitations in manufacture and wider adoption. Figure 1 shows the stages of pre-mixing a liquid and solid with the device's sliding valve rod arrangement.

Additionally, the versatility and simplicity of the design allows for a variant of the Capa Valve system to create a multi-chamber device where two or more separate liquids can be dispensed sequentially via a single injection. A typical application for this arrangement would be the injection of a liquid API followed by a saline flush. The valves within the syringe barrel have excellent inherent container closure integrity, so seal each chamber fully until such times as the valve is activated. Upon reaching the end of its stroke, the stopper comes into contact with the bottom of the syringe, at which point the valve opens to allow the liquid in the second chamber to flow through the valve

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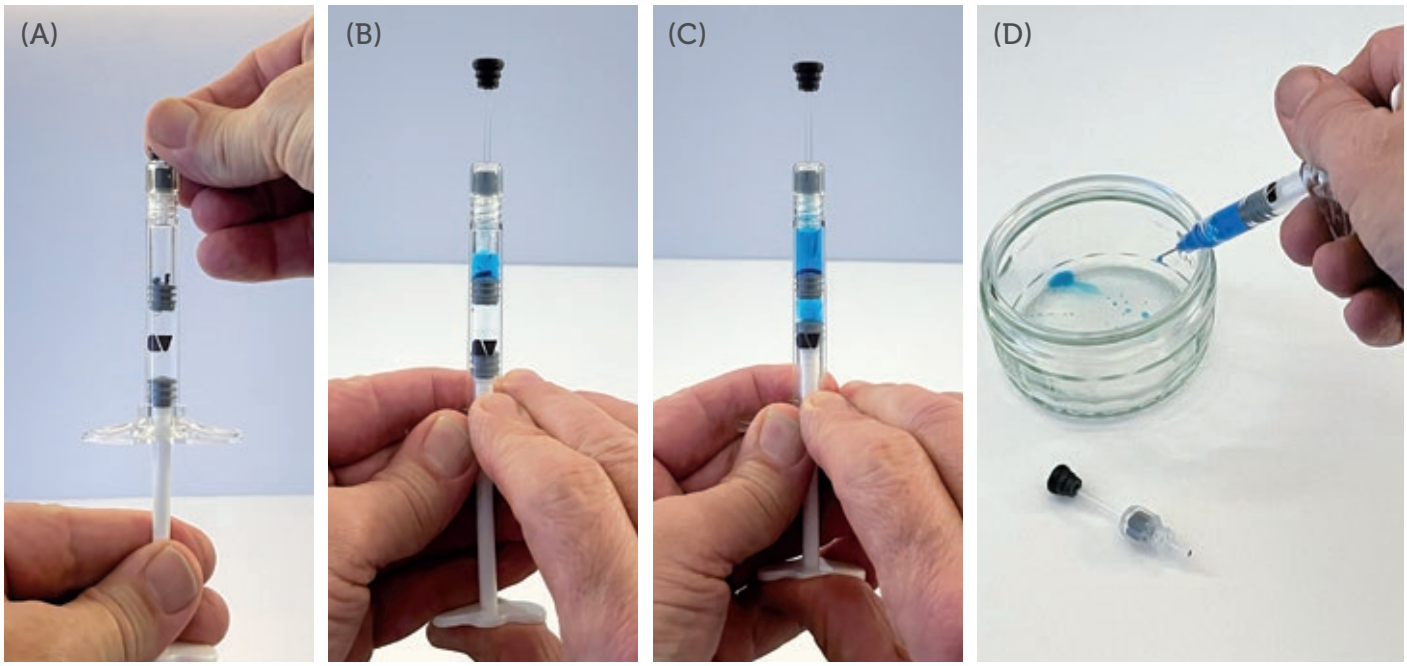

Figure 1: Liquid-solid pre-mix.

and into the needle for injection. Figure 2 shows the stages of injection for sequentially injecting three separate liquids using two valves within a standard syringe.

Another distinct and novel use of the Capa Valve technology for near-patient injection is the installation of the valve at the end of the syringe and filling the chamber between this valve and the plunger stopper with a flush. There are a number of companies offering a PFS with a flush, however, by installing the valve at the bottom of the syringe, it is possible to create a PFS with a flush that can draw up any drug of choice into the PFS (Figure 3).

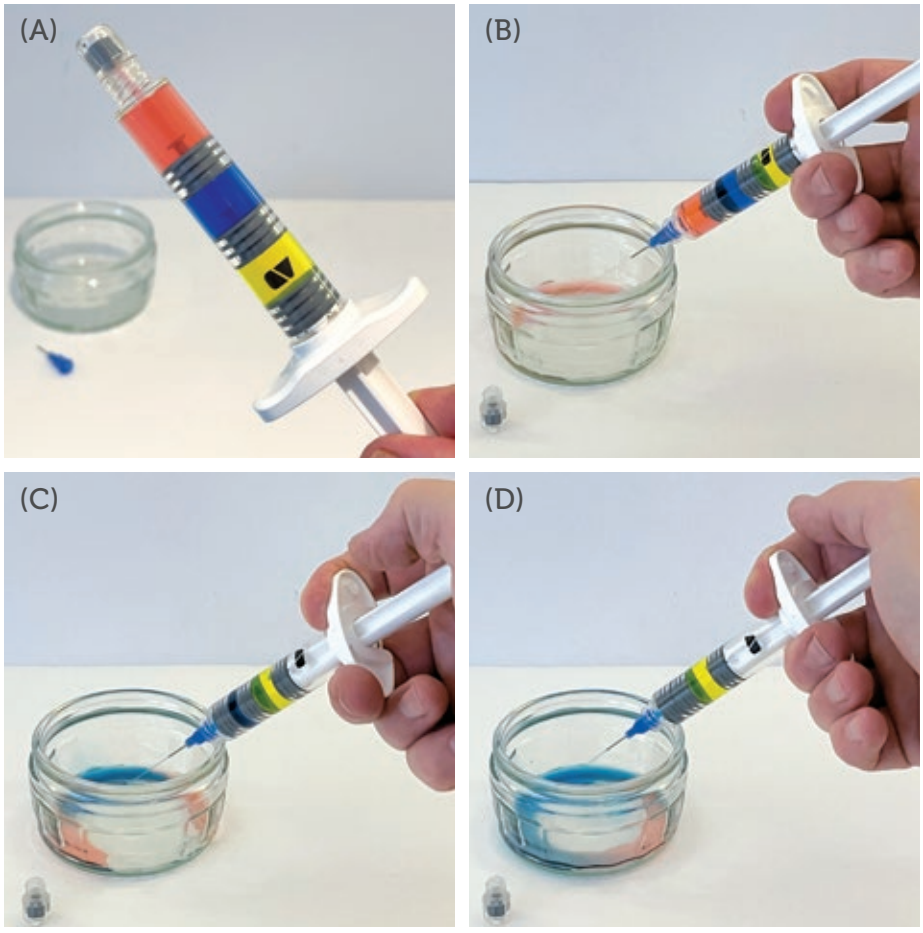

Figure 2: Sequential dispense of three separate liquids.

The variant of the technology that enables pre-mixing liquids or a solid and a liquid uses the same principle of having a stopper with a central hole located part-way down the barrel of the syringe, but for pre-mixing the hole is sealed with a cylindrical rod attached to the syringe cap. The sealing rod (valve rod) is either removed by removing the syringe cap or, for use in a contaminated environment, the valve rod can slide through a seal in the cap to unseal the stopper, thereby avoiding drawing in any air from the immediate environment during mixing, which is done by backflushing the valve.

MARKET NEED AND THE CAPA VALVE VALUE PROPOSITION

The costly, time-consuming and relatively high-risk process of reconstituting lyophilised drugs or PIs can be addressed by a PFS using the Capa Valve technology. The technology provides both a packaging solution and a mixing solution, as the action of back-flushing the drug and diluent through the valve generates a gentle but effective mixing of liquid-solid or liquid-viscous liquid combinations. This mixing technique can also be used for mixing viscous liquids and the emulsification of oil-based products, such as vitamin K, for injection.

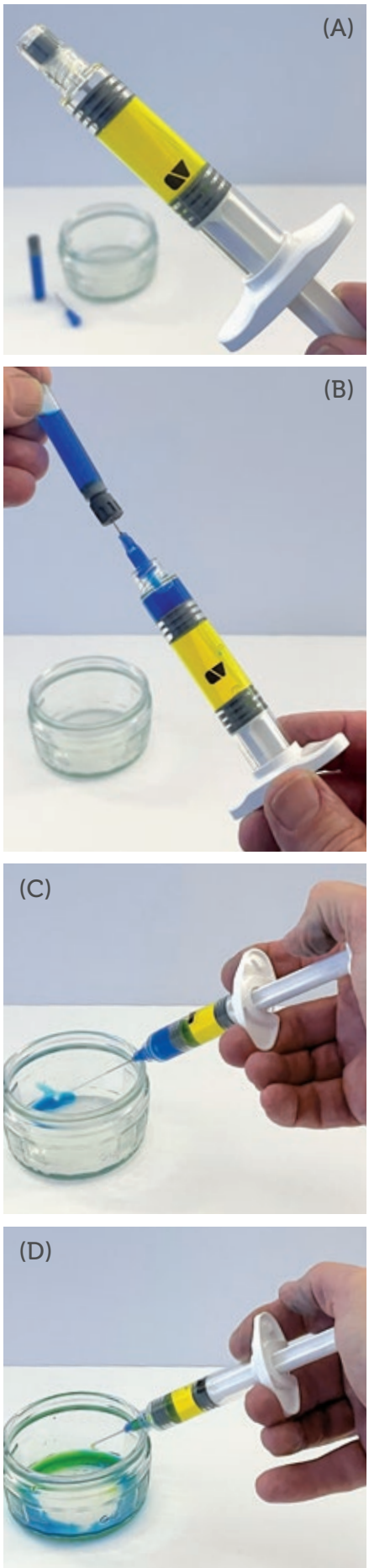

Figure 3: Draw up and sequential delivery.

> "The Capa Valve technology was originally developed to address the significant growth and application of PFSs in the growing market of injectable lyophilised drugs, which require reconstitution before administration."

The Capa Valve technology was originally developed to address the significant growth and application of PFSs in the growing market of injectable lyophilised drugs, which require reconstitution before administration. There is an abundance of information providing data supporting the rapid growth of lyophilised injectables (Figure 4).

The use of lyophilisation for both pharmaceutical and biopharmaceutical manufacturing has grown around 13.5% per year over the last five years.[1] At present, around 16 of the top 100 pharmaceutical drugs are lyophilised.[2] The percentage of lyophilised biological drugs is even greater – 35%.[2] This growing market for biologics requires storage and delivery systems – Acumen Research & Consulting predicts the market value for novel drug reconstitution systems at US$5.1 billion (£4 billion) by 2030.[3]

Just one example of an application for potential use of the Capa Valve is in the routine immunisation schedule in the UK, for which around five million injections of lyophilised drugs are delivered each year by the NHS (Figure 4).

TRADITIONAL RECONSTITUTION PRACTICE AND CURRENT NOVEL DEVICES

Currently, there are risks involved in the reconstitution and delivery of lyophilised drugs for injection, such as contamination, incorrect diluent drug ratio, partial reconstitution and incorrect dosage. Additionally, the time taken for reconstitution can be lengthy and the packaging can be excessive, which carries both financial cost and environmental implications. The current practice of administering a lyophilised drug by injection requires a trained healthcare professional to perform the reconstitution, meaning that these drugs are currently not suitable for self-administration in a home environment.

At present, there are a few companies offering dual-chamber syringes for either sequential delivery of two liquids or pre-mixing of a diluent and powdered or lyophilised drug. However, these companies' devices have only seen limited adoption for widespread use. Without exception, these current DCDs feature a custom-design syringe, often using a bypass valve within the syringe, which significantly increases manufacturing costs, prohibiting widespread adoption. Complex tooling for these bespoke syringes also generates a significant carbon footprint in the process of bringing these into the market.

The Capa Valve solution is the installation of two small, low-cost parts within existing standard syringes suitable for prefilled applications. This system can reconstitute a diluent and a powder, a lyophilised cake or a second liquid extremely efficiently (in seconds) using a standard syringe prefilled with the desired drug combination. This prefilled solution addresses many risks associated with current practices for reconstitution and the ease and speed of reconstitution and administration by injection lends itself to both self-administration and emergency situations. All of the Capa Valve variants have been tested and conform to the ISO 11608-3:2012 standard for break-loose and glide forces.

The Capa Valve technology could not only save significant time and money within the healthcare community, it also perfectly complements the growing market for lyophilised drugs. There are significant benefits in developing drugs in lyophilised form, such as increased shelf-life, lower associated waste, reduced packaging and decreased logistics costs. Therefore,

> "The Capa Valve solution is the installation of two small, low-cost parts within existing standard syringes suitable for prefilled applications."

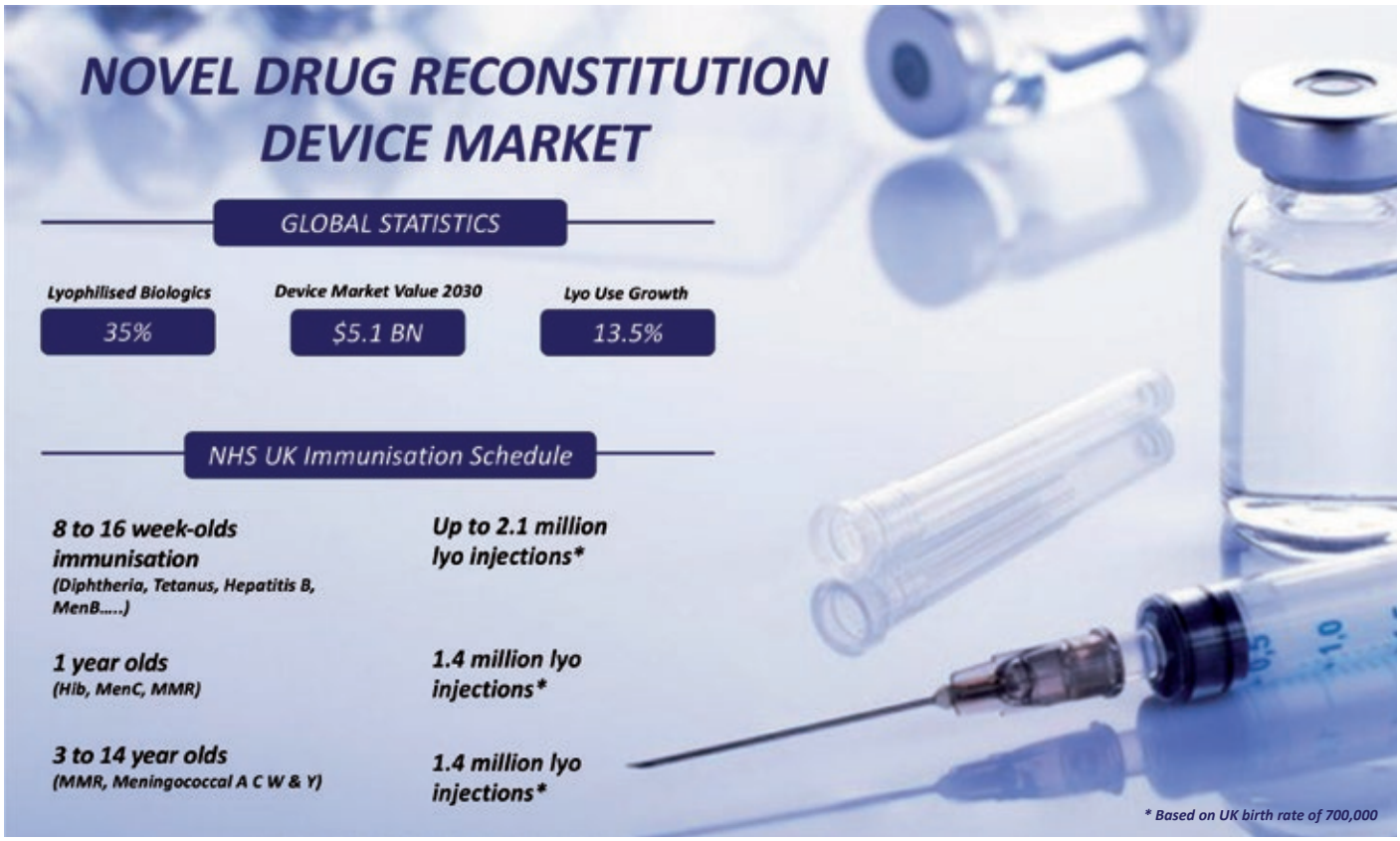

Figure 4: Market opportunity for lyophilised injectable novel device.

a low-cost solution for both storage and delivery of lyophilised drugs will provide the necessary incentive to continue to develop this more environmentally friendly and convenient form of drug.

FILL/FINISH AND SCALABILITY

The simplicity of the Capa Valve design does not pose significant challenges to the fill/finish process or automation of PFS production. There is minimal disruption to the primary chamber and existing infrastructures can be used with little or no modification. The installation of the sequential valve uses the same process as the installation of the central stopper in a dual-chamber bypass syringe. Figure 5 shows the fill/finish stages for the pre-mix variant.

BUSINESS MODEL AND GROWTH STRATEGY

Capa Valve is currently negotiating a sizeable manufacturing contract based in Europe for the worldwide supply of the technology. The company is also working with several companies looking to license the technology for a broad range of applications, including nutraceuticals, pharmaceuticals and biologics. Capa Valve will be at the CPHI PharmaPack 2024 exhibition, located at Stand J32.

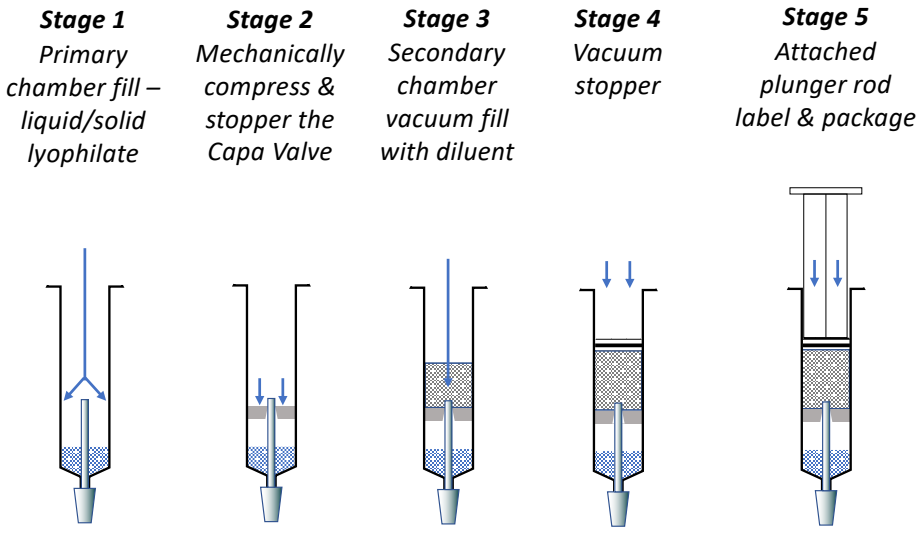

Figure 5: Fill-finish stages of the Capa Valve pre-mix variant.

ABOUT THE COMPANY

Capa Valve, founded in 2010, is a start-up company with two directors – Kevin Abbott (Managing Director) and Dr Phil Green (Technical Director) – who have recently appointed an experienced medical consultant, Dr Dale Charlton, as Chief Scientific Officer. The company has developed and patented a variety of valve systems suitable for installation into any size of standard medical syringe to enable the sequential dispensing of two liquids or to reconstitute a diluent and a powder, a lyophilised cake or a second liquid extremely efficiently. The company is currently in negotiation with several interested parties wishing to license in the technology, as well as negotiating the manufacture of the valve system.

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ABOUT THE AUTHORS

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

Dale Charlton, PhD, is a Freelance Consultant for automation and fill/finish. Dr Charlton has spent a lifelong career in the life science and biotechnology sector. He obtained a PhD within Pfizer's Drug Discovery Group and worked on API and biotech manufacture before moving into pharmaceutical fill/finish. He took up a position as the Director of Business Development at Optima Pharma in sterile production automation and worked for several contract design and manufacturing organisations offering development and finished drug services. Dr Charlton has a unique understanding of the entire drug development lifecycle and offers insight from both the pharma and supplier perspective.

Kevin Abbott, a plumber by trade, developed a piece of equipment in 2011 to fill a domestic central heating system with rust inhibitor and mains water. The prototype system worked well, so Mr Abbott looked into patenting the device. The patent agent advised that, despite its simplicity, the valve was indeed novel and, if miniaturised, could be used in medical syringes to provide dual-stage dispensing of two different liquids. Mr Abbott's original patents, granted in Europe, the UK and the US, form the basis of new configurations for a more recent patent application.

ON drugDELIVERY

2024/25 EDITORIAL CALENDAR

Publication Month	Issue Topic
March	Ophthalmic Drug Delivery
April	Pulmonary & Nasal Drug Delivery
Apr/May	Drug Delivery & Environmental Sustainability
May	Delivering Injectables: Devices & Formulations
May/Jun	Oral Drug Delivery
June	Connecting Drug Delivery
Jun/Jul	Industrialising Drug Delivery
September	Wearable Injectors
October	Prefilled Syringes & Injection Devices
Oct/Nov	Drug Delivery & Environmental Sustainability
November	Pulmonary & Nasal Drug Delivery
December	Connecting Drug Delivery
January 2025	Prefilled Syringes & Injection Devices
February	Skin Drug Delivery: Dermal, Transdermal & Microneedles
March	Ophthalmic Drug Delivery

DISCUSSION PRIMER: PHARMAPACK

At Pharmapack Europe 2024, at Paris Expo Porte de Versailles (Paris, France), on January 24–25, 2024, over 5,000 attendees and more than 370 exhibitors will congregate at the heart of the pharmaceutical drug delivery and packaging industry. Key developers and innovators from companies like BD, Nemera, Aptar Pharma, West Pharmaceutical Services and many more will showcase some of their latest innovations. Ahead of this event, Pharmapack's organisers spoke with three industry experts, Alastair Willoughby, Jamie Greenwood and Chris Hurlstone, all from Team Consulting, to get their perspectives on the major trends expected to be top discussion topics at the event, and to play a significant role in the industry throughout 2024 and beyond.

PHARMAPACK By CPHI

Launched in 1997, Pharmapack is a leading European event for pharmaceutical packaging, drug delivery and medical devices and machinery. Over the past 25+ years, the event has grown from a conference with a small table-top exhibition to an event hosting over 300 exhibitors and welcoming attendees from 75 different countries.

team

Team Consulting is a world-class partner in drug delivery device design and development. For over 37 years its multidisciplinary team of experts has applied the latest approaches in design theory, engineering ingenuity and human factors to deliver products that are not only regulatory compliant but loved by end users. Working with leading pharma companies and innovative start-ups across the globe, Team Consulting thrives on helping its clients deliver the right technologies for their drug delivery needs.

OPTIONS TO CONSIDER WHEN DEVELOPING SUSTAINABLE MEDICAL DEVICES

ALASTAIR WILLOUGHBY, Head of Mechanical Engineering Group

The drive for sustainability in medical devices has continued to gain momentum as more sustainability goals are set and deadlines for carbon reduction approach. One of the key trends in this area within the drug delivery sectors, among others, is the move away from single-use devices to reusable ones, minimising the material usage and waste associated with single-use devices. This move could provide significant savings in carbon footprint, but the full impact analysis needs to consider the costs of preparing a device for reuse – whether through cleaning and re-sterilisation, reprocessing or incorporating a disposable element.

> "The cost of a reusable device, financial or in carbon footprint, may not provide a significant win, while potentially contributing to other challenges, such as transportation or more complex user interactions."

In some cases, the cost of a reusable device, financial or in carbon footprint, may not provide a significant win, while potentially contributing to other challenges, such as transportation or more complex user interactions. One example of this would be a device where the disposable element, such as a prefilled syringe, has a high financial and environmental unit cost, which, combined with a higher device cost to allow for reusability, may mean that, for a short course of treatment, a series of single-use devices may be better. As with all aspects of sustainable product design, the wider implications of design decisions must be considered.

LARGE DOSES AND ALTERNATIVE THERAPIES – THE NEED FOR RESPIRATORY DRUG DELIVERY INNOVATION

JAMIE GREENWOOD, Managing Consultant

Innovation has been relatively slow-moving in the respiratory drug delivery space in recent years. The innovation that has occurred has relied on the big players developing products for the traditional therapy areas of asthma and chronic obstructive pulmonary disease (COPD), rather than innovators developing their own devices. Meanwhile, "alternative" therapies (and whatever devices may be required to deliver them) appear to have been stuck on the backburner, with plans to advance these "at some point in the future".

However, with 2024 now upon us, the winds are shifting, and we are seeing signs of some green shoots of innovation, both in inhaled pulmonary and intranasal drug delivery. The long-promised alternative therapies for conditions other than asthma and COPD, including lung cancer, idiopathic pulmonary fibrosis, Parkinson's disease and more advanced antibiotics, also appear to be getting closer. Added to this, there are also signs that device developers are starting to mobilise and develop devices to match the particular requirements of these new therapy areas.

For example, there has been interest in intranasal drug delivery of both liquid and dry powder dose forms, targeting both central nervous system (CNS) and systemic delivery. Significantly, these intranasal treatments have been extended to treatment areas that were previously the sole preserve of injectables, such as administering lifesaving medications in one-opportunity emergency situations to reverse opioid overdose or Type 1 anaphylaxis.

> "Significantly, these intranasal treatments have been extended to treatment areas that were previously the sole preserve of injectables."

Similarly, following advances in formulation techniques for larger molecules, such as peptides and nucleic acids, there is now a new challenge for drug delivery devices to be able to handle higher dose sizes of what are often delicate formulations. This has led to a shift in the design landscape for inhaled pulmonary drug delivery devices, of which many have been developed to deliver no more than 10–15 mg of powder per use. There is now an emerging need for effective aerosol drug delivery devices that can deliver higher masses of formulations, often in excess of 25 mg. However, these requirements cannot be easily accommodated by simply re-engineering currently available products.

As such, it looks likely that this trajectory will continue in 2024; overlaid with other longer-running trends, such as improved sustainability and lower cost points, it can be expected that more drug and device developers will be scrambling to address these emerging unmet needs.

THE GROWTH OF PERSONALISED MEDICINE

CHRIS HURLSTONE, Technical Director

Recent years have seen a rapid growth in the area of "personalised" or "precision" medicine, where treatments and interventions are identified and delivered at the level of the individual, rather than as a "one-size-fits-all" solution for a population or patient group. There have been a number of drivers for this – for example, a surge in the development of new biosensor technologies, partly driven by the global response to the covid-19 pandemic, alongside the continued growth of digital and connected technologies, has resulted in a massive increase in the opportunities for diagnostics. Additionally, major advances in genetic sequencing, drug manufacturing processes and delivery device technologies have facilitated the development, approval and delivery of new personalised therapeutics.

At the level of the individual, the use of wearable sensors and at-home testing kits (e.g. for blood or saliva) has allowed individuals to proactively monitor themselves for ailments ranging from general wellness to cancers. At the national healthcare system level, advances in fields such as genetic sequencing, pharmacogenomics, scanning technologies and artificial intelligence have combined to create hugely increased opportunities for the development and deployment of screening programmes and companion diagnostics.

Companion diagnostics, which provide information on whether a therapeutic product will be both effective and safe for a specific individual, have seen ground-breaking changes. Examples of these

> "New personalised treatments exist in a number of areas, particularly CGTs, with approved products in both the US and Europe now well into double figures."

include the ability to check whether a tumour has a specific gene change or biomarker that can be targeted by the proposed drug (effectiveness) and whether the impact of using a drug has had a negative impact on the patient's physiology, such as blood count (safety).

New personalised treatments exist in a number of areas, particularly cell and gene therapies (CGTs), with approved products in both the US and Europe now well into double figures. Most CGTs are in the field of oncology but there are also applications in disease areas such as cardiology, CNS disorders and metabolic conditions, such as diabetes.

The attractiveness of a therapy that can deliver a permanent cure in a single "one and done" treatment, as a replacement for ongoing weekly or monthly injections, is clear, but there are hurdles to overcome – a key example being the need for healthcare practices and systems to adapt to this new approach. Another sizeable and much talked about obstacle is the significant cost. For example, Libmeldy (atidarsagene autotemcel), developed by Orchard Therapeutics (London, UK) and approved in the UK for the treatment of rare and fatal genetic disorders in infants, costs £2.8 million per treatment, and Roctavian (valoctocogene roxaparvovec), developed by BioMarin Pharmaceutical (San Rafael, CA, US) and approved in the US for the treatment of haemophilia, costs US$2.9 million (£2.3 million) per patient.

These costs are partly driven by the highly complex processes – manufacturing, laboratory handling and surgical procedures – inherently entailed in producing and delivering these treatments. However, advances in these areas will support further growth, and this is already happening for CGTs based on messenger RNA (mRNA).

Looking specifically at mRNA research, progress was well underway long before covid-19, but the demand introduced by the pandemic supported the rapid development of mRNA vaccines. Now there is a situation whereby these learnings and pathways can potentially be applied to help secure faster approval of mRNA-based CGTs for oncology and other disease areas. In parallel, GMP manufacturing processes for lipid nanoparticles, which can form the basis of delivery mechanisms for mRNA gene therapies, are being developed and commercialised, which should help reduce costs and therefore enable increased access.

> "The attractiveness of a therapy that can deliver a permanent cure in a single 'one and done' treatment, as a replacement for ongoing weekly or monthly injections, is clear, but there are hurdles to overcome."

> "The increase in personalised medicine is also supported by the continued development of innovative delivery devices."

The increase in personalised medicine is also supported by the continued development of innovative delivery devices. These are often needed to support targeted delivery of new therapies to specific parts of the body and can leverage advances in technologies such as robotics and minimally invasive surgery, imaging and monitoring, precision manufacturing and digital systems.

Pharmapack Europe 2024 will take place in Paris, France, on January 24–25, 2024. For more information, visit: *www.pharmapackeurope.com*.

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Alastair Willoughby, Head of Mechanical Engineering, is Team Consulting's lead for its cross-functional sustainability offering, where he works with his team to create robust, sustainable device designs. He is an experienced engineer with over 17 years of experience in medical device development and technical consultancy.

Jamie Greenwood, Managing Consultant, is a versatile scientist with a track record spanning 20 years of technical leadership in product development, both in the medical and consumer product sectors. He has a particular interest and specialism in drug delivery and has worked on many of today's marketed dry powder inhalers.

Chris Hurlstone, Technical Director, has more than 25 years of experience in developing technologies and devices for healthcare markets, with a particular focus on drug delivery systems. A named inventor on numerous patents, Mr Hurlstone has a strong track-record in delivering innovative and robust engineering solutions.

OWEN MUMFORD
Pharmaceutical Services

PRACTICAL PATHWAYS TO SUSTAINABILITY

In this article, Alex Fong, Head of Insight, and Olivia Houselander, Business Development Manager, both at Owen Mumford, discuss the importance of sustainability in the healthcare sector and the challenges that must be overcome to achieve it in a meaningful and lasting way.

There is wide consensus around the importance of transitioning to a more sustainable future – both in the healthcare industry at large and in the pharmaceutical sector that serves it.[1] This extends, naturally, to examining the environmental impact of single-use devices for delivering drugs to the patient.

However, the journey towards a greener, more sustainable future must be structured by each healthcare institution in a way that does not reduce the efficacy of treatments for patients and does not heap unaffordable costs on healthcare organisations, which are already under enormous financial pressure.

THERE'S PLASTIC AND THEN THERE'S PLASTIC

When it comes to reducing the use of plastics, context and prioritisation are helpful starting points. The first step for most healthcare institutions is to classify medical plastics into a series of categories according to their ability to be substituted without loss of utility, sterility or safety. A glance at most studies on the issue of replacing medical plastics with more environmentally friendly alternatives shows that the greatest opportunities lie in packaging, disposable masks, gloves and coverings, wound care and so on.

One study found that most medical plastic waste (70%) is made up of commodity plastics, used to make tubing, films, packaging, connectors, labware, intravenous bags, catheters, face masks, housings, luers, membranes, sutures, etc.[2] Syringes, in contrast, form just one part of the remaining 30%. Therefore, it would seem logical to first address commodity plastic alternatives to achieve near-term environmental goals, rather than prioritise parenteral drug delivery where drug stability, anti-contamination and infection control are paramount. As the standard UK NHS advice on infection control notes, "Needles and syringes are single-use devices, they should never be used more than once or reused to draw up additional medication."[3]

> "The idea of a general substitute material for the petroleum-derived plastics used in most drug delivery devices is very attractive."

Of course, the idea of a general substitute material for the petroleum-derived plastics used in most drug delivery devices is very attractive, and significant effort is being put into research and development in this area. Materials are coming down the line and, in time, production in the industry will substitute with either recycled materials or bio-based plastics. However, at this precise moment, healthcare systems around the world need a stock of delivery devices and prefilled syringes to manage clinical demand. Practical management of this situation requires a transition plan that recognises the reality – it will take the industry quite some years to move to sustainable alternatives and deliver them at scale. Suppliers and buyers will be best served by establishing a collaborative approach that manages this transition to produce the best clinical and patient-welfare outcomes.

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"Healthcare organisations must face the challenge of planning a path to greater sustainability while also maintaining focus on the paramount interests of patients."

The sector has also carefully considered biodegradable options. This subject is considered to have an inherent flaw, in that biodegradability is sometimes in contrast with stability issues around drug integrity when considering prefillable pharmaceutical products. Therefore, current thinking is now focusing more on *reusable* drug delivery products that are also easily *remanufactured* and where their disposable element can be easily *recycled*.

In the meantime, healthcare organisations must face the challenge of planning a path to greater sustainability while also maintaining focus on the paramount interests of patients. Inevitably, this will mean purchasing plastic, single-use drug delivery products for the immediate future. However, these can be examined to minimise the carbon footprint of the products being bought, and collaborative forward planning with the supply-side can set achievable milestones for sustainability across a period of years.

SUSTAINABILITY BY DESIGN

The Owen Mumford Pharmaceutical Services team has designed Aidaptus, a true platform autoinjector with a wide design envelope, to be compatible with a range of formulations, fill volumes, needle sizes and primary containers, thereby providing pharma companies with flexibility. As there are often changes to formulation and dosage during the development of injectable drug products, as well as throughout their lifecycle, this flexibility is invaluable (Figure 1).

Specifically, it reduces the work and risk associated with changes in formulation, such as additional verification testing, human factors studies and regulatory documentation. It also contributes to sustainability by offering a single platform for multiple applications, reducing environmental impact at the manufacturing level.

It is possible to introduce environmental improvements through "sustainability by design" approach. In so doing, a number of specific sustainability considerations can be built into product design and engineering. For example:

- Ease of disassembly can have a major impact on recycling costs and methods
- Device size optimisation, device simplification and packaging reduction can reduce waste and transport impact
- Harmonising raw materials and production methods between different products can save on cost and waste, while also opening the possibility of greater agility for production tasks between production lines.

For disposable products, a reduction in the amount of single-use plastic associated with each treatment (while maintaining safe and effective usability) can be achieved with careful consideration at the design stage. Similarly, removing metal components has a major impact as the processing and shipping of metals has a far higher carbon impact than those of polymers.

Many of the key principles of sustainable product design begin with understanding and developing a product lifecycle, not just a product – considering concept development, material selection, design and engineering, manufacturing, packaging, transportation, sales, use and end-of-life disposal – right from the start. This approach is already deployed for manufacturing efficiency, time to market, risk reduction, safety and regulatory compliance, and packaging and transportation costs. It is simply a case of extending existing disciplines to also

Figure 1: Owen Mumford Pharmaceutical Services designed Aidaptus, with a wide design envelope, to be compatible with a range of formulations, fill volumes, needle sizes and primary containers.

evaluate energy efficiency, environmental impact, material usage and recycling. In some aspects, existing US FDA and EMA quality system requirements touch on these environmental considerations – particularly around tracking, materials safety, efficacy and disposal. Similarly, lean manufacturing methodologies seek to reduce inefficiency in several key related areas, such as overproduction, waiting time, transportation, processing, inventory, motion and scrap.

THE CHALLENGES OF REUSABILITY AND INTERCHANGEABILITY

The current reality is that most devices – especially parenteral or other invasive products – will have to retain a disposable element to meet regulatory safety and hygiene requirements. When it comes to autoinjectors, currently, the most compelling solution is to design a minimum disposable unit within a reliably reusable "shell".

In some therapies, such as diabetes, devices have become more digitally connected, delivering remarkable therapeutic and cost benefits for remote patient management and safe self-administration. However, from a sustainability point of view, the costs of disposable electronics would simply not be viable, and – as previously noted – would not be acceptable in the light of electronics disposal regulations. All the design science must then be focused on creating a simple, repeatable interface between the two component sections, ensuring that functionality and efficacy are not impaired.

Nevertheless, such reusable devices may hit another hurdle in the drive to more sustainable drug delivery – namely, biosimilar interchangeability.

Cost is not the only consideration when switching from biologics to biosimilars; the patient experience may also be affected by any change in drug formulation or the drug delivery device provided. As one study notes, "There is scarce information on the patient's attitude toward such switching, especially studies comparing the injection devices."[4] To safely identify the most suitable device for their biosimilar product, pharmaceutical companies should have access to data from human factors testing and other sources that attests to a device's ease of use. This data would then also support regulatory applications for interchangeability status.

However, if the interchangeability path is to be considered, it may be more straightforward to opt for disposable devices; introducing a substantially different reusable or remanufacturable device is less likely to ease the switch. This may then have the effect of perpetuating the existence of less sustainable devices. The alternative is to introduce delivery devices that prioritise sustainability but that may be less acceptable to the patient from a usability point of view. The choice between sustainability and competitiveness (for pharma companies) or adoption likelihood (for regulators and clinicians) is a dilemma indeed.

When it comes to the device component, the FDA stipulates that any regulatory application should provide evidence that the impact of switching between delivery devices has been assessed, stating, "Data and information supporting the appropriate use and performance testing of the delivery device constituent part of the proposed interchangeable product should be submitted."[5]

CONCLUSION

In conclusion, there is no question that the general momentum in the industry is towards more sustainable drug delivery products. However, healthcare organisations must deliver the best possible patient services today, with the tools currently that they have available and under current regulatory regimes. Similarly, pharma companies must remain competitive in fierce markets. While patient wellbeing remains paramount, current regulatory and market forces may govern the actual pace of change to more sustainable materials and products being deployed.

Therefore, practical judgements have to be made about the drug delivery devices deployed in the near term, with a more strategic "journey" towards adopting more sustainable alternatives as they arrive on the market and gain regulatory approval. As is so often the case, collaboration between buyer and supplier is likely to achieve the best and most practically effective pathways to a more sustainable future.

ABOUT THE COMPANY

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

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ABOUT THE AUTHORS

Alex Fong, MBA, Head of Insight at Owen Mumford, is an experienced senior manager in the insight, analytics and strategy fields. He has applied these skills in a broad range of Industries including the FMCG/CPG, retail, telecoms and management consulting sectors.

Olivia Houselander, Business Development Manager at Owen Mumford Pharmaceutical Services, joined Owen Mumford as a Product Manager in 2008 and currently serves as an accomplished Business Development Manager in the Pharmaceutical Services division. In this role, she applies her extensive experience in medical devices, marketing strategy, and product launch and development to support continued business growth and create innovative product launches, making her an asset in the dynamic healthcare landscape.

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Owen Mumford
Pharmaceutical Services

AN ECO-FRIENDLY AND ECONOMICAL APPROACH TO AUTOINJECTORS

Here, John Palmer-Felgate, Founder of Eco-inject, introduces the company's patented innovation – a single-use, two-step autoinjector that is both eco-friendly and economical.

The Eco-inject autoinjector has been specifically designed to provide an efficient and user-friendly drug delivery device that minimises carbon emissions and is deliverable at a competitively low cost. A single compact platform for the Eco-inject device provides the option to incorporate either 1 or 2.25 mL prefilled syringes (Figure 1), while maintaining a common tooling and assembly set-up. The unique "latch and release" mechanism employed within the platform facilitates the use of biopolymers for every plastic component.

MEETING THE NEEDS OF THE EVOLVING MARKET

The market for autoinjectors is increasing rapidly, facilitated by the wider availability of generic and biosimilar drugs – as many blockbuster drugs come off patent – and driven by a greater demand for home therapies. Concurrently, there is acute pressure on pharmaceutical companies and healthcare providers to set and meet targets to reduce their carbon footprint.

Figure 1: The Eco-inject can incorporate either 1 or 2.25 mL prefilled syringes.

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"Many existing autoinjectors were developed long before sustainability was recognised as an important requirement."

Many existing autoinjectors were developed long before sustainability was recognised as an important requirement. Also, when used to deliver high-value originator drug products, device cost was less important. The launch of biosimilar and generic therapies, available at lower price points, is driving the demand for lower-cost autoinjectors to deliver these therapies.

Most healthcare buyers are now implementing sustainability impact assessments to guide their purchase decisions. Single-use autoinjector therapies typically carry a very high carbon footprint compared with other drug products, largely as a result of their fossil fuel-derived plastic device parts. Therefore, there is a risk that the use of these devices may be restricted unless their carbon footprint can be dramatically reduced.

By considering sustainability at all stages of the design process and across the product lifecycle, Eco-inject offers a solution to both the demand to minimise carbon footprint and the increasing requirement for low-cost autoinjectors.

QUEST FOR SUSTAINABILITY

Autoinjectors are typically used by home users who are not medically trained, which is vital to consider when designing any new autoinjector. A new device must be as easy and intuitive to use as currently marketed devices (Figure 2).

For many people, questions that will spring to mind when considering a product's sustainability include:

- Is it reusable?
- Is it recyclable?
- What has it been made from?

Many drugs administered via autoinjectors are harmful if they contaminate or leak into the local eco-system. Needles that become contaminated after injections must be disposed of in a sharps waste handling stream, typically ending with commercial incineration. These factors present a significant challenge to the demand for autoinjectors to be reusable and/or recyclable.

The used product would need to be disassembled for its constituent parts to be disposed of and/or reused in different waste pathways. This would require a user to disassemble and separate parts of the product, which increases the risk of needlestick injury (to users and waste handlers). The potential confusion between contaminated and recyclable parts also presents an unacceptable risk within the recycling loop.

In addition, reusable devices often include electrical components and require additional handling steps, which sometimes means the user has to reprime a drive system or plug in to recharge. Where the frequency of use of these devices is only once or twice a month, or where patients suffer from multiple comorbidities, it is often not practical to train users to take devices apart reliably and safely or to learn to cope with multiple handling steps or electrical complexities.

Figure 2: Eco-inject is easy and intuitive to use.

Eco-inject has been developed with sustainability at the very core of its design, right from first concepts through to final secondary packaging. It offers simple usability and safe disposal while achieving dramatic carbon savings.

The volume of required plastic components and manufacturing elements has been substantially reduced in Eco-inject, while the metal parts are 100% recoverable and recyclable, following commercial incineration. Carbon emissions are reduced at all stages of production and manufacture: from moulding process conditions and a novel single-tray sub-assembly solution through to final device packaging. These carbon savings are synonymous with financial savings, which are designed to appeal to companies seeking a low-cost autoinjector with a dramatically reduced carbon footprint.

Eco-inject's unique patented design, which incorporates 100% low-cost biopolymers, sets it apart in the current market for sustainable drug delivery products.

NOT JUST A SIMPLE SWAP

Converting an existing product to a more sustainable version, simply by swapping the type of plastic used, presents problems. Most types of biopolymer, currently producible at a reasonable cost, are based on ethylene or styrenics – and these biopolymers do not possess the mechanical properties required for high load paths, such as the load from a compressed drive spring during the shelf life of a drug/device product. Higher-grade biopolymers are available but these are significantly more expensive. Any plastic swap in an existing product would require revalidation and could require significant alterations to existing tooling, automation and handling systems, adding further to the overall cost.

> "Eco-inject's simple architecture and patented novel mechanisms have been specifically designed to work reliably using the available low-cost biopolymers."

UNPACKING BIOPOLYMERS

There is a widely perceived misunderstanding that all carbon emissions are "bad", with many climate-change initiatives focusing on decarbonisation – the process of reducing carbon emissions into the atmosphere. However, this is only addressing one key area of carbon management.

A Renewable Carbon Initiative paper on Comprehensive Carbon Management, published in October 2023, outlines the broader approach required to achieve sustainable carbon cycles, even when carbon-reliant materials are used in industry.

In it, vom Berg *et al* wrote: "Comprehensive carbon management goes beyond CO_2 emissions, capture and long-term storage – which it is often reduced to. It decouples the whole industry from fossil feedstock, eliminates the use of fossil carbon wherever possible and allocates renewable carbon (from biomass, CO_2 and recycling) as efficiently and effectively as possible where carbon use is unavoidable. The aim is to achieve the lowest possible CO_2 emissions, reducing the need for carbon dioxide removal to achieve net zero and to provide a secure supply of renewable carbon to all dependent industries, such as chemicals and materials. Only when carbon is recognised as a raw material in carbon management strategies can truly sustainable carbon cycles be achieved. With proper comprehensive carbon management, the carbon reliant material and energy sectors will be de-fossilised and the remaining energy sector will be decarbonised. And only for the remaining share of truly unavoidable emissions, carbon dioxide removal and carbon capture and storage should come into play."

Biopolymers can now be made, on an industrial scale, using biogenic carbon – harvested from sources such as wood pulp, anaerobic digesters (waste food compost) or waste from sugar production – to generate the chains of carbon and hydrogen required. This allows plastic to be produced without using any carbon derived from fossil fuels. Using only biopolymer plastic components to make Eco-inject devices facilitates the retention of familiar manufacturing, handling and disposal processes, while only using and releasing carbon within a closed-loop carbon cycle.

Eco-inject's simple architecture and patented novel mechanisms have been specifically designed to work reliably using available low-cost biopolymers. With the production and availability of these biopolymers now reaching maturity, this offers a timely opportunity for Eco-inject to enter the market.

WHO IS IT FOR?

The demand for at-home therapies, facilitated by autoinjectors, is expanding – driven by the appeal of convenience, patient independence, minimised travel requirements and reduced demand on overwhelmed healthcare systems. Medical conditions currently treated using therapies delivered by subcutaneous autoinjector include rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, multiple sclerosis and clinical obesity, as well as other inflammatory and autoimmune conditions.

Typical use of autoinjectors varies from once a week to once a month. However, other application areas could also include one-off or seasonal administration of preventative therapies, for example, flu or covid-19 vaccines. Autoinjectors enable a potentially intimidating injection process to be embraced by a wider user base and help to ensure that medicines are administered correctly and safely.

Eco-inject is keen to connect with contract manufacturers and pharmaceutical companies that may have an interest in licensing its platform technology technology and bringing it to market. Eco-inject devices are available, on request, for handling assessment and evaluation.

ABOUT THE COMPANY

Eco-inject is a start-up injection-device company based near London, UK. The company is passionate about striving to reduce the carbon footprint of medical products, while maintaining optimal usability features. It has extensive knowledge and experience of developing drug delivery devices.

ABOUT THE AUTHOR

John Palmer-Felgate is an experienced industrial designer specialising in medical devices, with a distinguished career spanning over two decades. His expertise lies in generating innovative solutions for point-of-care healthcare needs, including drug delivery devices (inhalers and injection systems) and diagnostic point-of-care devices. Mr Palmer-Felgate understands the importance of considering the complete product design journey, from conceptualisation to production, with a keen focus on seeking elegantly simple mechanisms using moulded plastic and metal components. His broad understanding of the highly regulated landscape of medical device design ensures that each product adheres to the most stringent quality and compliance standards. With a diverse background encompassing consultancy roles and tenures within major pharmaceutical corporations, he brings a wealth of experience and a holistic perspective to every product he designs.

Stevanato Group

STAINLESS STEEL NEEDLES: QUANTIFYING COBALT RISK TO COMPLY WITH EU MEDICAL DEVICE REGULATION

In this article, Laura Berardi, PhD, Regulatory and Scientific Affairs Specialist – Drug Containment Solutions, Glass Department at Stevanato Group, discusses the reclassification of cobalt as a Category 1B carcinogen and presents a series of analytical studies into the toxicological risk present in needles and complete syringes.

From digitally enabled autoinjectors sophisticated syringes, all medical products and devices are designed around the same clear and simple objective of improving patient wellbeing. Their success is dependent on the integration of a variety of component parts, all of which must contribute positively to the whole.

If these strict parameters are not satisfied, however, there is potential for a paradoxical situation to arise where a medical device or component, despite being designed to benefit a patient, becomes a source of discomfort or physical harm. At the most extreme end of the spectrum, the potential exists for a device to unknowingly introduce unwanted compounds or elements into a patient's system, contributing to the development of life-limiting illnesses.

An example of such an element is cobalt. A naturally occurring trace metal, cobalt is present in the environment and is employed in a variety of commercial applications, from rechargeable batteries to agricultural fertilisers. While it can be ingested through respiration or via the skin, cobalt typically enters the human body through the consumption of food or vitamins, and at normal blood plasma concentration levels of less than 0.2 µg/L it is beneficial as a contributor to the production and regulation of red blood cells, platelets and DNA, while also supporting the synthesis of fatty acids and energy production.[1,2]

> "Cobalt has been shown to have serious harmful effects on the lungs, triggering allergies and skin reactions as well as having a carcinogenic effect."

At levels above this, however, cobalt has been identified as a potentially serious patient risk. Cobalt has been shown to have serious harmful effects on the lungs, triggering allergies and skin reactions as well as having a carcinogenic effect.

Indeed, in 2017, the Risk Assessment Committee of the European Chemicals Agency proposed reclassifying cobalt as a Category 1B carcinogen based on evidence from studies that found that exposure at toxic levels resulted in an increased incidence of lung cancers.

Furthermore, the International Agency for Research on Cancer conducted an evaluation of the carcinogenicity of cobalt and other metals, which resulted in cobalt metal and soluble cobalt(II) salts being designated as "agents that are probable carcinogens to humans".[3]

The reclassification and reassessment of cobalt, while not directly driven by concerns relating to medical devices, has had knock-on effects for the pharmaceutical

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> "The repeated contact with cobalt-containing needles has the potential to result in toxic levels of cobalt migrating from the material and into the patient."

sector. Cobalt's properties, such as biocompatibility, corrosion resistance, strength and durability, mean that it can be incorporated into certain materials and components used in medical devices at times. It can also be present as an unintentional impurity, with small amounts sometimes present within stainless steel grades and, therefore, ending up in products such as needles.

Theoretically, this situation could present a risk for patients who either receive or self-administer injections on a frequent basis. In such cases, the repeated contact with cobalt-containing needles has the potential to result in toxic levels of cobalt migrating from the material and into the patient.

Part 3 of Annex VI to the CLP Regulation (EC) No 1272/2008, also the European Medical Device Regulation (MDR), dictates that medical devices containing >0.1% w/w of substances that are Category 1A or 1B carcinogenic, mutagenic or toxic to reproduction (CMR) must incorporate appropriate labelling and a justification for the use of that substance. This is set out within Annex I of the MDR in paragraphs 10.4.1 (Design and manufacture of devices) and 10.4.5 (Labelling), which refer to substances classified as CMR for integral medicinal products and medicinal products with co-packaged devices.[4]

While the MDR provides a clear threshold for accepted levels of CMR substances, it does not provide clear parameters for how these levels can be determined. More specifically, the MDR does not outline whether the CMR content and concentration levels should be measured at a component level or in the context of the entire product, following the completion of all manufacturing and assembly processes and after being exposed to storage conditions. For pharmaceutical companies following this guidance and seeking to guarantee patient safety, this raises important questions over how the MDR should be properly interpreted and, at a practical level, whether analysis of individual product components provides a sufficient basis from which to confirm compliance in relation to safe CMR content and concentration levels.

Stevanato Group, as a market-leading supplier of drug containment solutions and drug delivery systems, sought to provide clarity on these questions by conducting a series of analytical studies into the potential toxicological risk present in needles and complete syringes. As well as reinforcing the company's technical capabilities in analytical services, this project also underlines Stevanato Group's commitment to providing pharma partners with the highest level of support in the supply of patient-safe drug delivery components and devices, ensuring that risks are fully managed within complex production environments and throughout multi-stakeholder supply chains.

A chemical characterisation study was designed to determine extractable amounts of chemical compounds present at a product and component level, allowing the toxicological risk to be verified. The first part involved extraction analysis of complete 1 mL EZ-fill® syringes assembled with stainless steel needles (AISI 304) from three different suppliers and separate extraction analysis carried out on needle components from three different suppliers that were not incorporated into a final assembled product.

The 1 mL EZ-fill® syringes, having undergone double ethylene oxide sterilisation, were extracted with ultrapure water (UPW) at 121°C for 60 minutes and with hexane at 58°C for 24 hours. The extracts were then subject to a wide range of analytical methods ensuring detection and identification of glue-based organic compounds, elements and anions.

Separately, the isolated needles were exposed to three increasingly aggressive conditions to generate an extract: UPW; UPW pH2 (± 0.5); and UPW pH9 (± 0.5). This analysis was conducted using closed-vessel shaking incubation (~50 min-1) at 50°C for 72 hours.

In the second part of the study, the surface of the needles was closely analysed, both in isolation and as part of an assembled syringe. This analysis was conducted using scanning electron microscopy – energy dispersive spectroscopy (SEM-EDS), which generates a profile of the compounds on the surface of the samples and information on the morphology of the needles. Specifically, the analysis was performed using a ZEISS Sigma field emission scanning electron microscope (FE-SEM) with 1.5 nm of maximum resolution.

The technique involves using a focused electron beam as a probe to inspect the surface of the solid material, with a focus on the needle bevel. Different integrated detectors can be used to collect the generated particles, allowing for evaluation of the sample's morphology. EDS analysis was performed on the same area as the SEM inspection with a Quantax Bruker detector to characterise the elemental composition of the stainless steel.

In the extraction analysis, the results of the needle samples tested with UPW, UPW pH2 and UPW pH9 provided a measure of the amount of various extractable

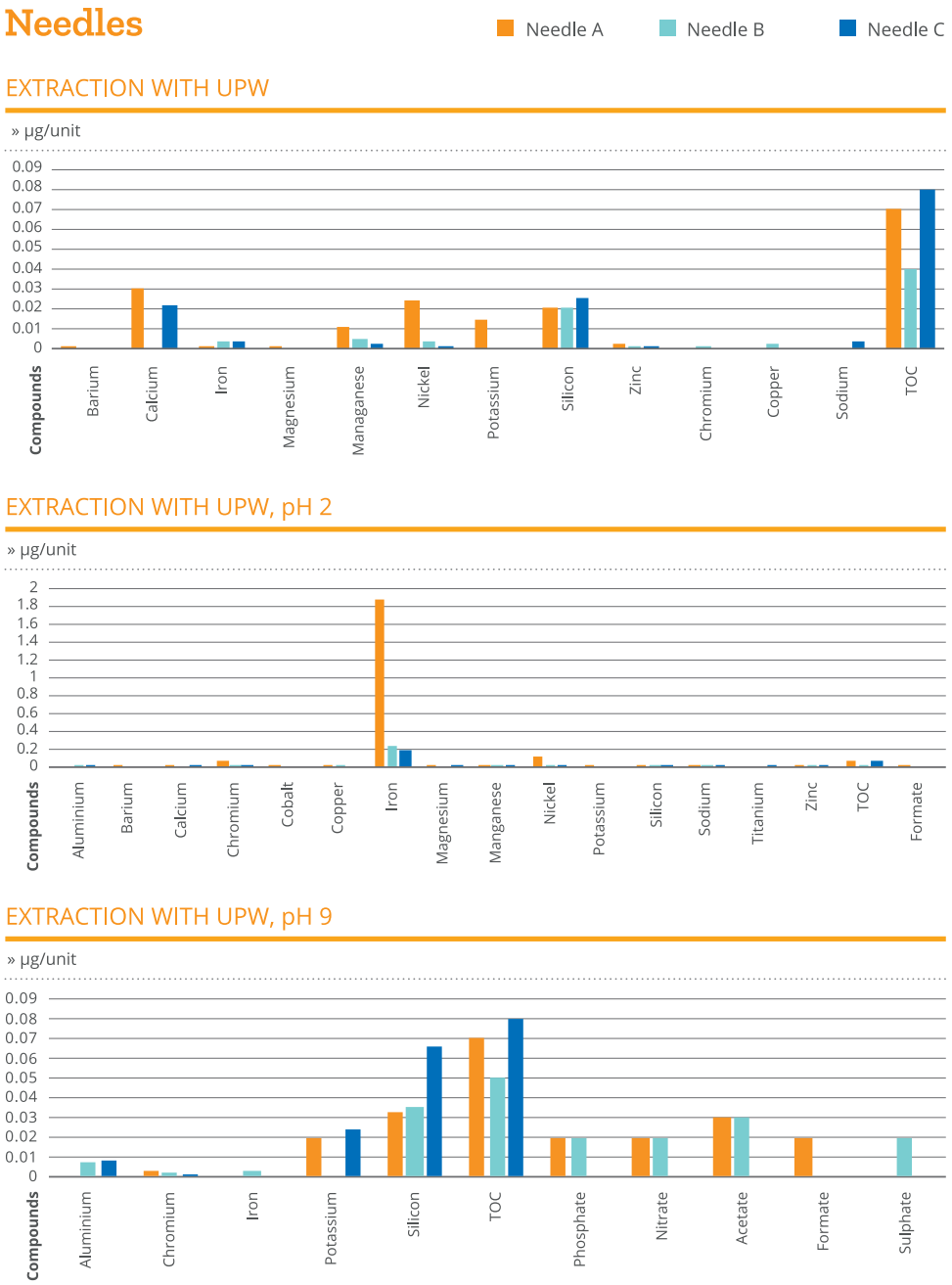

Figure 1: A chemical characterisation study was designed to determine extractable amounts of chemical compounds present at a product and component level, allowing the toxicological risk to be verified.

compounds in each test article unit. In the case of UPW, total organic carbon (TOC) was identified in the highest amount, ranging between 0.04 and 0.08 µg/unit. The next highest compounds recorded were calcium (0.03 µg/unit), nickel (0.025 µg/unit) and silicon (0.026 µg/unit).

In the case of the UPW pH2 extraction, the compound recorded at the highest level was iron, with an outlying peak result of 1.89 µg/unit for one of the sample needles. All other compounds were recorded at levels of 0.1 µg/unit or below, with many measured at negligible levels. In the case of the UPW pH9 extraction, ¬TOC and silicon were the only compounds to be recorded at a level of 0.03 µg/unit or above. Crucially, for all samples across all extraction tests, the presence of cobalt was not detected in any needle (Figure 1).

The extraction analysis carried out on the 1 mL EZ-fill® syringes revealed silicon as the compound at the highest level, ranging between 0.018 and 0.055 µg/unit. Apart from sodium, which had a range of 0.012–0.018 µg/unit, all other compounds were found to be at negligible levels. Some compounds were only detected on certain samples: sulphur was only found on syringe units employing two of the needle types, for example, while tungsten and zinc were found on syringes that employed the third needle type (Figure 2).

The results from the second part of the study, which analysed the surface of the needles as both standalone components and assembled within EZ-fill® syringes, found no morphological differences between the component needle samples and the assembled syringe samples. The spectrum *[Continued on Page 72…]*

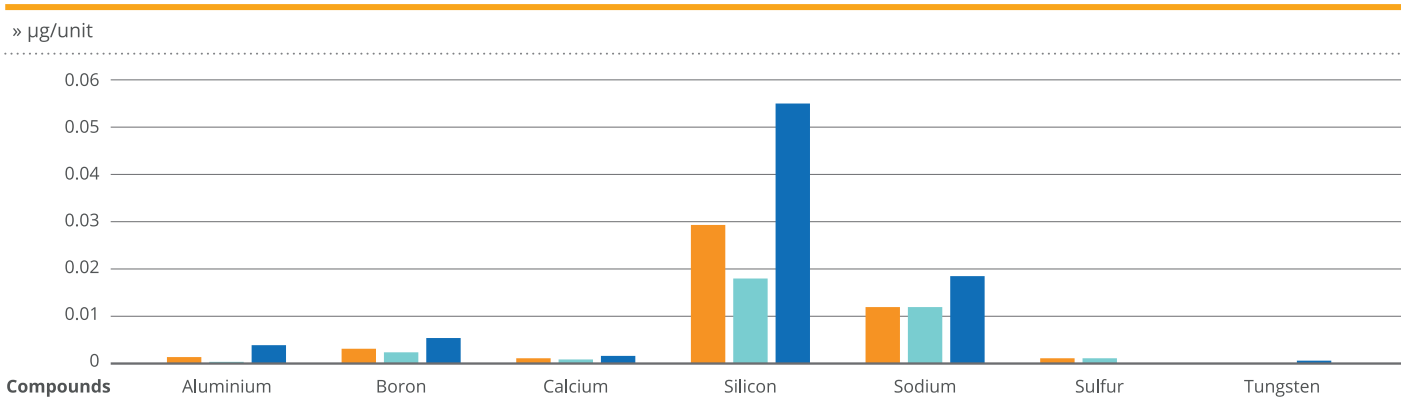

Figure 2: 1 mL EZ-fill® syringes with three different needles and double ethylene oxide sterilisation.

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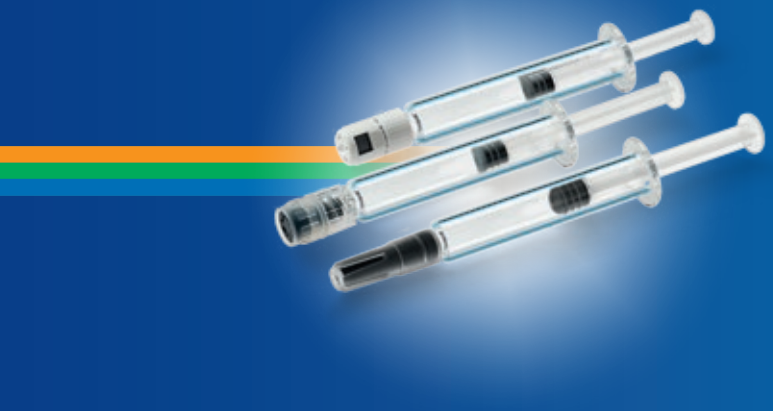

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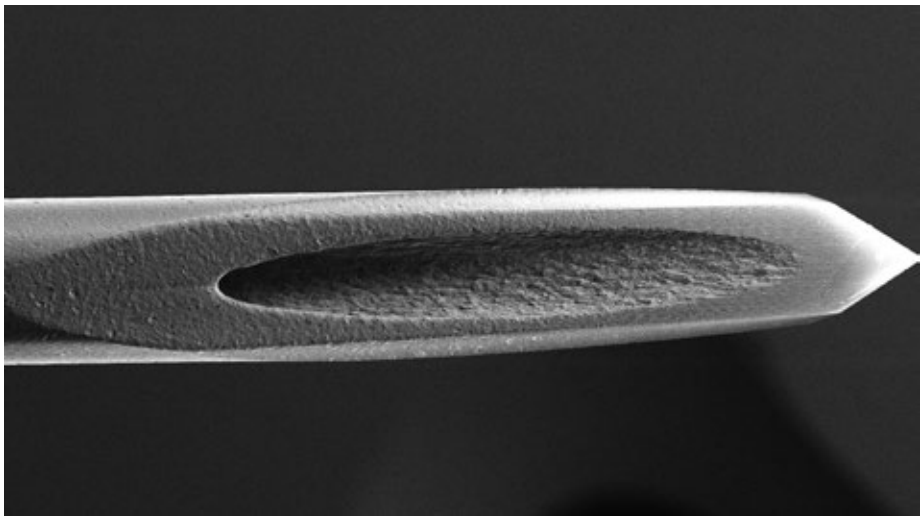

Figure 3: The spectrum profile generated by the energy dispersive spectroscopy pointed to higher quantities of silicon, oxygen and carbon on the assembled needles as a result of the manufacturing process, but it did not highlight the presence of cobalt.

[…Continued from Page 70] profile generated by the energy dispersive spectroscopy pointed to higher quantities of silicon, oxygen and carbon on the assembled needles as a result of the manufacturing process, but it did not highlight the presence of cobalt (Figure 3).

Taken together, the detailed data obtained from both parts of this extensive study conducted by Stevanato Group provides a clear picture of the chemical compounds that are both present on and contained within assembled syringe products and individual needle components. The insight derived is invaluable for pharmaceutical companies developing medical products compliant with the MDR.

In the face of potential uncertainty over the presence and concentration of a substance such as cobalt, which is classified as CMR, these findings provide unequivocal certainty that levels are within compliant levels at a product and component level. As such, they clarify that it is possible to estimate the CMR content and concentration of the syringe as a complete medical product by analysing the product components alone, providing a clear pathway for compliance with the MDR.

At a broader level, the study underlines Stevanato Group's integrated support for pharma partners. Through its Technology Excellence Centers, the company offers analytical services to secure the generation of objective data to support its customers' choices. In particular, Stevanato Group's Chemical Analysis Area is focused on mitigating the risk of chemical interaction with drugs. Thanks to its multi-analytical approach, the company helps to select the proper container closure systems at each stage of the drug development journey to bring medical products to market that meet regulatory demand and satisfy the universal objective of enhancing – and not jeopardising – patient wellbeing.

"In the face of potential uncertainty over the presence and concentration of a substance such as cobalt, which is classified as CMR, these findings provide unequivocal certainty that levels are within compliant levels at a product and component level."

ABOUT THE COMPANY

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

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ABOUT THE AUTHOR

Laura Berardi has a PhD in Crop Science focused on molecular biology and several years of experience in medical devices, and a considerable knowledge of biological approaches and studies, as well as highly developing skills in the regulatory field. Dr Berardi joined Stevanato Group in 2021, managing regulatory submission and developing regulatory strategy. As Scientific Affairs Expert she also works on activities on biocompatibility and extractables studies on container closure solutions and drug delivery systems. Dr Berardi plans and conducts regulatory interactions with health authorities for the registration of drug delivery systems and container closure solutions. Additionally, she continuously builds and maintains sound scientific knowledge and expertise in product areas and regulations through participation in events and meetings.

Celanese

The chemistry inside innovation™

SANTOPRENE® TPV – A NEXT STEP IN ELASTOMERIC COMPONENTS FOR CONVENTIONAL, SAFETY AND PREFILLED SYRINGES AND AUTOINJECTORS

Here, Shiva Douse, Market Development Manager, Jeff Smith, Global Application Development Manager, and Brad Wessman, Principal Field Development Engineer, all at Celanese, introduce Santoprene® TPV, a novel medical-grade thermoplastic elastomer for use in syringes and autoinjectors that offers significant benefits over traditional thermoset rubbers.

INTRODUCTION

Across the pharmaceutical industry, a variety of factors are coming together to drive ever-increasing interest in subcutaneous and intramuscular parenteral delivery, especially via prefilled syringes (PFSs) and autoinjectors. For one, the huge potential of biologics can best be tapped into via the parenteral route, as the delicate protein molecules are unsuitable for delivery via the hostile environment of the gastrointestinal tract. Another factor is the push towards moving administration of medicines from the clinic to the home, with both patient convenience and environmental concerns fuelling this trend.

With this surging interest, it falls to drug delivery device designers to make their products stand out in the market, both in terms of device quality and value. As such, innovation is a major part of the parenteral delivery landscape, with device designers pushing boundaries on safety, patient-centricity, manufacturability and product quality. A critical

Figure 1: Santoprene® TPV is ideal for single-use and prefilled syringe seals and other medical devices that require long-term sealing performance, flexibility or a soft touch for human contact.

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"As a specialist materials provider, Celanese is constantly innovating to provide the medical and drug delivery industries with the necessary materials for their components."

component of achieving this is material selection, which comes with a variety of considerations, including material properties, supply and processability.

One of the critical materials in a syringe is the elastomer used for the plunger stopper, which may also be used for the syringe or needle cap (Figure 1). A similar stopper application exists in autoinjectors, which enclose a PFS driven by a mechanical delivery system. Celanese is constantly innovating to provide the medical and drug delivery industries with the necessary materials for their components, including advanced thermoplastic elastomers. To this end, Celanese offers an ideal thermoplastic vulcanizate (TPV) solution for use in conventional, safety and prefilled syringes and autoinjectors – Santoprene® TPV.

THERMOPLASTIC ELASTOMERS VERSUS THERMOSET RUBBER

Traditionally, elastomeric components in syringes have been made of thermoset rubbers, the most common examples being styrene-butadiene rubber and butyl rubber. While these materials have excellent sealing properties, they require significantly more processing than thermoplastics. To produce parts by injection moulding a thermoset rubber, the raw materials must be mixed or compounded, then moulded and cured to produce a usable component, with waste product generated throughout the process that is scrapped in its entirety (Figure 2).

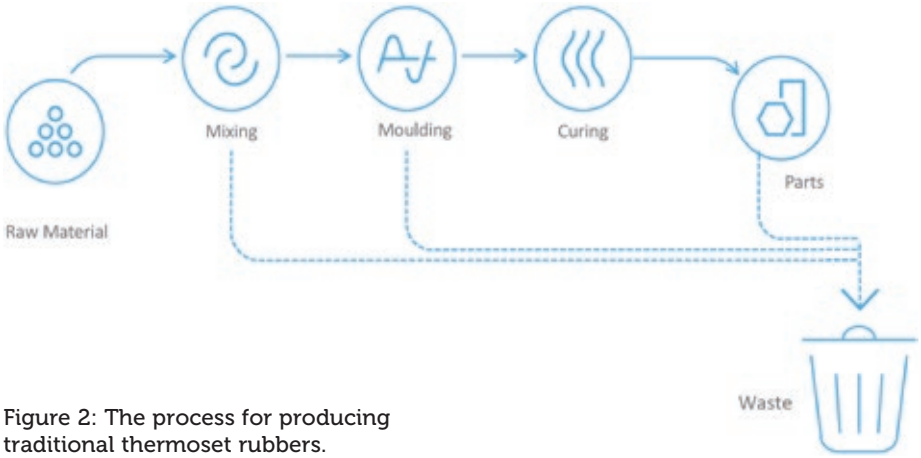

Figure 2: The process for producing traditional thermoset rubbers.

Thermoplastic elastomers, on the other hand, provide the elastomeric properties often sought when selecting thermoset rubber but are processible like a plastic. This includes manufacturing final products from a single pellet feedstock, which eliminates the mixing step prior to moulding and provides a cleaner material solution. The high-precision moulding translates to a flashless process that reduces scrap. Santoprene TPV also allows for waste material to be reprocessed and recycled into raw material, significantly reducing overall waste, as well as making the process more sustainable if adopted for certain applications. Additionally, the faster curing times of TPV compared with thermoset rubber significantly reduce cycle time and energy usage. Taken together, these factors can lead to a reduction in waste of up to 30% and in energy usage of up to 50% when compared with thermoset rubbers (Figure 3), which can be a powerful contributor towards meeting sustainability targets.

Figure 3: The process for producing thermoplastic elastomers, leading to major reductions in energy usage and waste production compared with that for thermoset rubbers (*calculations based on non-medical commercial part).

In addition to the economic and sustainability advantages, the production process of thermoplastic elastomers presents exciting possibilities for component design that thermoset rubbers do not allow. For example, thermoplastic elastomers are suitable for overmoulding processes or moulding softer and harder parts. This allows device developers to think more flexibly when designing syringe components and potentially to consolidate parts, reducing the overall number of components in the final device.

Maximising the efficiency of material use is a key factor in material selection, for both cost and sustainability considerations. As mentioned prior, thermoplastic elastomers enable in-process and end-of-life recycling, which significantly decreases overall waste, but that is not their only advantage. Thermoplastic elastomers typically have a lower density (by approximately 20%) than rubber compounds, meaning less material is required to make the same part, increasing the overall efficiency of the manufacturing process and reducing the weight of the final product.

SANTOPRENE® TPV – MEETING THE NEEDS OF MODERN SYRINGES AND AUTOINJECTORS

When designing a syringe or autoinjector, there are several requirements the developer must meet; not only must the device deliver the contained drug consistently and reliably, for a prefilled device, it must keep the contained drug sealed and sterile for the duration of its shelf life. This means that all components must be fully compatible with the drug, offer impeccable reliability and be suitable for manufacturing, fill-finish, storage and delivery processes.

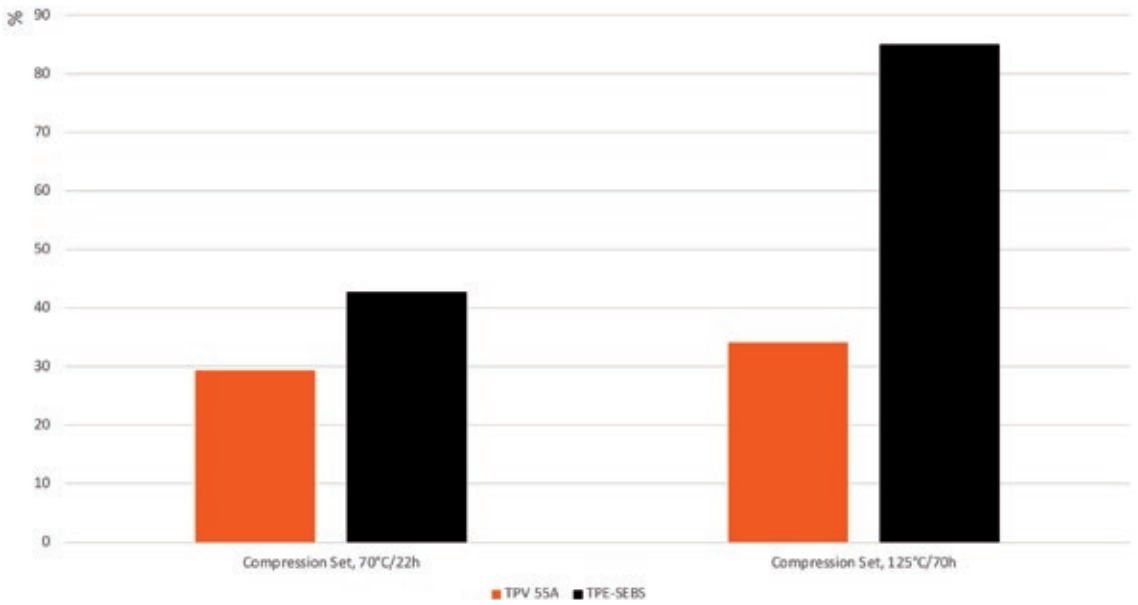

Figure 4: TPV has better compression set and long-term sealing performance compared with other thermoplastic elastomers.

"Santoprene TPV can maintain excellent seal integrity and is therefore ideal thermoplastic elastomer for use in conventional, safety and prefilled syringes and autoinjectors."

Excellent Seal Integrity

For elastomeric stoppers, the absolutely critical aspect is how well they form and maintain a seal within the barrel of the syringe. Poor seal integrity could lead to drug leakage or the therapeutic being contaminated by outside substances. A key indicator of seal integrity for an elastomer is its compression set and stress relaxation – compression set measures the permanent deformation once a compression force is removed, while stress relaxation measures the sealing force over time when strain is held constant. Compared with other medical-grade thermoplastic elastomers, Santoprene TPV demonstrates a very low compression set and better stress relaxation, meaning that Santoprene TPV components show minimal change after deformation, maintain seal integrity over longer periods of time and minimise the risk of leaks or failures (Figure 4). Santoprene TPV can maintain excellent seal integrity and is therefore ideal thermoplastic elastomer for use in conventional, safety and prefilled syringes and autoinjectors.

Low Coefficient of Friction

Next, the stopper must facilitate reliable, consistent delivery of the contained therapeutic. The fundamental aspect here is the material's coefficient of friction, which dictates the break-loose and glide forces. A high-quality stopper should have a low coefficient of friction to optimise usability, ensuring that patients and healthcare providers can depress the syringe plunger smoothly, without the need for excessive force. Santoprene TPV demonstrates this critical quality.

This aspect is critical for devices targeting self-administration by patients, especially for geriatric patients or those with limited dexterity. Often for indications targeting these populations, drug developers will opt for an autoinjector rather than a simple PFS, where the patient only needs to press a button and a spring or other driving force automatically depresses the plunger. Autoinjectors are also frequently used in emergency applications, such as delivering adrenaline (epinephrine) after an allergic reaction, where all device components must be optimised to ensure that the mechanism operates reliably upon device activation, even by an injection-naive user.

When device functionality would be improved by a lower coefficient of friction, a common approach to achieve this is to use an external lubricant, which has traditionally been silicone oil.[1] However, the interaction of silicone oil with biologics has come under scrutiny, particularly in PFSs with a longer shelf life. As such, the ideal solution would be to minimise the need for lubrication altogether if possible.

High Manufacturability

As part of optimising the stopper for use in a syringe or autoinjector, the device developer may opt for a wide variety of stopper designs. Santoprene TPV demonstrates high-precision dimensional tolerances, which can enable developers to use their ideal stopper design with fewer concessions to manufacturability.

Thermoplastic elastomers, such as Santoprene TPV, also open the door to advanced moulding techniques unsuitable for the thermoset rubbers currently in use. One such technique is overmoulding, in which a layer of Santoprene TPV can be moulded around an existing polymer component, enabling device developers to get the most of their materials and consolidate the overall number of parts in the device, which can contribute to improved reliability.

Another key aspect of manufacturing PFSs is sterilisation. All components in contact with the drug must be fully sterilised to eliminate the risk of contamination. Pharmaceutical manufacturers employ a variety of sterilisation techniques. Santoprene TPV is suitable for steam, gamma and ethylene oxide sterilisation, giving the manufacturer the flexibility to use the sterilisation method most suitable for the project overall.

Regulatory Compliance

One of the major hurdles that must be overcome by any pharmaceutical product on its way to market is meeting the demands of regulators. Celanese fully supports its customers by ensuring that Santoprene TPV meets all the necessary regulatory standards set out by the US Pharmacopeia, ISO and US FDA. Santoprene TPV has USP Class VI and ISO 10993-4, 5, 6, 10 and 11 compliance, and a drug master file is maintained with the FDA. Furthermore, Celanese can provide a notification of change on medical grades to give peace of mind to device manufacturers on material qualification.

CONCLUSION

The modern drug delivery landscape has placed a significant emphasis on the role of PFSs and autoinjectors as a key part of meeting the needs of pharma companies and patients alike. The trend towards more patient-centric care focused on self-administration at home demands injection devices that are robust and reliable enough to be used by laypeople rather than requiring the expertise of a healthcare professional in a hospital environment. Simultaneously, the rapid growth of the biologics sector has demanded drug delivery devices suitable for containing and delivering these large, often delicate molecules.

The drug delivery industry is rising to the challenges presented by these trends by innovating on traditional designs, making safer, more efficient, more reliable syringes. To keep up with device developers, materials providers have had to push further with their own innovation, creating more advanced medical-grade materials that can offer the reliability and flexibility to meet the demands of modern drug delivery devices.

Elastomers are no exception to this advancement. Modern thermoplastic elastomers, such as Celanese's Santoprene TPV, offer significant advantages over traditional thermoset rubbers when developing syringes and autoinjectors, especially in terms of manufacturability. Santoprene TPV offers excellent seal integrity and coefficient of friction, while also using thermoplastic manufacturing processes, with a single feedstock, reduced overall manufacturing costs, lower energy consumption and greater recyclability options.

As a well-established player in medical-grade materials, Celanese is able to help customers select the ideal grade of Santoprene TPV to meet the specific needs of their device. In partnering with Celanese, syringe and autoinjector developers gain access to a wealth of knowledge and expertise, as well as full regulatory support to facilitate the smoothest possible journey from device development to manufacture to market.

> "To keep up with device developers, materials providers have had to push further with their own innovation, creating more advanced medical-grade materials that can offer the reliability and flexibility to meet the demands of modern drug delivery devices."

ABOUT THE COMPANY

Celanese Corporation is a global chemical leader in the production of differentiated chemistry solutions and specialty materials used in most major industries and consumer applications. Its businesses use the full breadth of Celanese's global chemistry, technology and commercial expertise to create value for its customers, employees, shareholders and the corporation. As Celanese partners with its customers to solve their most critical business needs, the company strives to make a positive impact on its communities and the world through The Celanese Foundation. Based in Dallas (TX, US), Celanese employs approximately 13,000 employees worldwide and had 2022 net sales of $9.7 billion.

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ABOUT THE AUTHORS

Shiva Douse is a Marketing Manager with the Medical business of Celanese Engineered Materials. She holds a BS in Chemical Engineering from the University of Florida (US) and spent 15 years working in a wide range of roles in manufacturing and business at ExxonMobil Chemical Company before joining Celanese via the Santoprene® TPV acquisition in 2021. Ms Douse enjoys working with customers on areas of technology and innovation to bring new solutions to the market.

Jeff Smith is a Global Application Manager and product expert with experience in thermoplastic elastomers. He leads a team of technical experts to support new product and new application development for the Celanese elastomers portfolio. Prior to joining Celanese, Mr Smith worked at ExxonMobil for 23 years in market development and account management.

Brad Wessman is a Principal Field Development Engineer with the Industrial/Medical/Consumer (IMC) business of Celanese Engineered Materials. He holds a BS in Chemical Engineering from the University of Minnesota (US) and worked in medical device product development for over 20 years before joining Celanese in 2017. Mr Wessman works closely with product design firms, original equipment manufacturers and moulders to support troubleshooting of existing applications and the development of new designs using Celanese engineered materials to ensure a successful product launch.

Celanese

Dosage control optimized

Santoprene® TPV

For single-use and prefilled syringe plunger tips and stoppers

Increased adoption of injectable drugs and pre-filled syringes, rising demand for vaccinations, and a growing need for surgical procedures all mean the market for syringes is on an upward trend – and so is the need for innovative material solutions for syringe seals.

When considering which elastomer to specify for the seals mounted on the end of your syringe plunger, this material must:

- Provide a **leak-proof** seal with the syringe barrel
- Enable **optimized plunger movement** for accurate dosage control, **ease of injection**, and **patient comfort**

Santoprene® thermoplastic vulcanizate (TPV) delivers the compatibility and safety, high performance, and drug protection required to meet the critical needs of syringe plunger and pre-filled syringe applications.

This advanced material from Celanese is also well-suited for other elastomer applications across the medical device industry, including use in wearables, peristaltic pump tubing, and packaging.

Visit us at **celanese.com/santoprene-medical** to learn more!

DELIVERY SOLUTIONS FOR DEEP-COLD DRUGS

Here, Tom Van Ginneken, Head of Global Product Management, Polymer Solutions, at SCHOTT Pharma, considers how the growing pipeline of molecules that require cold storage has highlighted the need for better drug containment and delivery methods and highlights the potential SCHOTT TOPPAC® freeze syringes offer as a potential solution.

In recent years, there has been strong growth in drugs that need to be stored at low temperatures to remain stable. Messenger RNA (mRNA) vaccines are a notable example, developed during the covid-19 pandemic, and with potential to be used for other therapeutic applications, including influenza, respiratory syncytial virus and other infectious diseases. The US FDA has approved eight therapies across three different types of viral vectors: adeno associated virus, lentivirus and herpes simplex virus. To date, more than 20 cell and gene therapies have been approved, 25 viral-vector therapeutics are in late-stage development, and 120 have reached Phase II trials.

This represents an expanding pipeline of sensitive molecules that need to be stored at temperatures from -20°C down to -196°C to maintain drug stability. It is clear that current packaging products are not ideal for this purpose and that today's deep-cold drugs require a better containment and delivery solution.

Currently, these molecules are packaged either in vials or cryobags, but neither method is entirely satisfactory. In the case of vials, the drug transfer to a syringe requires a number of manual preparation steps. This is not only time-consuming but also increases the risk to patient safety through contamination or dosage errors. Cryobags are difficult to fill and are more susceptible to breakage or issues with container closure integrity (CCI).

Next-generation products are needed that can offer a combined storage and injection system, reduce the risk of breakage and CCI issues, and enable an easier and faster drug delivery process with less opportunity for medical errors. Prefilled syringes (PFSs) meet all these criteria, but their use in deep-cold storage also raises a number of questions. At extremely low temperatures (-100°C), rubber may lose elasticity, the materials used for a PFS may experience shrinkage at different rates, amounts of leachable silicone may increase (creating additional particles) and lipid nanoparticle (LNP) stability may be affected.

The primary concern is always patient safety, and there are three key areas where deep-cold storage could pose challenges – syringe functionality, CCI and drug stability. Before it reaches the patient, an mRNA vaccine in a PFS is frozen and will often have undergone one or more air transport cycles.

> "The primary concern is always patient safety, and there are three key areas where deep-cold storage could pose challenges – syringe functionality, CCI and drug stability."

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During preparation, storage and transportation, there may be multiple occasions where environmental forces can affect the device, and particularly its plunger, causing it to move within the syringe barrel. For example, when the PFS is frozen, the liquid formulation may expand, causing the plunger to move away from the distal (cone) end of the device or, conversely, move towards the needle should any air trapped in the syringe contract upon freezing. Whereas, during air transport, the atmosphere within an unpressurised aircraft hold, which may be half the pressure at ground level, could mean that the plunger moves away from the needle-end. In combination, the effect of these forces is difficult to predict and, once the plunger movement exceeds the distance between the first and last sealing lip, it is defined as breaching the sterility barrier, which presents a risk to patient safety.

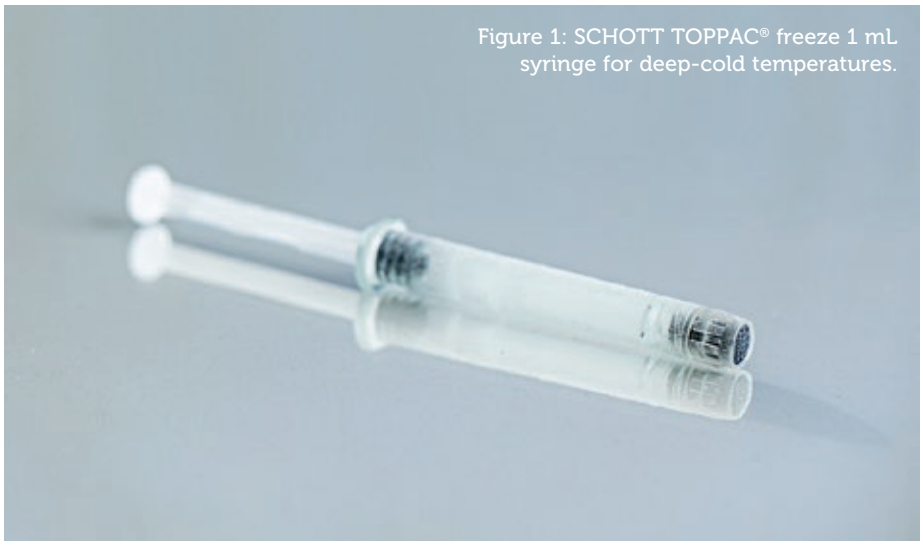

Figure 1: SCHOTT TOPPAC® freeze 1 mL syringe for deep-cold temperatures.

PLUNGER MOVEMENT AT LOW TEMPERATURE

SCHOTT Pharma performed a design of experiments (DoE) with different plunger materials, filling volumes, headspace sizes, filling media and freezing temperatures on SCHOTT TOPPAC® freeze 1 mL cyclic olefin co-polymer (COC) syringes (Figure 1) to evaluate the impact of these variables. The maximal plunger movement was determined for filled syringes that were frozen for 12 hours with one or more freezing cycles and at reduced ambient pressure, simulating the worst case of air transport in an unpressurised aircraft.

Three factors were shown to have a significant influence on plunger movement (Figure 2). The first of these was the fill volume. The higher the fill volume, the more it expands during freezing and the greater the resulting movement of the plunger. Second, the amount of headspace also affects the degree of plunger movement – during freezing, the air will contract in volume and force the plunger to move towards the cone, while the force of the under-pressure of the air transport simulation will push the plunger towards the flange.

The third factor is the material and the design of the plunger itself. Plungers that are optimised for break-loose and gliding properties will show greater movement. Factors that could influence the gliding properties include geometry, compression set, overlap with barrel, low friction coatings and sterilisation mode. Furthermore, the plunger's design impacts the sterile barrier, and it should be noted that the distance between the first and last sealing lip is not identical for all plungers. Therefore, it is important to understand each parameter

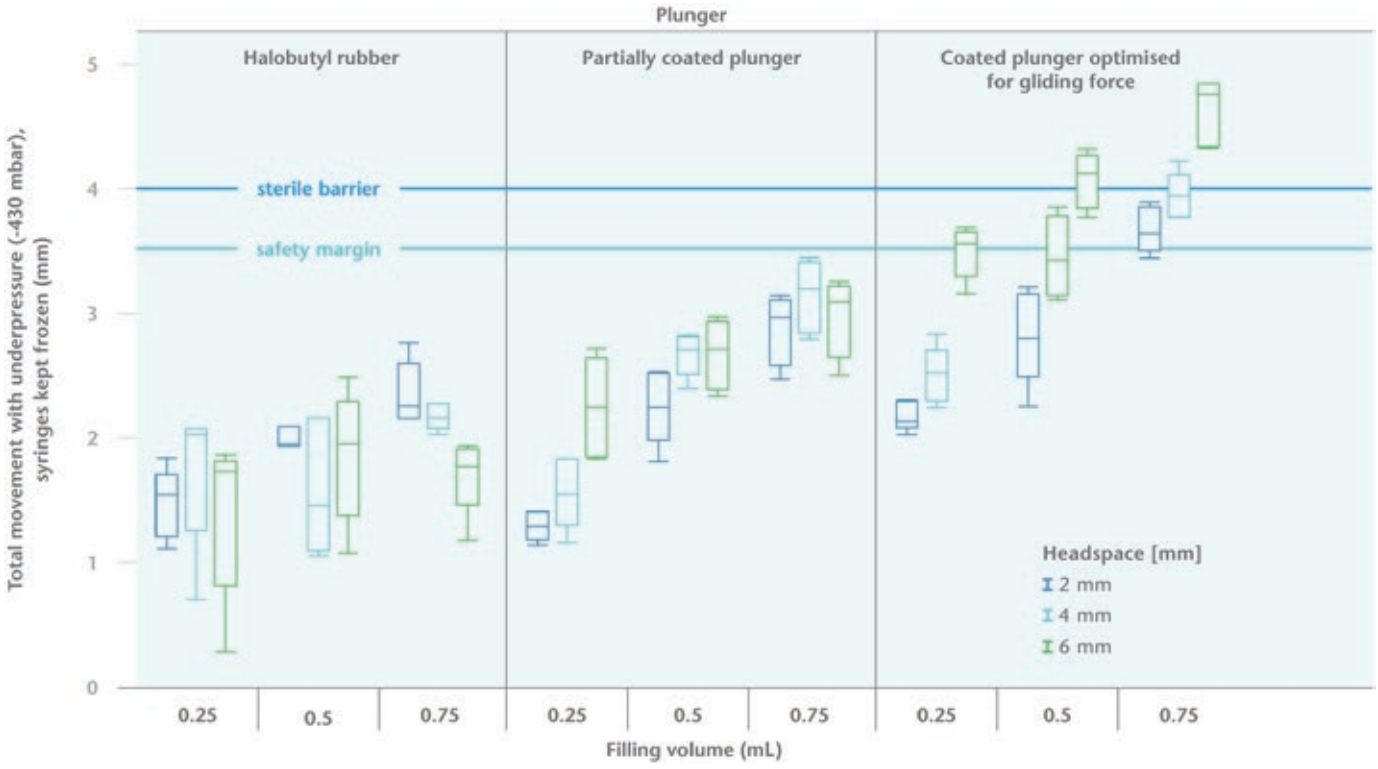

Figure 2: Maximal plunger movement (in mm) during storage at -20°C and at an under-pressure of 430 mBar.

to ensure the optimum selection of plunger material and design to suit the application.

Two other parameters were investigated as part of the DoEs – drug solution, in which water for injection (WFI) was compared with an mRNA placebo of 8.7% sucrose solution; and three different freezing temperatures: -20°C, -50°C and -80°C. Neither parameter was found to have any significant effect on plunger movement.

The main observation of the study is that choosing the correct primary packaging and filling parameters can control plunger movement and avoid breaching sterility during transportation and deep-cold storage. The recommendations are that a plunger with a higher break-loose and gliding force should be used, headspace should be reduced as far as possible and should not exceed 4 mm, and the fill volume should preferably be ≤0.5mL.

EFFECT OF FREEZE/THAW

It is also important that the syringe performance is not impaired by low temperature storage conditions. The syringe system would be useless if freezing increases the likelihood of breakage or hinders the plunger movement after the freeze/thaw cycle. SCHOTT Pharma therefore performed studies to compare polymer syringe functionality after freezing with syringes stored at room temperature to ascertain the influence of temperature, headspace and plunger type on break-loose and gliding forces.

Syringes were filled with WFI and subjected to three cycles of freezing to deep-cold temperatures and thawing to room temperature. The break-loose and gliding forces were tested at room temperature. No difference in break-loose and gliding forces was observed between -20°C, -50°C and -80°C storage, indicating that the temperature of the freeze/thaw process does not significantly affect the forces needed to perform the injection. Headspace also appeared to have no impact on break-loose and gliding forces.

Due to the stickiness effect of the rubber, break-loose forces tend to increase over time. In this application, because of the plunger movement during freeze/thaw, the thawing process already forces the plunger to move and, therefore, little increase in break-loose force is observed.

However, the plunger type did have a significant effect on the injection forces. Different types of plungers have different gliding profiles and characteristics. As expected, the plunger that was developed with improved gliding properties in mind performed the best.

CCI AT LOW TEMPERATURES

The second important question arising from deep-cold storage conditions is whether CCI is maintained at extremely low temperatures, guaranteeing a barrier against microbial ingress. A PFS consists of multiple components: a closure for the cone side, the plunger and the syringe barrel. These components may be made from a broad range of materials, such as glass or polymer for the syringe barrel and chlorobutyl or bromobutyl for the rubber components. Furthermore, various coatings can be used on the syringe barrel and plunger. All these materials have different thermal expansion coefficients and will shrink at different rates when frozen. An acceptable compromise will be necessary between good sealing properties and gliding forces because a reduced sealing overlap between plunger and barrel will drastically increase the risk of CCI issues.

Under mRNA-specific cold chain conditions, for example, the inner diameter of a COC syringe shrinks by roughly 0.044 mm while the rubber plunger's outer diameter shrinks by 0.050 mm, 0.047 mm and 0.040 mm for the three respective sealing lips. Since the shrinkage rate of the COC material is closely aligned to that of the rubber components, the risk of loss of overlap between syringe barrel and plunger, and therefore a CCI breach, is minimised, even at temperatures of -80°C (Figure 3). On the other hand, the thermal expansion coefficient for Type I glass is at least a factor of 10 smaller than COC or the rubber components. If glass is used as the primary packaging material, the container will shrink at a much lower rate than the rubber plunger, reducing the sealing overlap and potentially posing a risk of leakage or microbial ingress.

An external headspace study was also carried out to investigate further the reduced sealing overlap. Fifteen empty COC syringes were stored for 24 hours on dry ice at -80°C, with temperature excursions up to -100°C, then tested with a qualified Lighthouse Instruments (VA, US) FMS-carbon dioxide headspace analyser (Model FMSCO2). Measuring the amount of CO_2 in the headspace enables any leakage during cold storage to be identified.

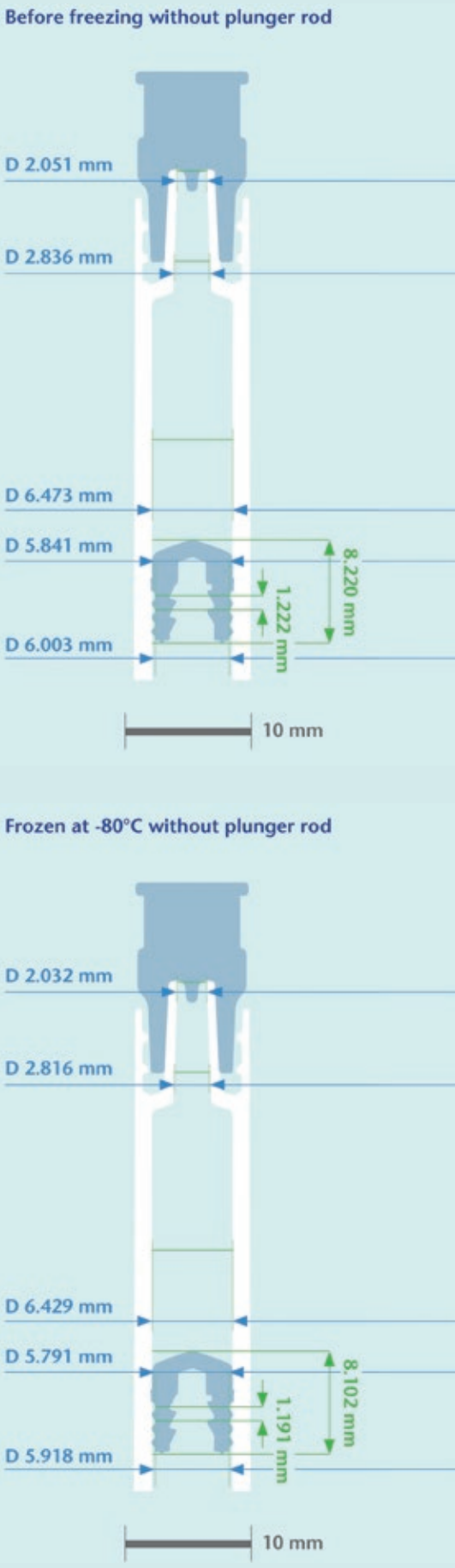

Figure 3: Computed tomography (CT) scan of identical COC syringe systems at different temperatures.

"While silicone oil is normally not toxic to the human body, an abundance of it can create subvisible particles that could react with the drug and reduce efficacy."

Different positive control samples – syringes with laser-drilled holes in the plunger, or a needle or microwire bypassing the sealing lips of the plunger – were used to confirm the test method. The cone closure and the plunger were also individually tested to locate the source of any leakage. None of the 15 samples showed signs of CO_2 ingress, indicating that, even at -100°C, the COC syringe system maintains CCI. Furthermore, CCI was maintained even after prolonged storage.

SILICONISATION AND DRUG STABILITY

The third element that may affect patient safety as a result of very low temperature storage is drug stability. A standard PFS has a lubrication layer of sprayed-on silicone oil to allow the plunger to move inside the barrel. While silicone oil is normally not toxic to the human body, an abundance of it can create subvisible particles that could react with the drug and reduce efficacy. Determining the amount of leachable-free silicone gives an indication of the potential risk of drug-lubricant interaction.

SCHOTT Pharma conducted a study comparing standard silicone-oil spraying and a cross-linked silicone technology. For each variation, five SCHOTT TOPPAC® freeze syringes were filled with WFI and subjected to either three freeze-thaw cycles at -20°C or storage at 5°C. The extract from the five samples was pooled and analysed by graphite furnace atomic absorption for free silicone oil. This test method has a detection limit of 0.2 mg/L.

The study showed clear differences between the two lubrication technologies. Even for the reference samples stored at 5°C, the leachable silicone amount for sprayed-on silicone oil was at least five times higher than for the SCHOTT TOPPAC® freeze syringes using cross-linked silicone. The results were even more pronounced at lower temperatures. After three freeze-thaw cycles at -20°C, the leachable silicone quantities increased for both technologies, but 24 times more free silicone oil was observed for the syringes with sprayed-on silicone (Table 1). The results collected at -20°C are likely to apply to temperatures down to -80°C as the thermodynamic phase transition (crystallisation) effect of the freezing process puts stress on the lubrication layer rather than the temperature itself.

The choice of siliconisation technology also has a significant impact on subvisible particles at freezing temperatures. Lower storage temperatures seem to increase particle load, and this effect seems to increase over time. The immobilised silicone layer from cross-linked siliconisation showed the lowest particle levels at freezing temperatures over storage periods of 12 hours, 31 days and 121 days when compared with sprayed-on silicone oil, although it should be noted that all results were within those stipulated in US Pharmacopeia <788>. There was a high probability that all subvisible particles observed originated from siliconisation – a silicone-free syringe used as a control showed no particles.

It is clearly important to consider the impact of siliconisation technologies on a specific drug application as there could be consequences for drug stability. The results of this study indicate that cross-linked siliconisation technology for deep-cold applications offers superior results in leachable silicone quantities and sub-visible particle burden. This cross-linked siliconisation process is standard for the SCHOTT TOPPAC® COC syringe portfolio, and not only provides good drug stability properties but also stable gliding performance at different storage conditions.

	Time	Free silicone (mg/L) 3x frozen at -20°C and thawed	Free silicone compared with standard SCHOTT TOPPAC®	Free silicone (mg/L) stored at 5°C	Free silicone compared with standard SCHOTT TOPPAC®
SCHOTT TOPPAC® cross-linked siliconisation **Standard cross-linked silicone**	0d	0.23	N/A	<0.2	N/A
SCHOTT TOPPAC® spray siliconisation **Sprayed on DC360, 0.55 mg/barrel**	0d	5.6	24 TIMES	1.09	5 TIMES

Table 1: Leachable-free silicone quantities of two siliconisation technologies.

PRIMARY PACKAGING COMPATIBILITY

A further consideration relating to drug stability is the compatibility of the primary packaging with the LNPs that are used to encapsulate the mRNA and protect it while it travels to the dedicated cells to perform its therapeutic function. The stability of these LNPs is vital to maintaining the efficacy of the mRNA. SCHOTT Pharma selected three analytical methods to characterise the syringe compatibility with LNPs: LNP particle size, polydispersity index (PDI) and LNP adsorption.

In tests carried out in collaboration with the *Institut für Pharmazeutische und Biomedizinische Wissenschaften* (IPBW) at the University of Mainz (Germany), SCHOTT TOPPAC® freeze syringes were compared with glass vials after storage at -80°C and for different ageing time points. LNP particle size was measured using a dynamic light scattering technique from Zetasizer (Malvern Panalytical, UK), and no significant difference was observed between the solution stored in a glass vial or that in a polymer syringe.

The same technique was used to measure the PDI, which gives an overview of the homogeneity of the particle size and provides feedback on particle

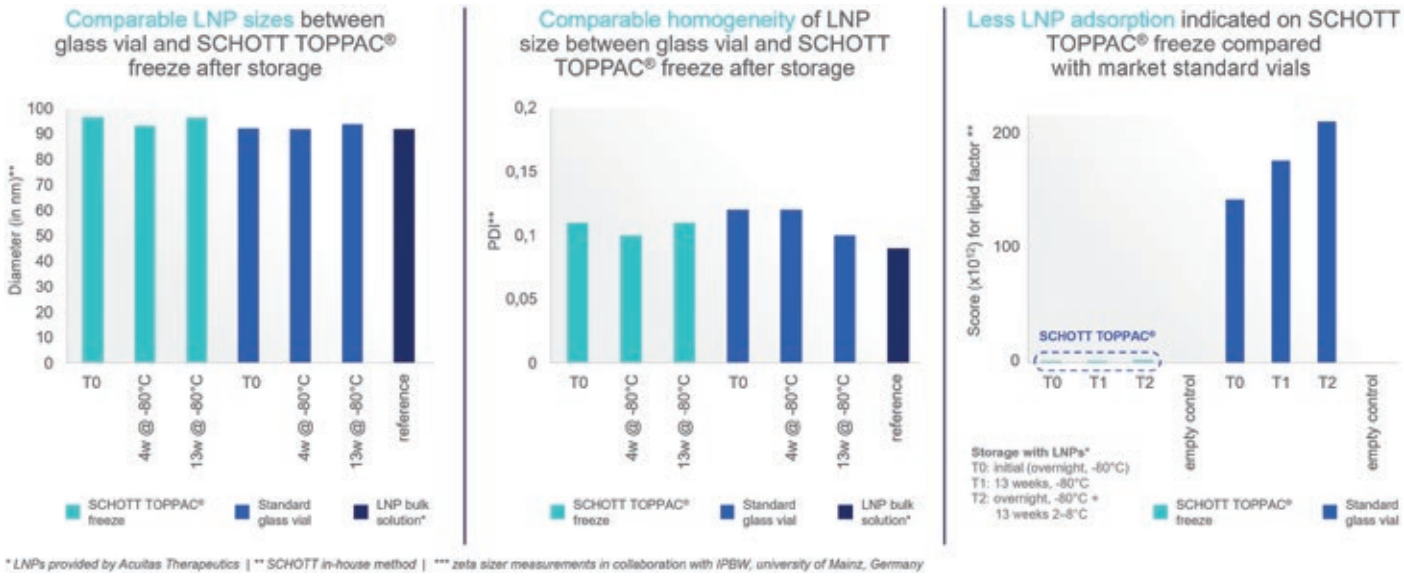

Figure 4: Compatibility data for LNPs at least as good for SCHOTT TOPPAC® freeze compared with market-standard glass vials.

stability and/or potential agglomeration. The lower the PDI, the lower the particle size distribution, and, therefore, the higher the LNP stability, with values of 0.3 and below most commonly deemed acceptable for drug delivery applications using lipid-based carriers. When SCHOTT TOPPAC® freeze syringes were compared with glass vials after storage at -80°C, once again, no significant difference was observed between LNP PDI in solution stored in a glass vial or a polymer syringe.

LNP adsorption on the inside surface of the container can reduce the concentration of the API, with a lower adsorption level indicating the container's chemical inertness. Again, tests were carried out for market standard glass vials and SCHOTT TOPPAC® freeze at storage temperatures of -80°C and 2–8°C and for different ageing time points.

ABOUT THE AUTHOR

Tom Van Ginneken is the Head of Product Management for Polymer Solutions at SCHOTT Pharma. His educational background includes studying chemical engineering in Antwerp (Belgium) and earning an MBA from the University of Sankt Gallen (Switzerland). Following three years in the chemical and pharmaceutical sector in Belgium, Mr Van Ginneken joined SCHOTT Pharma in 2008.

The inner surface of the SCHOTT TOPPAC® freeze syringes and glass vials were analysed, and deposits identified using time-of-flight secondary ion mass spectrometry (ToF-SIMS). A multivariate curve resolution technique was applied to extract a pure component spectrum from a ToF-SIMS spectrum to enable the selection of important fragment ions of each material in a sample. These pure spectra could then be matched with signal patterns expected for the analysed sample (e.g. silicone). A lower LNP adsorption effect was noticed for polymer syringes compared with glass vials (Figure 4).

CONCLUSION

In conclusion, there are a number of considerations when selecting the most appropriate PFS for a deep-cold drug. Analysis of the requirements for mRNA-based vaccines showed several reasons why the SCHOTT TOPPAC® freeze syringe is ideally suited for deep-cold temperature drug storage:

1. Plunger movement does not breach the PFS sterile barrier, but understanding the syringe and fill-and-finishing parameters helps to control this phenomenon
2. COC syringes can maintain container closure integrity down to -100°C because the thermal expansion coefficients of the different syringe components are similar.
3. Cross-linked siliconisation reduces the risk for any drug interaction and loss of efficacy by offering superior performance for leachable silicone oil quantities and sub-visible particles
4. Normal syringe functionalities are maintained even at storage temperatures down to -100°C
5. LNP stability in polymer syringes is comparable with glass vials.

SCHOTT TOPPAC® freeze can therefore be trusted to ensure patient safety in the three key areas of drug stability, syringe functionality and CCI.

ABOUT THE COMPANY

SCHOTT Pharma designs solutions grounded in science to ensure that medications are safe and easy to use for people around the world – because human health matters. The company's portfolio comprises drug containment and delivery solutions for injectable drugs ranging from prefillable glass and polymer syringes to cartridges, vials and ampoules. SCHOTT Pharma employs a team of around 4,700 people from over 65 nations to contribute to global healthcare. The company is represented in all main pharmaceutical hubs, with 16 manufacturing sites across Europe, Asia and North and South America. With over 1,000 patents and technologies developed in-house, a state-of-the-art R&D center in Switzerland and around 130 employees in R&D, the company is focused on developing innovations for the future. SCHOTT Pharma, headquartered in Mainz (Germany), is part of SCHOTT AG and owned by the Carl Zeiss Foundation, and so is committed to sustainable development for society and the environment and has the strategic goal of becoming climate-neutral by 2030.

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SCHOTT PHARMA

FROM CONCEPT TO CURE: MASTERING LIQUID SILICONE RUBBER FOR MEDICAL DEVICE DESIGN

In this piece, Kamaal de Silva, Principal Mechanical Engineer at Springboard, discusses the potential value of liquid silicone rubber in medical device design, including how its processing differs from other elastomers and how the challenges involved in its design and implementation can be overcome with specialist knowledge and experience.

Liquid silicone rubber (LSR) is frequently used in implants due to its bio-inert nature, meaning that it has a very low propensity to initiate a response or interaction when introduced to biological tissue.[1] It is also a common choice in non-implantable drug delivery devices, as it lowers development risk when performing the relevant biocompatibility tests recommended in ISO 10993 and US Pharmacopeia Class VI. This property also makes LSR suitable for the drug flow path, where reliable performance in extractables and leachables testing is critical. For example, Raumedic (Helmbrechts, Germany) provides a range of customised silicone syringe plungers with this as one of its unique selling points.[2]

MORE THAN MEETS THE SKIN

Compared with other elastomers, silicone rubbers have the best compression set performance. Typical values are around 10%–20%,[3] compared with other elastomers with compression sets of 40%–70%.[4] This makes LSR a more robust choice for seals in devices with a long service and/or shelf life. When comparing different LSR grades, it is important to keep in mind that there are differing standards for compression set testing that can affect the number quoted on the datasheet. Different additives, and even manufacturing conditions, can further improve or impair this property – for example, self-adhesive grades can exhibit a much higher compression set of 40%–60%.[5]

> "When comparing different LSR grades, it is important to keep in mind that there are differing standards for compression set testing that can affect the number quoted on the datasheet."

All rubbers typically exhibit high friction, with coefficients of around 0.5–1.0. However, LSR is likely to be a suitable choice when compared with its peers if a complex dynamic seal is required while avoiding any additional coating processes. Harder silicones with a higher durometer score typically exhibit a lower coefficient of friction, however, their decreased compliance results in a smaller tolerance window for effective sealing and friction forces. The surface finish of both sealing surfaces is also extremely important, where more polished surfaces can increase the coefficient significantly. Finally, the friction performance of similar grades from different manufacturers can vary, so it is advisable to carry out functional testing with a range of options to maximise the chance of design success. Most LSR suppliers provide a range of low-friction LSR grades, however the coefficients of friction are usually not quoted. It is therefore prudent to be sceptical of any marketing claims, especially if grades have contradictory attributes such as "low friction" and "self-adhesive".

Two-shot (2K) LSR overmoulding is a common operation in the world of silicone. The most advanced high-volume systems use a rotating table with parallel substrate and LSR injections to increase throughput. Automated pick and place systems are also used at lower volumes and, at the prototyping stage, the moulder will do this manually. Part design requires some care, where any high-contact-force dynamic seals may also require mechanical interlocking features to back up any chemical adhesion

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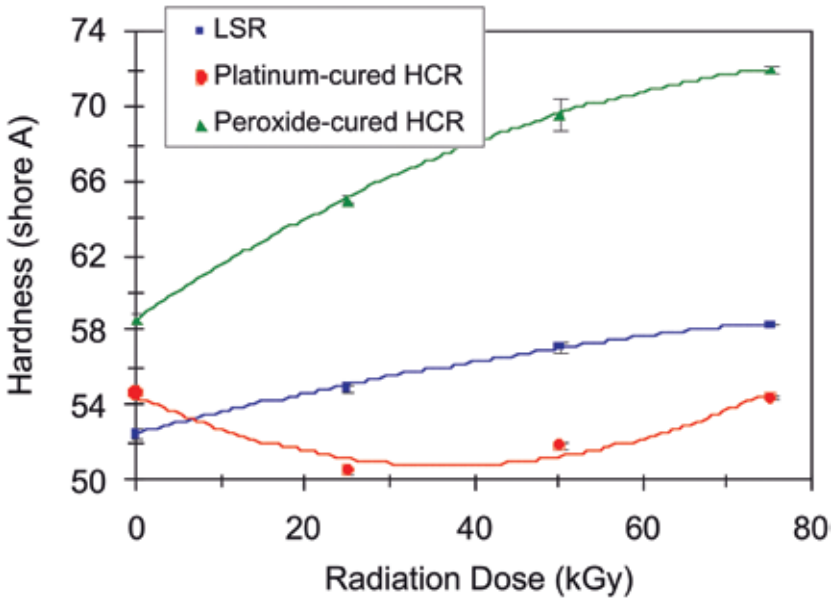

Figure 1: Effect of gamma radiation on durometer hardness of silicone rubbers.[7]

that comes from using a primer or self-adhesive grade. Typical materials to pair with LSR include polybutylene terephthalate (PBT), polyamide (PA), polycarbonate (PC) and polyethylene terephthalate (PET).

Despite its propensity to crosslink and slightly harden, platinum-cured LSR is compatible with gamma or X-ray sterilisation. At industry-standard radiation doses of 25 kGy, Gautriaud *et al* noted an increase of the shore hardness of Wacker's (Munich, Germany) Elastosil® 3003/50 by four points, as seen in Figure 1.[6,7] If this increase is accounted for in the design phase, it is possible to employ this method for end-of-line sterilisation to reach any surfaces that are sealed away.

THE LSR PROCESS IS A BIT DIFFERENT

LSR is typically supplied as A and B components in pails, mixed in a 50:50 ratio at room temperature and then pushed into a hot mould tool. Tool temperatures of around 200°C allow curing times in the order of seconds. A longer cure time at lower temperatures may be used at the prototyping stage without a drop in part quality.

Note that the properties, such as the viscosity, of the mixed A and B components can vary significantly between different material grades, which can end up causing unforeseen headaches for a moulder trying to use the same equipment over a range of grades. Additionally, the flowability of the mixed components can affect the expected tolerance ranges of any surfaces.

The tolerance of an LSR part is highly dependent on the manufacturer of the tool and the design of the part. Typically, shrink rates are high but consistent throughout the part. As long as the LSR is unconstrained during shrinking, a quality tool can produce LSR parts accurately. Walls as thin as 0.25 mm are possible, but the flipside of this is that LSR will flash very easily. If possible, move any parting lines and ejector pins away from sealing surfaces to minimise the chance of leakage.

Figure 2: Manual LSR mould tool for low-volume prototype components.

> "With the right partner, accurate prototypes can be made using a pump and heated tool that is opened and shut manually."

Even large contract manufacturers are unlikely to have professional LSR moulding machines, leaving the practice to specialists like Trelleborg (Trelleborg, Sweden) or Raumedic. However, with the right partner, accurate prototypes can be made using a pump and heated tool that is opened and shut manually. An example of this set-up is shown in Figure 2.

Manufacturers only familiar with mechanical probe-based co-ordinate measuring machines (CMMs) may also struggle to measure the part. A brief summary of measurement methods for LSR can be found in Table 1.

HYPERELASTIC FINITE ELEMENT ANALYSIS

Finite element analysis (FEA) of rubber components is a common point of discussion, due to the difficulty and amount of up-front investment required to prototype them. For medical device engineers, an FEA model

Method	Remarks
Mechanical CMM	Not reliable, as the probe deforms the part on measurement
Optical CMM	Possible, however, if the part is translucent, lighting and edge finding can be a challenge
CT Scanner (e.g. Zeiss Metrotom)	Works well, as long as the size of the scanning window is not too large for the desired scanning resolution

Table 1: Measurement methods for LSR.

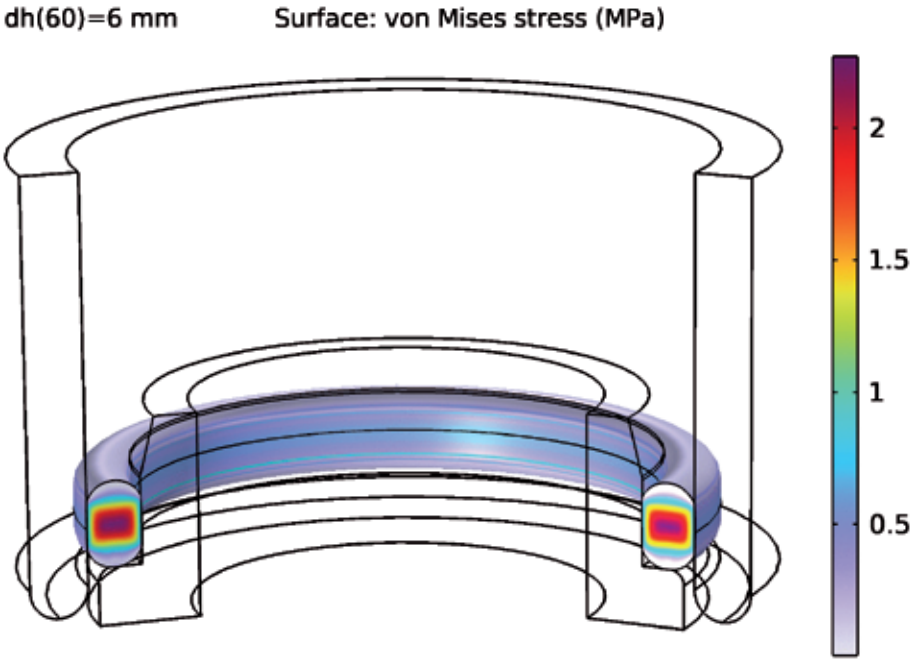

Figure 3: Hyperelastic FEA model of the assembly of two components and an LSR O-ring.

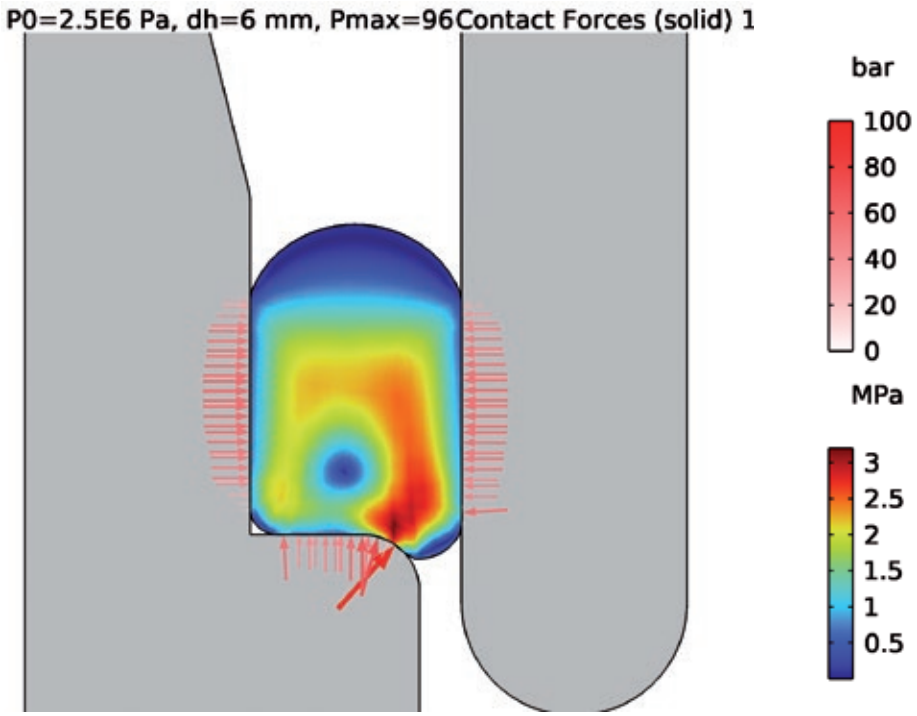

Figure 4: Pressurisation of the assembled O-ring from Figure 3.

also provides the ability to try a variety of dimensions across the tolerance ranges and map the contact pressures along the seal. This helps to build confidence that the design will be robust to sigma level six or "five nines".

A "gold standard" FEA model would start with a set of the following material tests,[8] ranked in order of importance:

1. An equibiaxial tension test – as LSR is nearly incompressible, this creates a loading state equivalent to pure compression, without the friction that would be impossible to avoid with a simple compression test
2. A planar tension test (pure shear) – also due to the LSR being nearly incompressible, using a wide sample creates a state of pure shear at a 45° angle.
3. A simple tension test.

The results of these tests can then be curve-fitted against different material models, such as Mooney-Rivlin, Neo-Hookean, Arruda-Boyce, Ogden or Yeoh. The curve with the best fit is then selected for use with the final FEA model.

The problem with the "gold standard" approach is that engineers are unlikely to know exactly which material grade is the most preferable at the outset. Also, material suppliers are unlikely to share data for niche material test methods, so performing these tests requires extra investment. As a first pass, it is possible to use a set of Mooney-Rivlin parameters for hyperelastic materials shared across the FEA community,[9,10] which have been found to be good enough when trying different concept designs and material shore hardnesses. If there is still a desire to revisit the FEA for design optimisation before tooling, the material tests can be conducted with the selected grade to confirm the result and conduct any optimisation tweaks.

A demonstration of a hyperelastic FEA model is shown in Figures 3 and 4, where Figure 3 shows the assembly of two components which are sealed by an LSR O-ring, and Figure 4 shows the effect of pressurisation from the top side. The surface stress at the sealing faces is equivalent to the contact pressure, which can be used to determine the integrity of the seal. Conducting hyperelastic FEA requires a skilled operator with an understanding of common pitfalls in model set-up – for example, meshing producing artefacts, such as hourglassing, during the solve.

"For medical device designers, any statistical analysis must be robust against the tough requirements set by regulators."

GAUGING REAL-WORLD PERFORMANCE

A full suite of mechanical testing equipment is required to test LSR components, some examples of which are shown in Figure 5. Force testers are extremely useful for running long-term seal compression tests in parallel. A torque tester can be indispensable for the testing of dynamic rubber seals driven by a motor or clock spring.

For medical device designers, any statistical analysis must be robust against the tough requirements set by regulators. This is especially relevant when producing components that seal, where tolerance stacks must be tightly controlled to ensure that there is adequate contact pressure for effective fluid retention.

SUMMARY

In summary, LSR is a unique and useful material with excellent biocompatibility, compression set and friction properties without additives. The LSR moulding process differs significantly from standard injection moulding, and therefore requires a specific skillset and experience to design for, model and manufacture effectively.

If you are working on a device with a critical compliant seal and need to make important design decisions, or if you have any general questions in this area, please feel free to contact the author.

ABOUT THE COMPANY

Springboard is a technology and design consultancy, and forms Sanner Group's Design Centre of Excellence. Springboard creates and develops new products and technology, including products in the field of medtech and drug delivery devices, assisting companies in resolving technical challenges and decreasing time to market.

Figure 5: Mecmesin (Horsham, UK) force and torque testers.

ABOUT THE AUTHOR

Kamaal de Silva is an experienced engineer who has led design and development projects at Springboard on a range of drug delivery devices, including infusion pumps, on-body delivery systems, autoinjectors, pen injectors and soft mist inhalers. He is committed to developing innovative hardware and software-based solutions that enhance user experiences, improve healthcare outcomes and satisfy key business requirements. Mr de Silva studied Mechanical Engineering at Imperial College London (UK). The knowledge he has accrued throughout his career has led to a comprehensive understanding of design, manufacturing and scientific principles that he can leverage to create robust, risk-averse designs.

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MITSUBISHI GAS CHEMICAL

CONTAINER CLOSURE INTEGRITY OF OXYCAPT™ VIAL AT -80°C WITH DRY ICE

In this article, Hiroki Hasegawa, MD, Assistant Research Manager, and Tomohiro Suzuki, Associate General Manager, both at Mitsubishi Gas Chemical, highlight the overall benefits of OXYCAPT, the company's multilayer plastic vial, as a primary container for biologics and gene and cell therapies and discuss the company's recent investigation into OXYCAPT's performance at -80°C under dry ice conditions.

OXYCAPT™ OVERVIEW

OXYCAPT™ is a multilayer plastic vial developed by Mitsubishi Gas Chemical (MGC) that offers a number of advantageous qualities as a primary drug container (Figure 1). The material consists of three layers – the drug contact layer and the outer layer are made of cyclo-olefin polymer (COP), and the oxygen barrier layer is made of MGC's novel polyester (Figure 2). MGC continuously conducts tests to confirm OXYCAPT's excellent properties, including:

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

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

Figure 1: OXYCAPT multilayer plastic vial.

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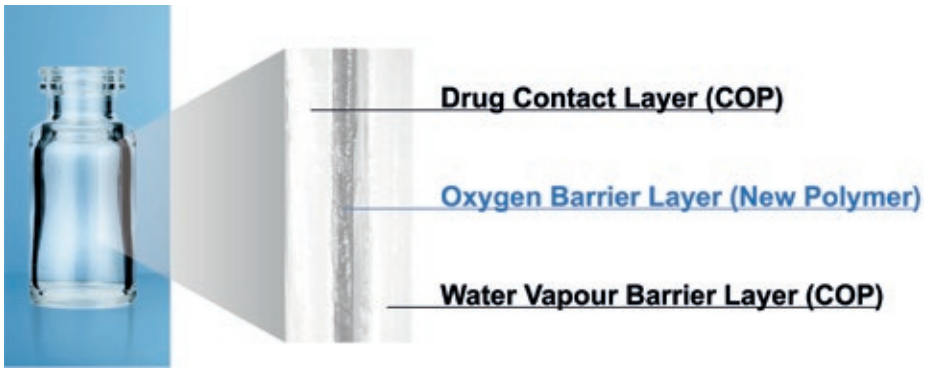


Figure 2: Multilayer structure of OXYCAPT.

"Studies have shown an extremely low level of extractables from OXYCAPT."

OXYCAPT provides an excellent oxygen barrier. For example, the oxygen barrier of an OXYCAPT vial is about 20 times better than that of a COP monolayer vial. Furthermore, OXYCAPT provides an excellent UV barrier. While about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT. MGC has confirmed that this feature contributes to the stability of biologics.

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

Studies have shown an extremely low level of extractables from OXYCAPT. One study was conducted to confirm the levels of volatile, semi-volatile and non-volatile impurities from OXYCAPT. Water and four solutions (50% ethanol, NaCl, NaOH and H_3PO_4) were selected, and impurities were measured by gas chromatography mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control, impurities were not detected in the OXYCAPT containers. A second study confirmed that inorganic extractables levels from OXYCAPT were similar to those from COP, which is well known for being an extremely pure polymer with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

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

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

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

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

CONTAINER CLOSURE INTEGRITY AT -80°C

All pharmaceutical containers must maintain integrity against microbial contamination and have a gas barrier when a drug is sensitive to oxygen or carbon dioxide (CO_2). Figure 3 shows a typical scheme of storage and transportation for gene therapy. During storage and transportation, packages, including vials, are exposed to temperatures of around -80°C in a deep freezer or dry ice, which is a potential risk to container closure integrity (CCI) due to differences in the coefficient of thermal expansion (CTE) of the vial and rubber closure materials.

"During storage and transportation, packages, including vials, are exposed to temperatures of around -80°C in a deep freezer or dry ice, which is a potential risk to CCI due to differences in the CTE of the vial and rubber closure materials."

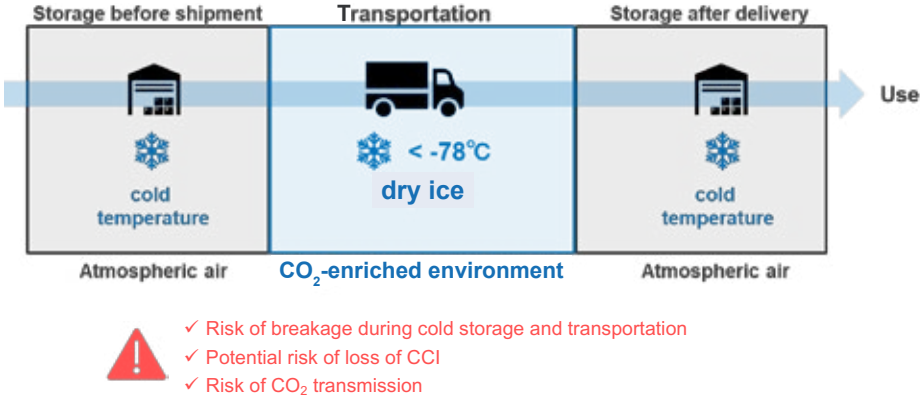


Figure 3: Typical scheme of storage and transportation for gene therapy.

Entry	Vial configuration	Vial	Rubber Closure	Aluminium seal cap
1	OXYCAPT/Rubber closure 1	OXYCAPT-P 10 mL Vial	Bromo butyl rubber	Standard one with closure 1
2	OXYCAPT/Press-on-cap closure 2	OXYCAPT-P 10 mL Vial	Press-on-cap closure	
3	OXYCAPT/Rubber closure 1/Positive control	OXYCAPT-P 10 mL Vial	Bromo butyl rubber	Standard one with closure 1

Table 1: Test sample combinations of OXYCAPT vial and rubber closures.

The CCI of Type I glass vials is particularly at risk from very low temperature compared with plastic vials because the CTE of typical Type I glass is a factor of 10 smaller than that of rubber, including a halogenated butyl rubber. On the other hand, standard plastic vials have a potential risk of CO_2 transmission when in storage with dry ice. Based on MGC's calculation by measurement of the transmission rate of CO_2 through a polymer film, OXYCAPT has a CO_2 barrier more than four times better than comparable COP monolayer vials. This means that OXYCAPT vial has the potential to significantly contribute to protecting drugs, including biologics and gene and cell therapies, when they are in transport with dry ice.

To examine this potential benefit further, MGC performed a CCI test with dry ice. Table 1 shows the test sample combinations of OXYCAPT vial and rubber closures. Rubber Closure 1 is a typical closure made of bromo butyl rubber with a glass transition temperature of -65°C. MGC also prepared press-on-cap closures and OXYCAPT's positive control with a fine hole of a 5 µm nominal diameter.

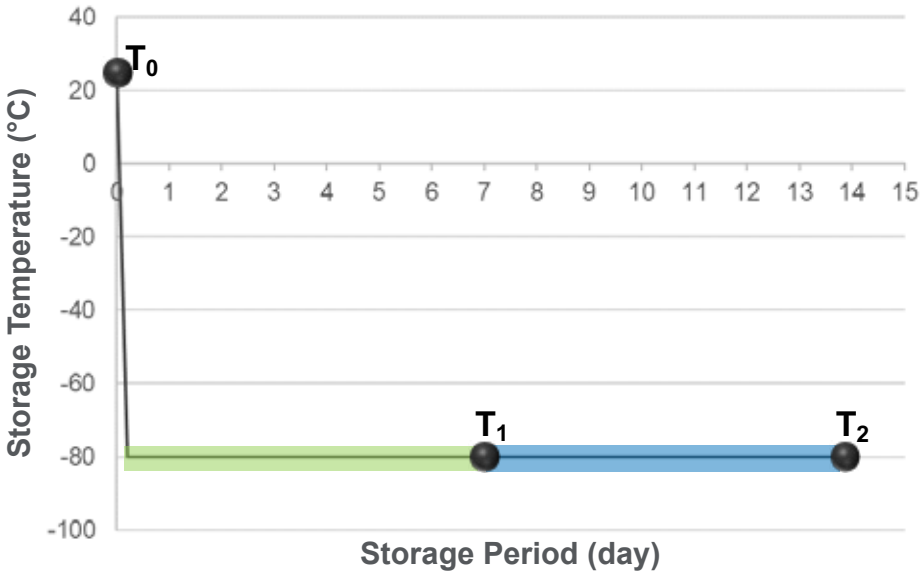


Figure 4: Test procedure of storage in deep freezer and insulation box with dry ice.

Figure 4 shows the test procedure, which includes storage in a deep freezer and an insulation box with dry ice. First, all the vials, closures and aluminium seals were inserted into a chamber where the air was replaced with nitrogen, then they were assembled by hand in the chamber. After preparing the samples, MGC measured the partial pressure of CO_2 in the vials' headspace for all the samples (T_0). The samples were then stored in a deep freezer at -80°C for seven days. After storage in the freezer, the CO_2 pressure of the headspace was measured (T_1). Next, the remaining samples were immediately inserted into an insulation box that was filled with 30 kg of dry ice, as shown at Figure 5. After storage in the CO_2-enriched environment, CO_2 pressure in the headspace was measured (T_2).

Headspace pressure of CO_2 was measured with an FMS-Carbon Dioxide, manufactured by LIGHTHOUSE Instruments (VA, US).

Figure 5: Dry-ice blocks in insulation box.

"Standard plastic vials have a potential risk of CO_2 transmission when in storage with dry ice."

Entry	Vial	Stopper	T_0 The number of all samples	T_1 (7 days)	T_2 (7 + 7 days)
1	OXYCAPT	Rubber closure 1	40	20	20
2	OXYCAPT	Press-on-cap closure 2	40	20	20
1'	OXYCAPT, Positive control	Rubber closure 1	10	5	5

Table 2: Sample number for each measurement time point.

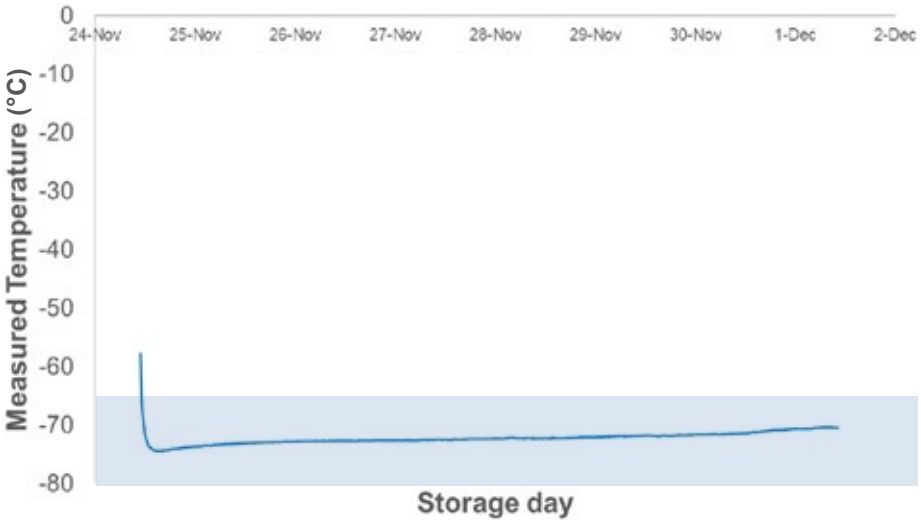


Figure 6: Logging temperature data in the insulation box.

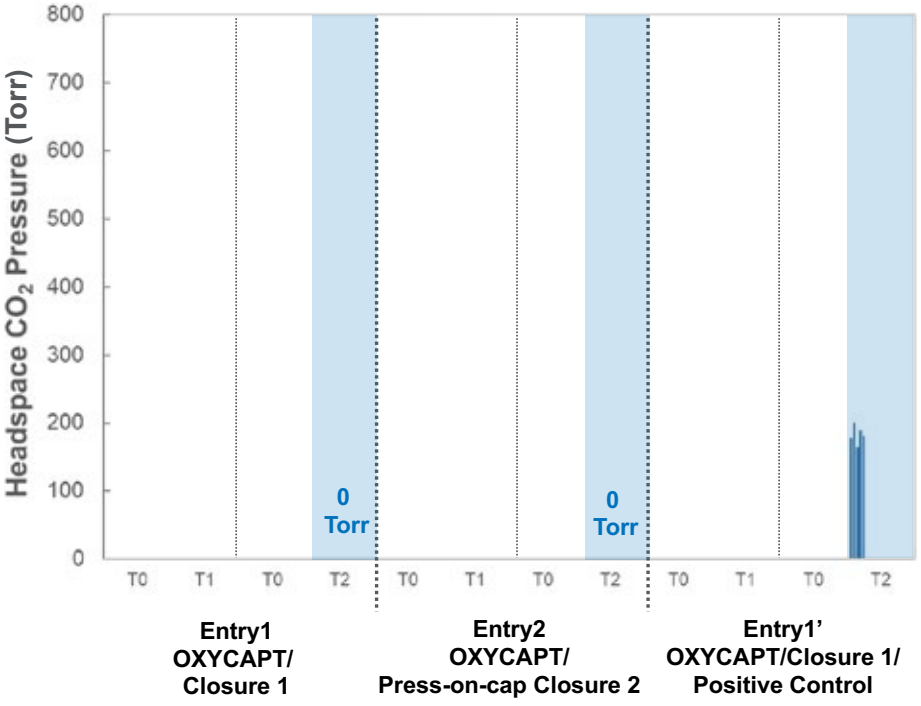


Figure 7: Headspace CO_2-enriched pressure for Entry 1, 2 and 1'.

"CO_2 ingress was not be observed in either combination of OXYCAPT and the two types of closure, even at T_2."

The instrument is based on frequency modulation spectroscopy (FMS), which is a non-destructive method. Table 2 shows the sample number for each measurement time point. The measured vials were disposed of after the measurements at T_1 and the remaining ones were measured at T_2.

At temperatures lower than -65°C, bromo butyl rubber loses its elastic properties, which may lead to loss of airtightness at the interface between vial and rubber closure. Therefore, maintaining a temperature inside the insulation box of under -65°C is crucial for measuring the leakage precisely in this test. Figure 6 shows a temperature log inside the insulation box during the test, which was kept below -70°C for seven days.

Figure 7 shows the results of headspace CO_2 pressure for Entries 1, 2 and 1'. Regarding OXYCAPT positive control of Entry 1', the mean value of CO_2 pressure was 183 Torr at T_2 under a CO_2-enriched environment. However, there was no CO_2 ingress at T_1, as the initial seven-day storage was conducted under atmospheric conditions without dry ice. On the other hand, CO_2 ingress was not observed in either combination of OXYCAPT and the two types of closure (Entry1 and Entry2), even at T_2. This study demonstrated that OXYCAPT has an excellent CCI under a CO_2-enriched environment for seven days.

CONCLUSION

There are several factors that can affect CCI for a combination of vials and closures, including capping force and type of closure, among others. In addition, CO_2 transmission is potentially observed in long-term storage with dry ice and an increase in temperature during storage. MGC intends to devise and perform additional CCI tests to clarify the efficiency of OXYCAPT vials compared with other plastic and glass vials. Furthermore, MGC is also planning to conduct similar studies at -180°C to confirm the effectiveness for gene and cell therapies.

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

ABOUT THE COMPANY

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

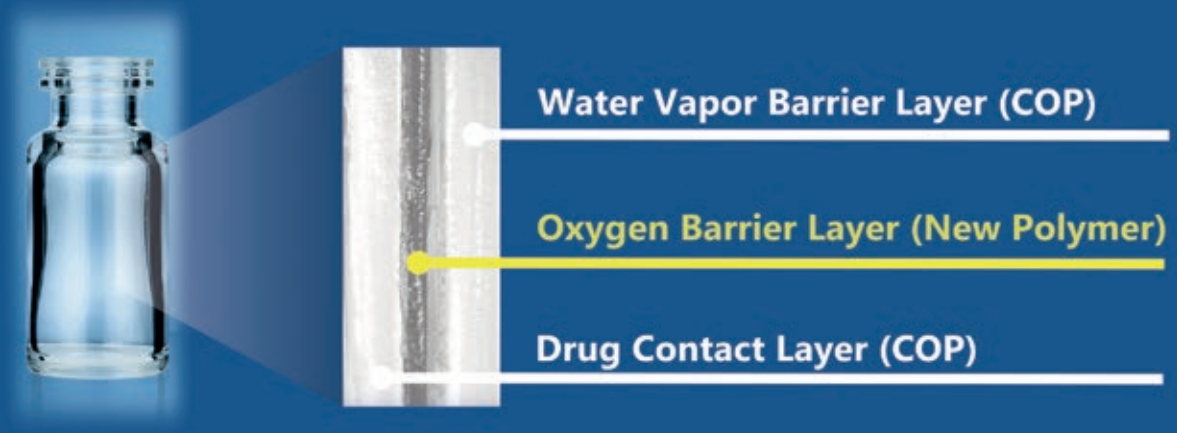
ABOUT THE AUTHORS

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

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

OXYCAPT™ Multilayer Plastic Vial

Multilayer Structure



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

2, 6, 10, 20mL Vial

Nest & Tub for Vial

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INTERVIEW

In this exclusive interview, Lilli Zakarija talks with ONdrugDelivery's Guy Furness about how EdgeOne Medical provides a critical service to companies undertaking drug delivery device development programmes, from small biotech start-ups all the way up to major pharmaceutical players. As part of this discussion, Ms Zakarija delves into the evolution of the drug delivery device industry over the past decades, some common pitfalls companies fall into during device development and what makes this sector such an exciting one to work in.

LILLI ZAKARIJA, EDGEONE MEDICAL

Lilli Zakarija is Co-Founder and President of EdgeOne Medical and has over 20 years of experience in the medical device industry. Her expertise includes development and global launch of various single-use, disposable medical devices and combination products, strategic/technical development of device platforms and IP management. Throughout her career she has held management roles in engineering and project management and, prior to founding EdgeOne Medical, Ms Zakarija established and led the global engineering function supporting all device and combination product related needs for the bioscience division of Baxter Healthcare.

Ms Zakarija has a Bachelor of Science in Biomedical Engineering and a Master's in Engineering Management from Northwestern University, and an Executive MBA from Kellogg School of Management. In addition, Ms Zakarija currently serves on the National Board of Directors for Women in Bio (WIB), is Adjunct Faculty for NUvention Medical, Board of Advisors for BME department at Northwestern University and is a mentor in the FoundHer programme at Querrey InQbation Lab.

Q How has the world of delivery device development for prefilled syringes and injection devices changed since you started EdgeOne in 2012?

A Looking back at our industry, I view it from two perspectives. From the business side, when EdgeOne was founded in 2012, it serendipitously coincided with the US FDA's implementation of its combination product regulations – we were getting established just as the industry was learning to adapt to these new regulations. This kind of adaptation was common in medical device development but new to the pharmaceutical side, so there was resistance to overcome. Over time, the industry evolved to integrate various technologies into combination products, and what we have now became the norm.

On the other hand, as an engineer, I see this evolution as three-dimensional. Initially, it was about mechanical combination products, like prefilled syringes, autoinjectors, pen injectors and inhalers. Then further evolution introduced a second dimension in the form of digital and connected devices, which brought more complexity and required more resources, knowledge and partnerships. The third, most recent dimension is what I like to call "complex systems", driven mainly by gene and cell therapy companies. These systems incorporate integrated hardware, disposables and software, and often require multiple systems to deliver therapies to targeted organs – it's a new level of complexity.

This evolution has transformed our approach from just integrating devices into development processes to navigating a complex landscape of combination products. Despite the complexity, one constant remains – the process. It's what makes each development programme unique and exciting. As an organisation, we view ourselves as experts in that process, specialising in guiding different types of complex programmes through this process. It's fascinating to think about potential future dimensions that will emerge as technologies advance.

Q Given all the changes the industry has seen, what are some of the common issues and problems you see in combination product development?

A As I mentioned, the one real constant at EdgeOne is the process, as defined by the FDA and ISO standards. Despite the unique challenges presented by different product types, a common issue is what we call the "culmination point", which involves the design control process leading to critical testing before IND submission. During a development programme, there are numerous interdependent activities, such as requirements management, risk management, component selection, device design and test planning. However, everything converges at the testing phase prior to submission. This point is critical, as it's where you generate the objective evidence for regulatory agencies to show readiness for clinical trials or commercialisation.

At EdgeOne, we focus on helping development teams de-risk this stage. If you go in unprepared, things can start to unravel, such as not having the right requirements, realising your testing plans are flawed or lacking robust designs. Ideally, you should reach this point with high confidence. Our goal is to ensure that our partners don't experience delays or failures due to unresolved issues at this stage, which is often critical on the path to submission.

In a way, EdgeOne was born from this pain point. When I was leading the device development team for the Bioscience division at Baxter, I recognised the need for providers who could assist with device verification (DV) testing. I would talk to potential providers who said they could deliver what I was looking for but, when I pressed them on what they were going to do, the answer was often "what you tell us to do". Faced with that, I just thought that, if you were

Figure 1: EdgeOne Medical's headquarters in Wheeling (IL, US) – more than just a testing house.

really good at this, you'd already know what to do, already understand the process. I wanted a partner that would work with me rather than just for me, that would be experienced and knowledgeable enough to ask me all the right questions, and that simply didn't exist.

That's why we founded EdgeOne to be more than a testing house – we engage in the entire design control process, providing design history file documents and taking development programmes from start to finish (Figure 1). It's crucial not to underestimate the significance of the culmination point, where everything comes together, and to ensure that everything possible has been done to de-risk it for the success of the entire programme.

Q Has EdgeOne's evolution over time been driven by avoiding that culmination point – expanding your scope to include services prior to and around testing, so as to avoid testing becoming a crunch point?

A Yes, a major reason for that being that we've been in our customers' shoes. Before EdgeOne, I was responsible for device development of combination products at Baxter, so we understand what our customers are trying to achieve, the requirements and how things should be interconnected. Educating our customers, especially those who are less informed, is a key part of our approach. We educate through the sales process, ensuring that they understand how to do things correctly, even if they don't choose us as their provider.

It's a natural evolution for us. Success in testing relies on ensuring that it's part of the process and planning for it, not just treating it as a transaction – here's the list of tests, give us the data and let's move on. EdgeOne is about understanding how these components integrate into the entire system. It's like a 3D chess game where all pieces have to move together in concert. Our clients are often surprised by the depth of our questions, but that's because we've experienced the pitfalls of development and aim to help our customers avoid them. We ensure a high chance of success by understanding the nuances of each programme.

Q Regarding EdgeOne's client base, do you mainly work with companies new to device development, or do you collaborate with large pharma and device companies with gaps in their experience?

A We work with all types of companies. From small start-ups where a scientist working on the molecule side is tasked with incorporating the device, to large pharma companies with established device teams. For example, just before the holidays, we were in the second part of the proposal process with a client who came to us and said "We don't know what we don't know, we need you to educate us". So, as part of our sales call, that's what we did, hopefully ensuring that, whether they use us or not, they will have gained valuable insights.

We range from being the entire device team for some clients to supporting large pharma companies that might have new device personnel, new projects or lack the resources to cover all their programmes. Our flexibility allows us to provide support as needed, depending on the client's resource bench and their organisational structure for R&D.

Q How can organisations ensure that they don't fall prey to the issues we've discussed?

A One key aspect is beginning with the end in mind. It's crucial to define key requirements not only in terms of what they are but also their limits. Sometimes, we find that some requirements provided by clients aren't even testable or don't make sense for the intended use. So, we work with our customers to revisit these requirements. In our industry, having to renegotiate the requirements due to failures during testing is the wrong way to do it. The right way is to ask, well in advance of starting testing, "What's my right requirement?", "What makes sense?" and "What makes sense for this product?"

A particular example of this is requirements around delivered volume. Sometimes, the set values are unachievable given the system's design, leading to unnecessary complexities and delays. Understanding and setting realistic requirements are vital for testing, and the product's end use.

The other key area is developing an appropriate testing strategy. This includes characterisation or, as we call it, feasibility testing with and without a simulant in order to de-risk the programme. For example, we've encountered scenarios where the drug was only introduced during the DV stage, leading to unforeseen issues, such as clogged needles in prefilled syringes. These incidents cause delays and require rapid problem-solving. A solid testing strategy, including decisions on sample sizes, test method validations and when to introduce the actual product is essential to catch potential issues early in the development process.

Q At this stage of development, are these programmes disclosed to the market? If there's a major issue with a public company's programme, could it impact them significantly?

A Sometimes, yes. It can be very detrimental. If a company had made public commitments in, say, its quarterly financial reports about its goals and, suddenly, it found that those goals were unattainable due to problems encountered in device testing then, yes, such setbacks have significant consequences within organisations. The culmination point often comes late in the game, and you can't afford delays when you're on a critical path with everyone's eyes on you. The data from testing is usually the last piece to be slotted into the submission package, followed by a quick 30-day review by the FDA before starting clinical trials.

When you're only months away from the excitement of starting clinical trials, the last thing you want is to find out that they won't start on time. The good news is that situations like that are entirely avoidable – it's about planning ahead. While you might still encounter unforeseen issues, many can be averted with proper planning, correct requirements and the right dialogue with all stakeholders. It's about avoiding unnecessary setbacks and ensuring a smooth journey towards clinical trials.

Q Considering the significant changes that we've seen in the drug delivery industry over the last 10 to 20 years, how well do you think regulators are keeping pace with the industry's ongoing evolution?

A Given that regulatory agencies are government bodies and tend to move slowly, I think they've done a commendable job. They've released substantial guidance on software as a medical device and digital innovations, for example. I teach a class at Northwestern University (IL, US) called "NUvention Medical", which includes graduate students from Northwestern's medical, engineering and business schools. They develop medical devices for unmet clinical needs, which can be physical devices or digital apps. I was impressed with the quantity and variety of guidances available on the FDA's website that are available to anyone considering development of a digital app.

The key approach by agencies that enables them to keep up as industry evolves, is allowing companies to present their plans and then providing them with clear feedback and input. This dialogue is crucial, especially in areas where the guidelines aren't completely clear. It's about getting feedback and adjusting accordingly. The agencies need practical experience from the industry to formulate their guidelines.

Looking ahead, the challenge for regulators will be adapting to advancements in the use of AI in the medical field. There are numerous questions around AI, like trustworthiness, data sourcing and validation. The industry is already contemplating how AI can transform our processes to become more efficient. AI's potential to create predictive correlations is immense, but regulatory agencies will require evidence over time to ensure that using it doesn't compromise patient safety and effective outcomes. The evolution in AI will be significant, and it should be a key focus for everyone in the industry.

Q Looking back at past trends and anticipating future changes, what excites you most about what's happening in the industry?

A There are two main points that excite me. Firstly, the industry is continually evolving. The changes we've seen over the last decade will persist and take new shapes, particularly with the addition of AI as a future disruptor. It's exciting to embrace change and, for those comfortable with it – as entrepreneurs such as myself tend to be – it feels like the next chapter is always going to be an exciting one. These changes won't all happen in 2024, but they're part of almost every conversation we're having.

Reflecting on 2023, a highlight for us was seeing several smaller biotech companies we work with get acquired, such as Chinook (WA, US, acquired by Novartis) and MiroMatrix (MN, US, acquired by United Therapeutics). Being part of the teams that helped these companies reach their acquisition goals was incredibly rewarding. Our aim with smaller biotech companies isn't customer retention over very long periods, as they often get bought out, but rather to ensure their success and programme effectiveness so that, when potential acquirers start to look at the details, their testing processes, and indeed the processes leading up to and around testing, are in great shape.

Looking ahead, embracing change is crucial. It's about enjoying the journey and seeing where it takes us. The constant evolution in our industry keeps it interesting and rewarding.

Q Is there anything else you'd like to add or any points you'd like to make that we haven't covered?

A One thing that comes to mind, tying into the theme of change and excitement, is the importance of having fun with what we do. It's one of our values at EdgeOne – this industry is dynamic and being able to enjoy the work and the challenges it brings is crucial. For me, it's always been about enjoying the journey and the work itself.

It can be about achieving milestones and successes, the excitement of new challenges and innovations coming our way and more. Fun encompasses the daily enjoyment of work, the positive attitude we bring and the camaraderie we have with our teammates and clients. At EdgeOne, we value what we call being "humorously serious", which means enjoying our work while being deeply committed to it. It's about loving the process, solving problems and working with people. We screen for this passion and attitude in our team.

For example, when I hear about innovative technologies and the problems they're solving, I'm often amazed. A recent example is MiroMatrix's work on growing porcine livers, decellularising and then recellularising them with the patient's blood for transplantation. How can you hear about that and not just think "Wow, I want to be a part of that"? Being a part of the process to bring such groundbreaking technologies to market is where the real fun lies. It's about the daily joys as much as the long-term rewards of seeing technologies succeed and make an impact.

ABOUT THE COMPANY

EdgeOne Medical is a global contract device development organisation that supports the compliant device development and testing of combination products. Since 2012, EdgeOne Medical has been elevating medical device and combination product development teams including in over half of the global top 20 biopharma companies. EdgeOne Medical has a unique combination of multi-disciplinary product development experts combined with in house ISO 13485 certified Testing Labs. These capabilities, known as *Edgineering*, and EdgeOne Labs provide clients with the peace of mind that they have complemented their teams with a partner with a successful track-record of de-risking, navigating, and accelerating device development programmes.

EdgeOne medical

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A NOVEL INSTRUMENT TO STREAMLINE COMBINATION PRODUCT DEVELOPMENT

In this article, Dr Daniel Primavessy, PhD, Project Manager, and Prof Dr Sigrid Saaler-Reinhardt, PhD, Scientific Advisor and Consultant, both at Midas Pharma, and Katarzyna Maksymowicz, Product Manager, and Marie Stockton, Marketing Manager, both at Gerresheimer, introduce the Gx Inbeneo® platform simulator. This tool supports pharmaceutical companies in bridging pharmaceutical formulation and medical device development processes, reducing time to market for patient-centric combination products.

Drug and device development are two disciplines that require specialised skills. The timelines and development processes involved are also distinct and subject to different regulations. This has led to separate departments being established in most pharmaceutical companies, which presents a challenge when bringing a final drug-device combination to market.

Drug development is complex and costly, requiring 10–15 years to introduce a drug product to the market. As pharmaceutical formulation employs physical chemistry, the unpredictability of molecular reactions in different concentrations necessitates an experimental and iterative approach. Formulation, volume and concentration adjustments are therefore made up to Phase II clinical studies where dose finding is conducted. Moreover, as the priority for formulation scientists is establishing suitable pharmacokinetics to ensure therapeutic efficacy and drug safety, the parameters of the device are often a secondary consideration. The definition of an appropriate delivery device, therefore, usually only begins shortly before clinical Phase III.

Device development, in contrast, is much quicker and more deterministic – but still takes several years from initial specification to market launch of a final combination product. If device experts can only begin their task once a formulation is fixed, they have the challenge of developing a solution that effectively delivers a predefined formulation, while also optimising the patient experience. This delay places pressure on the department and potentially impacts time to market.

> "The sensitive nature of biologics and the prerequisite for parenteral administration poses challenges for drug formulation and delivery."

IMPACT OF THE HOMECARE TREND ON FORMULATION DEVELOPMENT OF BIOLOGIC DRUGS

Biologic drugs are becoming increasingly popular due to their effectiveness in treating a range of diseases. However, the sensitive nature of biologics and the need for parenteral administration poses challenges for drug formulation and delivery. The traditional approach is intravenous (IV) administration in a clinical setting, but, while this is effective, it is also time consuming and can become burdensome for patients if they need to undergo frequent treatments.[1] Self-administration provides patients with greater independence and reduces the impact on healthcare systems. However, intramuscular and subcutaneous

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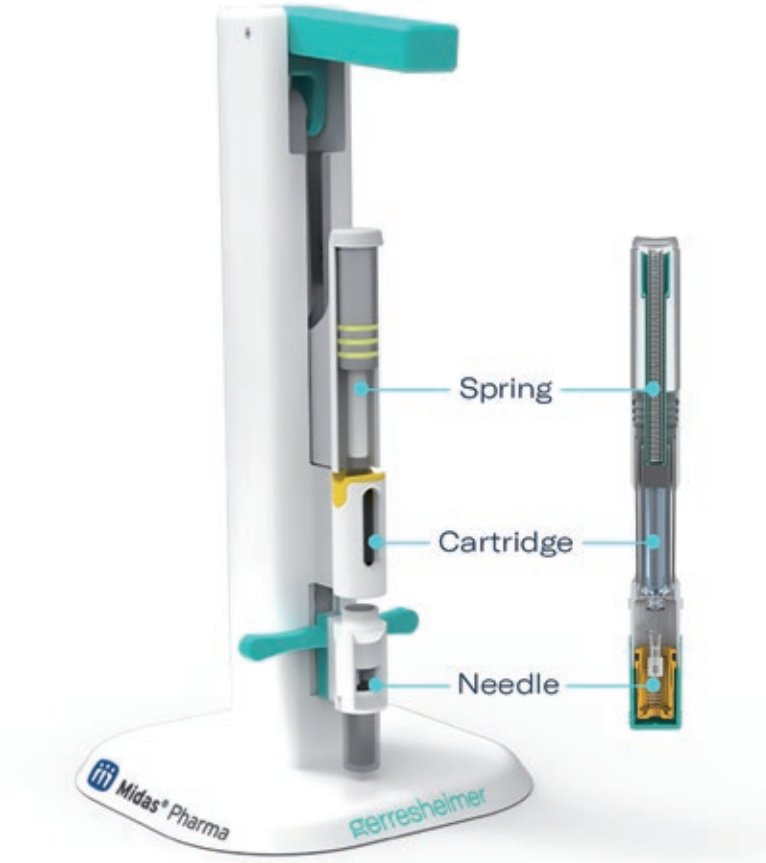

Figure 1: The design of the Gx Inbeneo® platform simulator directly correlates to the Gx Inbeneo® autoinjector platform with exchangeable spring, cartridge and needle.

(SC) administration are the only options for independent patient use. The transition from IV administration to SC self-administration has a significant impact on formulation development.[2]

With SC self-administration, the drug dose cannot be easily adjusted to body weight, which means that one-size-fits-all doses usually need to be developed, yet the pharmacokinetic profile of the drug product must facilitate a comparable therapeutic effect. Compared with IV infusions, injection volumes for SC self-administration are limited and, therefore, concentrations are usually higher.[3] Higher drug viscosity is a challenge for delivery devices, as it usually results in longer injection times or a larger needle, which can be uncomfortable for the patient. Thus, a delivery device needs to balance these two aspects for an optimal patient experience.

INTEGRATION OF THE GX INBENEO® DEVICE INTO FORMULATION DEVELOPMENT

To expedite time to market for a drug-device combination, and ensure that it supports patient comfort, it is beneficial to test how formulation adjustments impact specific device set-ups earlier than clinical Phase III. However, creating multiple prototypes is time consuming, complex and prohibitively expensive. This is why Gerresheimer, together with Midas Pharma, has developed the Gx Inbeneo® platform simulator, which simulates the Gx Inbeneo® autoinjector platform (Figure 1).

The Gx Inbeneo® is a cartridge-based, single-use autoinjector platform for SC self-administration. It features a patented pre-pressurised design and up to 3 mL fill volume. In contrast to some prefilled syringe systems with a staked-in needle, with the Gx Inbeneo® it is possible to select an appropriate spring and needle for a specific drug product. Injection time can therefore be adjusted to achieve the optimal patient experience.

> "The Gx Inbeneo® platform simulator mimics the Gx Inbeneo® platform, enabling different combinations of spring force, needle gauges and volume to be tested with a specific drug product."

The Gx Inbeneo® platform simulator mimics the Gx Inbeneo® platform, enabling different combinations of spring force, needle gauges and volume to be tested with a specific drug product. It thus enables practical evidence to be gathered, rather than having to rely on theoretical calculations based on Hagen-Poiseuille's law. Formulation scientists can therefore quickly assess how adjustments to concentration, volume and viscosity impact device configuration and injection times at any stage of the drug development process. After a test, the expelled drug can subsequently be analysed to ensure that there has been no impact on the drug compound.

As well as being a useful tool in earlier formulation stages, the Gx Inbeneo® platform simulator also aids definition of Gx Inbeneo® prototype configurations ready for clinical testing. The simulator can thus help reduce time pressure on the device department and limit the risk of delays or unforeseen issues far in advance of clinical Phase III.

ENABLING CONFIGURATION TESTING

The Gx Inbeneo® platform simulator enables different configurations of the Gx Inbeneo® autoinjector platform to be tested. The Gx Inbeneo® is intended for the safe, patient-centric delivery of sensitive biopharmaceuticals with a viscosity of up to 100 cP and in volumes of up to 3 mL[1] (Figure 2). To achieve this, the autoinjector has a cartridge-based, pre-pressurised design. This innovation employs a robust prefilled glass cartridge to retain the spring force, thus making the primary packaging the force barrier. It also features a double-ended needle that is separated from the primary container until use, which prevents clogging during storage. The needle has a different thickness at each end, with the thicker end of the needle piercing the septum of the primary container, while the end of the needle that pierces the patient's skin can be thinner. Higher viscosities can therefore be delivered faster than with a standard needle – enabling injection time to be balanced with patient comfort.

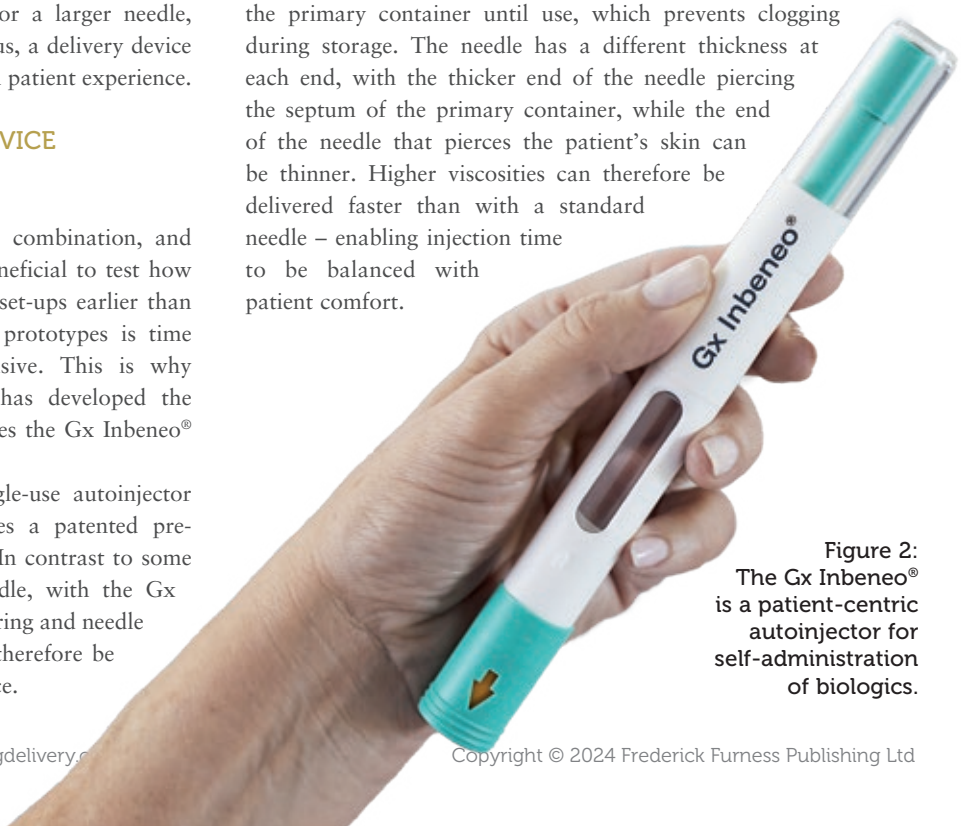

Figure 2: The Gx Inbeneo® is a patient-centric autoinjector for self-administration of biologics.

"Due to its quick and simple set-up, it is an extremely efficient tool in the early stages of drug development and throughout formulation adjustments, allowing for swift estimations of a formulation's behaviour in a final device configuration."

The Gx Inbeneo® platform has three variables: cartridge, patient needle gauge and spring force. The device accommodates both 3 mL and 1.5 mL ISO cartridges, needles of 25G, 27G or 29G at the patient end and springs of different forces. The Gx Inbeneo® platform simulator is supplied with all these options to enable different configurations to be tested. Springs are supplied within power packs, each with a different force.

Once the cartridge is filled with the drug formulation and placed into the simulator, along with chosen needles and springs, it can be manually activated. The needle then pierces the cartridge septum and the formulation is expelled through the needle into a vial. The duration of the simulated injection can be measured and the expelled drug product can be retrieved from the vial for further analysis.

EXPERIMENTAL DEMONSTRATION OF THE PLATFORM SIMULATOR

The capabilities and outcomes of various combinations were tested during three experiments. All data points shown are arithmetic means of quintuplets. Standard deviations were calculated from unbiased variance. The results highlighted the simulator's versatility in handling formulations with different viscosities and provided insights into potential correlations. The experiments took less than two hours to conduct, which effectively demonstrates the benefits of the Gx Inbeneo® platform simulator for making quick estimations of the behaviour of a formulation in combination with specific device parameters.

Experiment One

In the first experiment, a 30 cP glycerol-water solution was tested with the Gx Inbeneo® platform simulator (Figure 3). Firstly, using a 27G needle, injection times for three different spring forces were evaluated. As shown in Figure 3, an injection time of more than 50 seconds was observed for a low force with a 27G needle. The injection time for the liquid was then tested at a high pressure

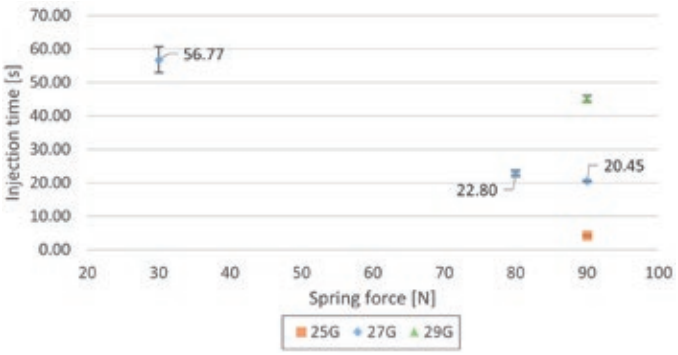

Figure 3: Injection times for 3 mL of 30 cP glycerol solution with three different needles and at different force levels using the Gx Inbeneo® platform simulator.

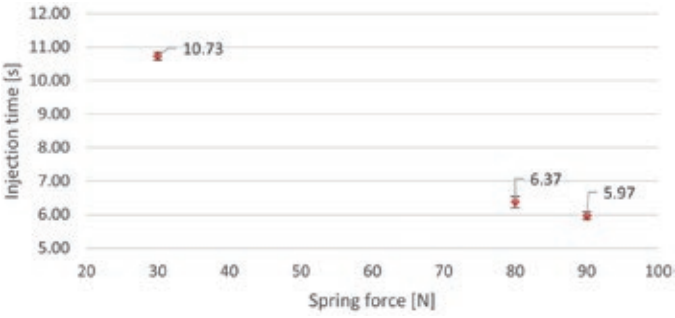

Figure 4: Injection times of 3 mL of 1 cP liquid (water) at three different force levels using the Gx Inbeneo® platform simulator.

of 90 N with 25G and 29G needles. With a lower gauge needle, the injection time was improved. However, to best balance delivery time and needle size for optimal patient comfort, a medium or high force with a 27G needle would be optimal for this viscosity.

Experiment Two

Figure 4 shows injection times of water, which has a viscosity of 1 cP, expelled with three different spring forces through a 29G needle. A high spring force of 90 N enabled an injection of 3 mL in <6 seconds. As this is extremely quick, a lower force may be advisable for a viscosity of 1 cP. Therefore, a force of 30 N was also tested, which still resulted in a favourable injection time of <11 seconds, representing a volume flow of 272 µL per second.

Experiment Three

To test the range of the autoinjector, a high viscosity benchmark of 2 mL of 200 cP glycerol solution was expelled with a 90 N spring force and a 25G needle. The liquid could be expelled with an injection time of 18.1 ± 0.21 seconds. This can still be considered an acceptable balance of injection time and needle gauge for the patient, given the volume and extremely high viscosity. At lower volumes, even higher viscosities may be suitable.

CONCLUSION

The Gx Inbeneo® platform simulator can be a valuable instrument for pharmaceutical companies, bridging the gap between pharmaceutical formulation and medical device development. Due to its quick and simple set-up, it is an extremely efficient tool in the early stages of drug development and throughout formulation adjustments, allowing for swift estimations of a formulation's behaviour in a final device configuration. This innovative approach can significantly streamline the drug-device integration process and potentially reduce overall timelines for bringing a combination product to market. The experiments with the Gx Inbeneo® platform simulator also demonstrate the benefits of the Gx Inbeneo® autoinjector for achieving fast injection times due to its double-ended needle and patented pre-pressurised design.

ABOUT THE COMPANIES

Midas Pharma is a mid-sized pharmaceutical company, founded in 1988 and based in Ingelheim, Germany. It offers products, services and expertise along the entire pharmaceutical value chain – from starting materials and APIs to the development of market-ready finished products and medical devices, as well as being a marketing authorisation holder for medicaments. For more than three decades,

the family-owned company has successfully contributed to the pharma sector and expanded its competencies. With more than 280 employees and 10 locations in all major pharmaceutical markets worldwide, Midas Pharma has excellent local know-how, local contacts and well-established networks in different pharmaceutical sectors.

Gerresheimer is a global partner for pharmaceutics, biotech, healthcare and cosmetics with a broad product range of packaging solutions and drug delivery systems. The company is an innovative solution provider from concept to delivery of the end product. Gerresheimer achieves its ambitious goals through a high level of innovation, industrial competence and focus on quality and customer focus. In developing innovative and sustainable solutions, Gerresheimer relies on a comprehensive international network, with numerous innovation and production centres in Europe, America and Asia. Gerresheimer produces close to its customers worldwide, with around 11,000 employees, and generated annual revenues in 2022 of €1.82 billion (£1.6 billion). With its products and solutions, Gerresheimer plays an essential role in people's health and wellbeing.

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ABOUT THE AUTHORS

Daniel Primavessy, PhD, studied Bioinformatics and Biotechnology at Saarland University (Saarbrücken, Germany) from 2003 to 2011 and did his PhD from 2011 to 2017 at Philipps-University (Marburg, Germany) on peptide encapsulation into polymeric nanoparticulate and microparticulate systems. He worked as a postdoc for two years at Saarland University and two years in a contract research organisation focusing on pulmonary *in vitro* instruments. In 2021, Dr Primavessy joined Midas Pharma. As a Project Manager and Scientist, his work focuses on the evaluation of pharmaceutical innovation projects in device and formulation technology and the development of pharmaceutical products.

Sigrid Saaler-Reinhardt, PhD, studied Biochemistry at the Free University of Berlin (Germany), received her PhD in Cell Biology and Oncology and became a Professor of Molecular Genetics at the Johannes Gutenberg-University (Mainz, Germany). She has more than 20 years of academic research and pharmaceutical industry experience – most of it at Midas Pharma, with responsibilities for R&D and intellectual property management, and subsequently for custom synthesis, biotechnology and drug-device combinations. Dr Saaler-Reinhardt is founder and consultant of her own company, EDUMO Consulting.

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

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

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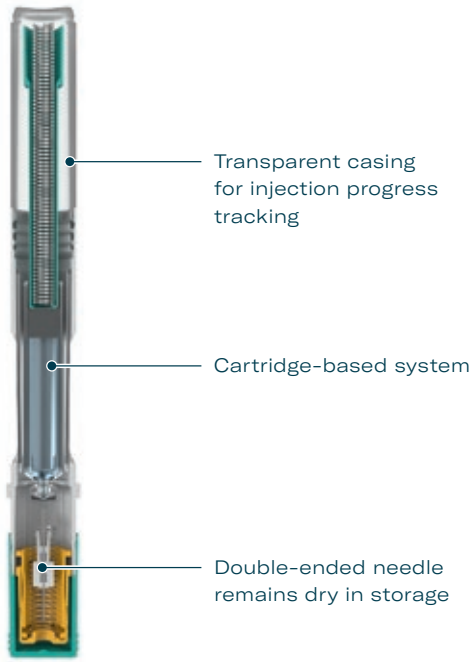

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EXPLORING EXTRACTABLE AND LEACHABLE TESTING STRATEGIES FOR PARENTERALS

In this article, Antonio Scatena, Director of Sales and Marketing, Scott Toth, PhD, Program Manager and Principal E&L Scientist, and Kyle Chenevert, Senior Scientist, all at Gateway Analytical, discuss the regulatory landscape regarding extractables and leachables for parenteral drugs and provide guidance on implementing a successful testing approach. Techniques and results interpretation are discussed, emphasising practical advice for developers working towards regulatory submission.

Contamination of a drug by extractables and leachables (E&Ls) can lead to drug recalls and significant commercial losses, as evidenced by a major recall of children's medicine in 2010 (McNeil Consumer Healthcare, PA, US) linked to the migration of 2,4,6 -tribromoanisole from shipping pallets,[1] and a recall of felodipine (Mutual Pharmaceutical, PA, US) due to benzophenone leaching from varnish on the packaging.[2]

In some cases, E&Ls can also result in adverse effects, as was observed in the early 2000s with the spike of pure red blood cell aplasia (PRCA) cases that were linked to the use of injected erythropoietin (EPO). In this case, rubber extractables were identified as the leading cause of EPO aggregate formation,[3] which may have elicited auto-immune responses in patients and resulted in PRCA.[4]

Examples like these highlight the critical role of E&L testing in ensuring drug safety, particularly for dosage forms such as injectables. These drugs fall into the US FDA's highest risk categories, as they are directly injected into the parenteral space. Furthermore, the likelihood of interaction between dose and packaging is high for liquid-state drugs.[5]

Extractable testing reveals compounds released by a given material under relatively aggressive conditions, while leachable testing seeks to detect and quantify the migration of compounds into a specific drug product formulation under representative storage conditions (Figure 1). Both are subject to extensive regulatory guidance and evolving industry practice, none of which is truly prescriptive. Instead, drug developers must demonstrate a rigorous

Figure 1: Extractables are compounds that could migrate into the product; leachables are compounds that migrate into the product under representative conditions.

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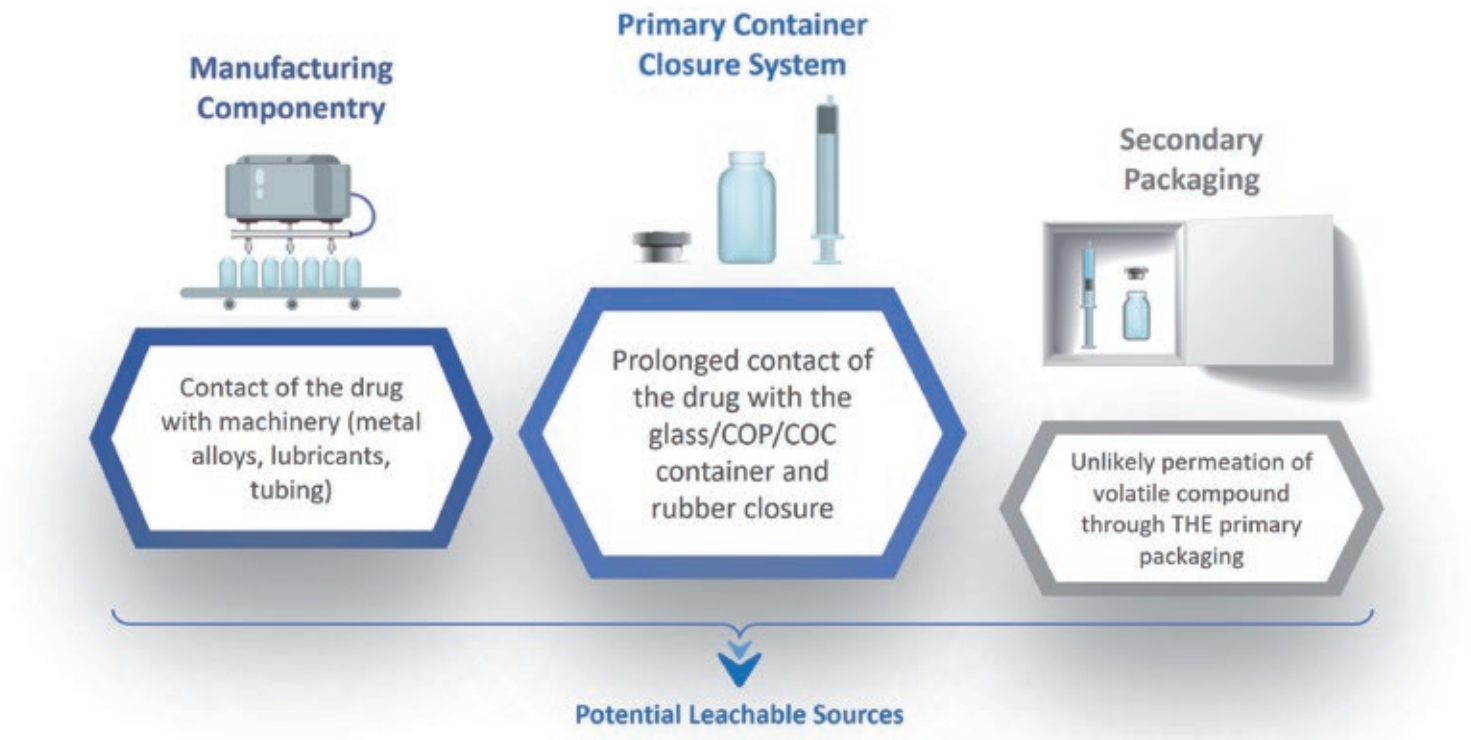

Figure 2: Sources of potential leachables include manufacturing componentry in contact during production, primary packaging, the container closure systems and secondary packaging.

and systematic approach that identifies problematic compounds for a specific drug product and minimises risk by ensuring their effective control.

EXTRACTABLES & LEACHABLES: SOURCES AND RISK

Primary packaging is a defining focus when it comes to E&L testing for parenterals, and rightly so, since it is not unusual for a ready-to-use drug product to be stored for up to 24 months. Solutions and suspensions for parenteral delivery are typically filled into vials, bottles and syringes made from glass or cyclo-olefin polymer or co-polymer (COP/COC) and closed with rubber components. Rubber manufacturers have developed various strategies for rubber lamination (such as ethylene tetrafluoroethylene film-coating), which aims to limit the risk of compound migration into the drug, further emphasising the focus on E&L risk-mitigation for primary packaging.

For some applications, solutions can be packaged in flexible containers made from polymers, such as polyethylene or polyvinylchloride (PVC). The associated container closure systems (CCSs) are particularly important with respect to leachables, not least because of their steadily evolving complexity. The growing use of CCSs with a multi-layered construction, incorporating plastics, adhesives and foils, has contributed to increased scrutiny of these components regarding the potential for releasing E&Ls ranging from pigments to plasticisers.

> "Drug developers must demonstrate a rigorous and systematic approach that identifies problematic compounds for a specific drug product and minimises risk by ensuring their effective control."

Primary packaging is the main source of E&Ls for parenteral drugs, but other sources, such as manufacturing componentry and secondary packaging, may also need to be considered (Figure 2). As a drug product advances through the manufacturing chain, it contacts various surfaces and materials, from vulcanised rubber tubing to lubricants and metal alloys. Typically, contact times are short, but not always, with processes such as filtration providing opportunities for extended interaction. While secondary packaging may be further down the list of likely causes of contamination, it can be a fruitful avenue of investigation when alternative sources have been eliminated.

Patient safety is the primary concern regarding E&Ls because migration into the drug product can result in the delivery of toxic impurities along with the API or adversely affect its stability and potency.[3] However, results from extractables or simulation studies are also helpful to drug developers when selecting packaging materials to preserve the long-term quality of the drug and maximise drug stability. For all parenteral drugs, but particularly for sensitive biologics such as monoclonal antibodies, recombinant peptides or mRNA vaccines, E&Ls may trigger aggregation, unfolding and/or oxidation, thereby limiting shelf life, compromising therapeutic efficacy and, in the worst case, affecting patient safety.[3-4]

THE REGULATORY LANDSCAPE AND CURRENT BEST PRACTICE

The FDA advocates a risk-based approach to E&Ls for parenterals, emphasising the need for developers to minimise adverse patient impacts through systematic study and assessment.[5] The absence of prescriptive protocols highlights the benefits of working with experts in the field, although there is published guidance to reference, notably from the Product Quality Research Institute

(PQRI).[6] Released in 2021, the latest PQRI guidance is especially helpful for clarity around the safety concern threshold (SCT) concept. Defining the SCT "as the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects" suggests an SCT of 1.5 µg/day as suitable for the majority of organic leachables in parenterals. This figure helps to define the sensitivity with which to look for migrating compounds. Insights from the FDA are also helpful in this regard, indicating that, for parenterals, the common practice is to report leachables at > 1 ppm, identify them at 10 ppm and qualify them at 20 ppm.[5]

US Pharmacopoeia (USP) <659> covers packaging and storage requirements with the following opening statement "Packaging materials must not interact physically or chemically with a packaged article in a manner that causes its safety, identity, strength, quality or purity to fail to conform to established requirements." Individual chapters specifically refer to commonly used packaging for pharma products – USP <381> for rubber closure, USP<660> for glass and USP <661> for plastic packaging. For rubber closure and plastic containers, extractables are specifically addressed in USP <1663> and leachables in USP <1664>, which both specify the test methods that need to be implemented for adequate evaluation.

Change is also underway regarding International Council of Harmonisation (ICH) guidance, with the much-anticipated ICH Q3E Guideline for Extractables and Leachables currently being finalised and expected to be adopted by 2026. The ICH M7 guideline, which relates specifically to mutagenic compounds, remains in place and is helpful for reference but, in practical terms, has been largely superseded by the PQRI document.

DESIGNING A STUDY

For effective study design, it is necessary to clearly differentiate E&L testing and understand how the two relate to one another. Extractable testing aims to identify a profile of compounds that could be released from a material used for packaging or manufacturing componentry by applying relatively harsh – though somewhat representative – conditions. By "pushing" candidate materials, extractable testing effectively determines a worst-case leachable profile. The results help to qualify alternative options for CCSs, establish quality control protocols for material acceptance/use and screen for the release of toxic materials. Extractable testing is often a proving ground for analytical techniques destined for application in leachable testing. In contrast, leachable testing determines which compounds migrate into a specific drug formulation under closely representative conditions and, as a result, is much more akin to stability testing.

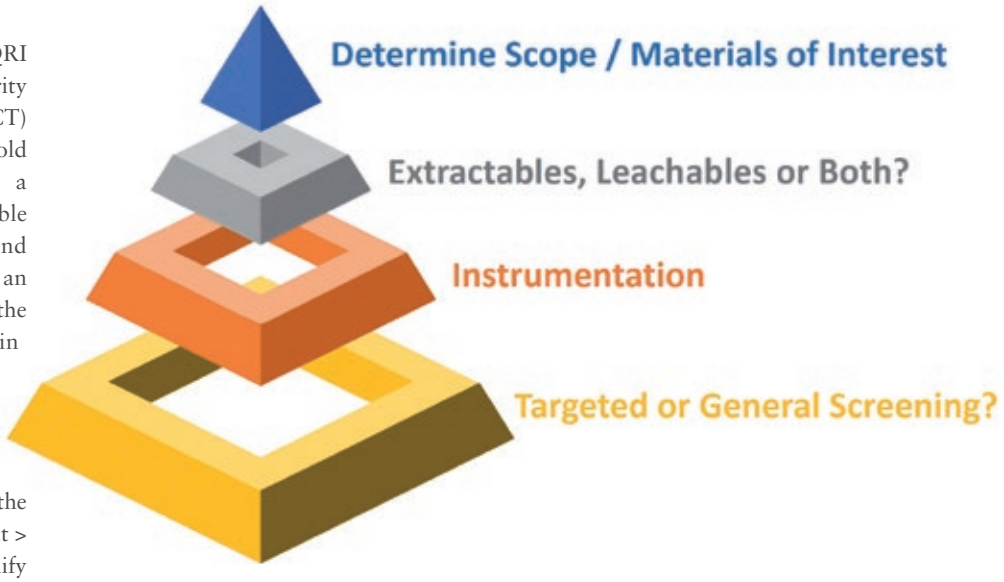

Figure 3: An E&L study requires careful consideration of several factors.

When designing a study, the first question is whether the scope includes both E&Ls or whether the focus is one or the other. Additional questions that are usefully answered at the outset include the following (Figure 3):

- What materials are of interest from the perspective of primary packaging, notably the CCS and manufacturing componentry?
- Are there specific compounds of concern, or is the intention to perform a broad screen? A broad screen will deliver an unbiased assessment of any compounds present, but sensitivity can be as much as five times greater for a targeted study.
- What analytical techniques and instrumentation are going to be relevant?
- What conditions are going to be appropriate for testing?

Consider this last point in greater detail by examining a general workflow for extractables testing (Figure 4).

Assessing each of these steps highlights the wide range of factors to consider when developing an extractable test protocol to apply sufficiently harsh conditions while remaining within the boundaries of remaining realistic. Some critical questions to address are:

- What form should the test sample take? Would there usually be any form of pre-treatment, such as washing or irradiation, that should be reflected in the test protocols?
- Which extraction technique(s) is most appropriate – microwave, reflux, Soxhlet, sonication or accelerated solvent extraction?
- Which solvents should be used – polar (e.g. water, isopropanol) or non-polar (e.g. dichloromethane, hexane), a range or a combination? Are additives needed to, for example, assess the impact of pH and/or surfactants?
- What are the appropriate contact time and temperature ranges? Temperature tends to be in the range of 25°C–40°C, with test times extending from a few hours up to 70 days.
- Is the accessible contact surface area suitable? A surface area-to-volume ratio of 6:1 cm^2/mL is routinely adopted.
- What will be the negative control? In other words, which highly inert materials – high-grade borosilicate glass

> "When designing a study, the first question is whether the scope includes both E&Ls or whether the focus is one or the other."

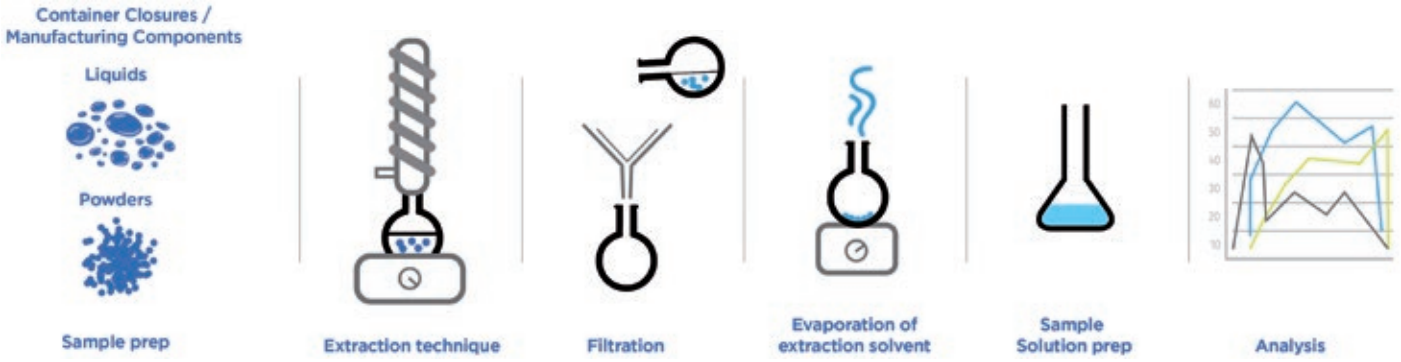

Figure 4: An execution flow for extractable testing highlights the need to consider various factors when developing an appropriate test strategy.

and polytetrafluoroethylene are common candidates – will be used to establish a baseline for comparative purposes?

- Is there an appropriate internal standard to track the efficiency of the sample work-up process – usually a molecule of comparable class/structure to those of interest?
- Does the sample require cleaning up to improve the quality of analytical data via, for example, filtration or concentration?
- Is further concentration required to reach the compound's analytical evaluation threshold (AET)? Possible concentration techniques include evaporation, liquid–liquid extraction, dispersive liquid–liquid microextraction, hanging droplet microextraction and solid-phase microextraction.
- Which analytical technique is most appropriate? Liquid chromatography ultraviolet mass spectrometry (LC-UV-MS) is valuable for non-volatile compounds, including oligomers and larger antioxidants; gas chromatography – MS (GC-MS) with liquid injection is useful for semi-volatile compounds, such as residual monomers, preservatives and plasticisers, with GC-MS for volatile compounds via headspace analysis better suited to inks, adhesives and process solvents; and inductively coupled plasma MS (ICPMS) useful for elemental analysis, notably metals.

This is a lengthy list of considerations, and many are equally applicable to leachable testing, highlighting the considerable effort involved in implementing an effective study. It is also important to recognise the value of standardisation in extractable testing, as it supports the effective comparison of alternative materials and broader use/sharing of extractable testing data, thereby reducing the associated workload. Information released by the BioPhorum Operations Group[7] is helpful in this regard and usefully referenced. For leachables, on the other hand, every drug product is unique, and individually tailored studies are therefore required.

PROGRESSING TO ACTIONABLE INSIGHT

The first step in processing and interpreting E&L test data is to identify compounds of interest. These may be targeted molecules associated with using certain materials or unknowns absent from the original drug formulation and negative control. For the latter, routes to identification include commercial MS libraries, molecular formula generation from empirical mass/isotope spacing on a high-resolution instrument and/or MS/MS fragmentation in combination with resident time matching with an authentic standard.

> "The first step in processing and interpreting E&L test data is to identify compounds of interest."

Having identified compounds of interest, the next step is determining the AET – "the threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment".[6] The AET brings specificity to the SCT, essentially converting it into a metric that takes account of how the drug will be used, since this, in turn, determines the extent of patient exposure (Figure 5). The administration method, the concentration of drug product, the amount per dose,

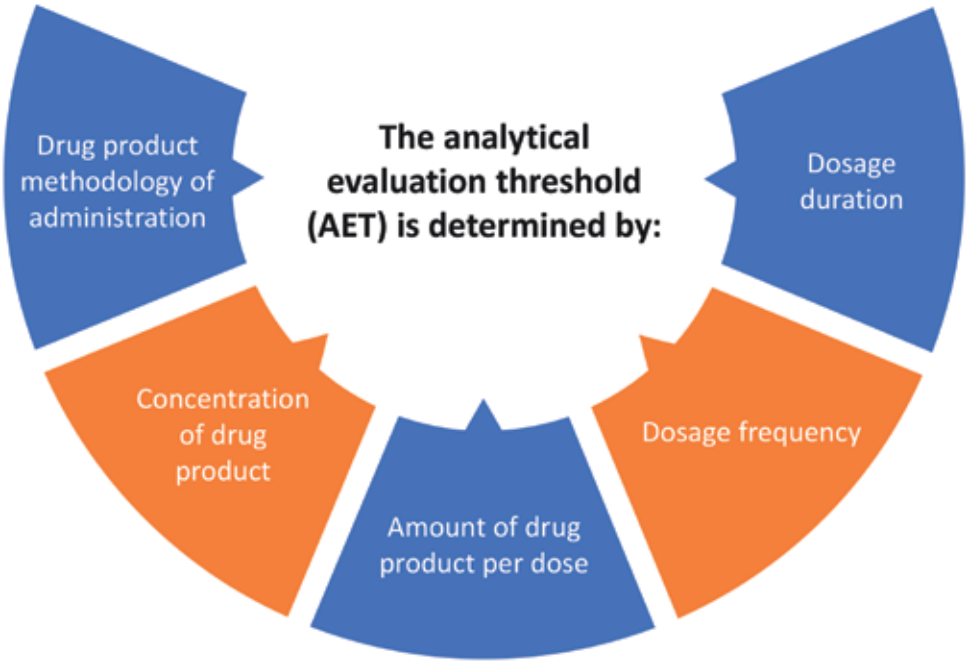

Figure 5: The AET is a critical concept in E&L testing, determined from consideration of the way in which the drug will be used.

dosage frequency and dosage duration all impact the AET, which is set to ensure adequate patient protection across intended use scenarios. For example, the AET for a vaccine delivered two to three times across a patient's lifetime will be significantly higher than that for an identical leachable detected in a parenteral for daily dosing to treat chronic disease. ICH M7 helps determine AETs, specifically for mutagens, and values the testing strategy in terms of stringency and precision. The lower AETs associated with a routinely used drug may necessitate the further refinement of test strategies to enhance sensitivity to the required level.

Ultimately, the outcome of a successful E&L study is a profile of the identity and concentration of all compounds of concern, their source (if known) and any additional data associated with potential risk to the patient. This can be used to make a toxicological assessment for the product, greenlighting further development or prompting modification. In this way, E&L studies form an integral and critical element of parenteral development and the associated regulatory submission. Ensuring that all materials that the drug product contacts throughout its lifetime are appropriate for use is a cornerstone of drug safety and an area of growing scrutiny, particularly for exacting, higher-risk products such as parenterals.

E&L studies are unique for each new drug and represent a significant forensic and analytical chemistry exercise. Working with experts can be the way forward for those new to the area or daunted by the challenge. Developing in-house abilities to successfully design and execute these vital studies requires significant investment and resources. Getting help can be highly productive in getting safer parenterals to market faster.

ABOUT THE AUTHORS

Antonio Scatena has over 13 years of experience in the pharmaceutical and biotechnology industries, occupying scientific, management, business development and sales and marketing roles. Mr Scatena's expertise centres around testing methods to support parenteral medicine development and manufacturing, specifically visual inspection, primary container-closure selection and validation and manufacturing materials compatibility testing. He holds a bachelor's degree in biochemistry from Indiana University of Pennsylvania and is the Director of Sales and Marketing at Gateway Analytical, an Aptar Pharma company.

Scott Toth, PhD, has over 10 years of experience performing routine and non-routine analytical testing to support pharmaceutical drug product development and manufacturing. Dr Toth's expertise spans the development of structural chemistry methods, including methods for trace impurity analysis, identification and stability studies using high- and ultrahigh-performance liquid chromatography coupled with high-resolution mass spectrometry. Dr Toth holds a doctorate in analytical chemistry from Purdue University and is the Program Manager and Principal E&L Scientist at Gateway Analytical.

Kyle Chenevert has over five years of professional experience focusing on developing and validating liquid chromatography-mass spectrometry methods for pharmaceutical drug development and manufacturing. Mr Chenevert performs literature reviews and technical writing as part of his responsibilities and remains current on changes in the regulatory landscape of the pharmaceutical industry. He holds a master's degree in chemistry from the University of North Carolina Wilmington and is an Analyst III in the E&L Laboratory at Gateway Analytical.

ABOUT THE COMPANY

Gateway Analytical, an Aptar Pharma company, is a specialised analytical testing laboratory that businesses around the world trust to provide solutions for their most challenging foreign particulate characterisation and materials analysis needs. Gateway Analytical's expert scientists, specialised test methods and comprehensive suite of instrumentation deliver the fast, accurate and reliable results that customers in the pharmaceutical, materials and medical device industries demand. With a strong focus on quality, Gateway Analytical is cGMP-compliant, FDA registered and inspected, and Drug Enforcement Administration licensed.

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FAST, STANDARD-COMPLIANT AND COST-EFFICIENT TESTING OF PREFILLED SYRINGES FOR OPTIMAL RESULTS

In this article, Peter Schmidt, Product Manager Medical/Pharma at ZwickRoell, presents the company's solutions for testing autoinjectors and wearables to ensure a systematic increase in productivity in the testing lab.

In 2022, approximately 50% of new drug approvals involved biologics – a trend that continues to rise. At the same time, the focus is shifting from filling aseptic vials to the use of prefilled syringes (PFSs). Among other things, these act as medication vessels in the form of autoinjectors or on-body delivery systems (OBDSs). ZwickRoell has developed modular testing systems to perform all the necessary tests for PFSs in accordance with ISO 11040-4/6/8, with the utmost efficiency and standard compliance.

PFS SOLUTIONS

New therapies based on biologics have already begun to change cancer treatments significantly, giving hope to many people who previously lacked effective treatment options. Currently, however, the only means of effective and accurate dosing of biologics is with PFSs, in contrast to tablets, capsules, suppositories, syrups or solutions.

> "For PFSs and autoinjectors, ZwickRoell offers modular solutions that support standard-compliant, flexible, and time- and cost-efficient testing."

For PFSs and autoinjectors, ZwickRoell offers modular solutions that support standard-compliant, flexible, and time- and cost-efficient testing. A wide variety of tests can be used for different applications with the same machine components because the PFS tools can be easily changed. Autoinjector testing machines enable operators to insert prefilled syringes easily into the fixture through special inserts and subsequently conduct the test.

ISO 11040: STANDARD-COMPLIANT TESTING FOR SECTIONS 4, 6 AND 8

ZwickRoell's modular solution for PFSs covers the ISO 11040 standard requirements, especially for sections 4, 6 and 8. These describe important tests, including needle penetration force, flange breakage resistance, needle pull-out force, glide force and closure system liquid leakage. Due to the modular set-up, all tests can be performed on a single machine, increasing both time and cost efficiency.

Set-up Suggestions

ZwickRoell is the only manufacturer to offer three systems for testing autoinjectors and wearables to ensure a systematic increase in productivity in the testing lab, particularly with regard to the error-free functionality of injection systems and compliance with strict quality standards – the single-column zwickiLine 2.5 kN (Figure 1), the multifunctional AllroundLine 5 kN and the zwickiLine system for OBDSs.

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Figure 1: Sequential testing systems save time and significantly reduce operator influence.

Additionally, the company's specialised customisation department addresses individual customer requests and devises application-based, tailor-made solutions, or presents suggestions for test equipment set-up options.

ZwickRoell believes that efficiency is an important topic for the pharmaceutical industry and its suppliers, such as manufacturers of syringes and autoinjectors, as well as service providers, such as contract development and manufacturing organisations and external testing service providers. Accurate and reliable solutions with significantly reduced user influence are essential and must be traceable in accordance with the US FDA 21 CFR Part 11 requirements.

ZWICKILINE: IMPLEMENTATION IN CLASS 5 AND CLASS 6 CLEANROOM TEST ENVIRONMENTS

In the pharmaceutical, medical and biotech sectors, cleanrooms are subject to strict regulations to eliminate the risk of contamination from germs and other harmful substances. ZwickRoell offers testing systems with ISO class 5 and 6 certifications; cleanroom compliance has been confirmed for zwickiLine materials testing machines, which can be used for production and testing in class 5 and 6 cleanrooms, according to DIN EN ISO 14644 1:2016-06, DIN EN ISO 14644-14 and VDI 2083 page 9.1. The test can be conducted without the need for time-consuming removal of specimens from the cleanroom. Additionally, the testing machine can be directly integrated into the production process within the cleanroom (Figure 2).

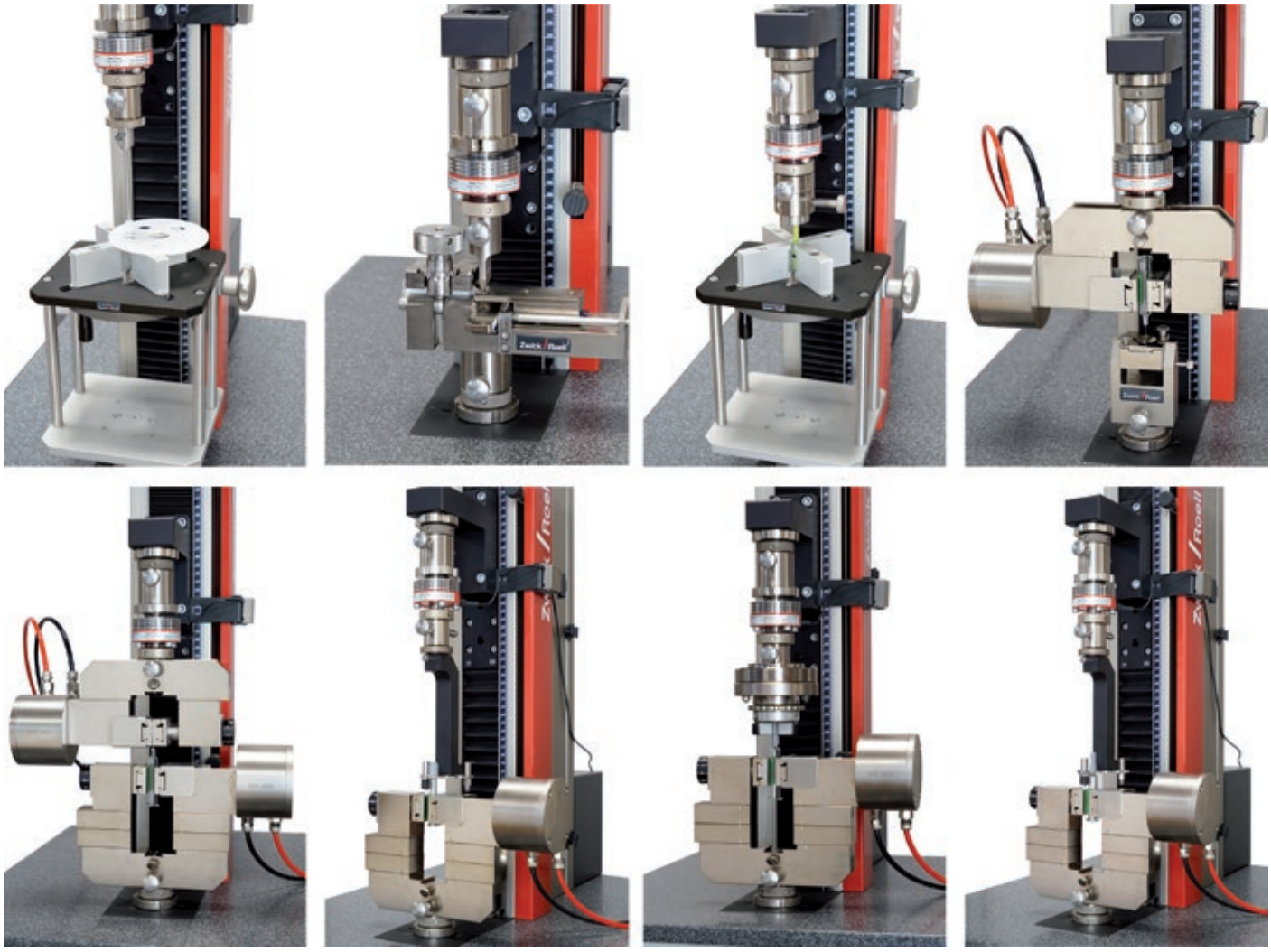

Figure 2: Simple, standard-compliant testing is guaranteed – test tools are easily interchangeable and standard requirements are preconfigured in the software.

SERIAL, PARALLEL AND AUTOMATED TESTING SOLUTIONS

Comprehensive validation is required for FDA and European Commission approval of new syringes and combination products. Sequential, serial and parallel testing systems can be adapted to customer-specific requirements. This ensures that specimens are fed to the machine in a uniform manner, enabling reproducible test results (Figure 3). The standard deviation is reduced by the testing systems delivering reliable results and minimising possible result-distorting operator influences. This improves both the measurement accuracy and reproducibility of the test results, which ultimately helps customers to run cost-efficient tests.

SUPPORT FROM USER REQUIREMENT SPECIFICATIONS TO FINAL QUALIFICATION

ZwickRoell offers comprehensive support with all aspects of PFS testing. This ranges from the preparation of user requirements and customer-specific specifications to design qualification, project implementation, and the final installation qualification and operational qualification processes. The company also offers a unique qualification service that covers static testing systems with or without torsion drive, complex systems (such as autoinjector testing systems) and serial and parallel testing systems (carousel, XY table), as well as fully automated systems with robots. Customers can choose between standardised qualification documents or individualised documents tailored to their specific user requirement specifications.

ABOUT THE COMPANY

ZwickRoell is a global leader in materials testing and a trusted partner for reliable test results. A fundamental requirement for reliable test results in materials and components testing is the perfect interaction among all testing machine components. For this reason, ZwickRoell 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 has grown into an expert and strong partner in the field of materials testing.

Figure 3: PFSs are tested using a simple syringe insert on the zwickiLine autoinjector testing machine.

ABOUT THE AUTHOR

Peter Schmidt, Product Manager Medical/Pharma for 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.

Testing systems

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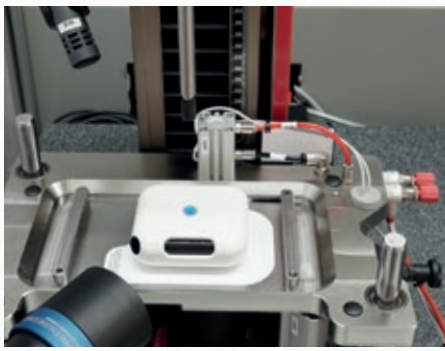
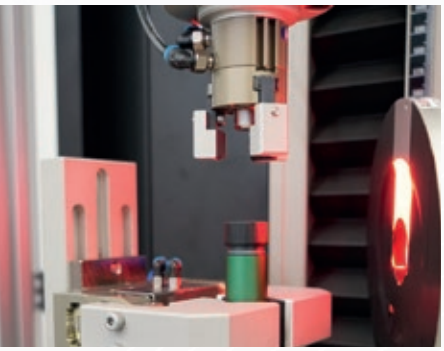
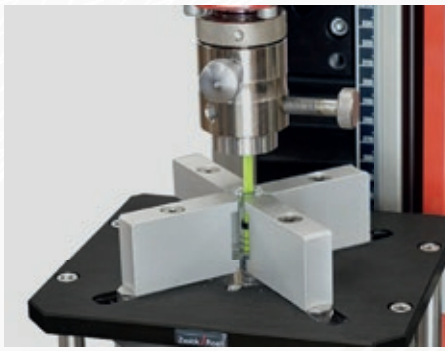

- Manual, semi-automatic and fully automated testing solutions for therapy systems (needles, (pre-filled) syringes, insulin pens, auto injectors)
- Traceable and tamper-proof test results in accordance with FDA 21 CFR Part 11
- ZwickRoell supports customers with DQ, IQ and OQ services

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NAVIGATING ISO 11608 WITH AUTOMATED EQUIPMENT FOR CUSTOMISED PEN AND AUTOINJECTOR TESTING

In this article, Hisham Jamal, Senior Account Manager, Medtech, and Carsten Köhler, DBA, Vice-President Sales and Project Management, Medtech, both at teamtechnik, discuss how the company's automated testing machines – built on the foundation of assembly automation legacy – seamlessly align with the ISO 11608 regulations, effectively shaping the future of pen and autoinjector testing.

The easy administration, high reliability and mobility of pen injectors and autoinjectors has led to widespread acceptance of these self-administered medical devices, resulting in a projected compound annual growth rate of 11%–16% from now until 2030.

Teamtechnik has been active in the development and manufacturing of these injection devices for more than 40 years and continues to support its global customer base with current and future manufacturing needs. Grounded in the assembly of these devices, teamtechnik's experience has offered unique insights into their intricate functionalities. This deep-seated understanding of the devices and their operation is what has guided the company in the development of its automated testing machines. This understanding is applied to ensure that the devices not only

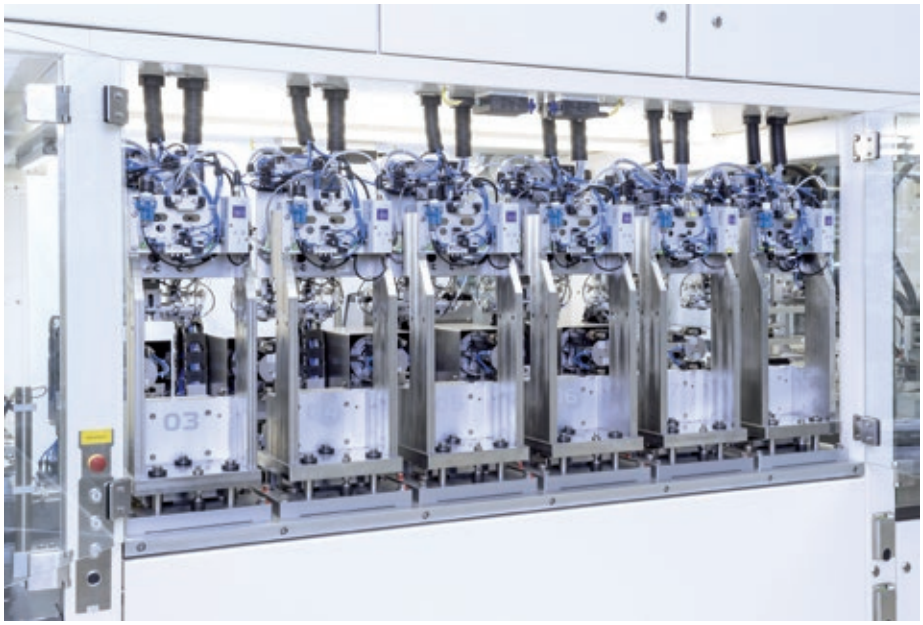

Figure 1: Process detail of an injector test system.

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function optimally but also adhere strictly to the quality and safety standards mandated by the international medical community.

From simple tabletop test benches to fully automated batch and/or 100% inline tests (depending on the product and functionality), teamtechnik's machines – designed with a blend of practical experience and keen understanding of ISO 11608 – are setting new standards in medical device testing (Figures 1 and 2).

UNDERSTANDING REGULATIONS

The medical regulations in the EU and other sophisticated markets are now viewing pen injectors and autoinjectors less as secondary packaging and more as a combination product as their popularity and demand soar on the global market – with a combination product defined as a fully integrated drug and delivery device unit. The regulations for these devices are therefore becoming more stringent in order to guarantee their quality, safety and efficacy.

The EU Medical Devices Regulation (MDR) 2017/745 mandates that combination products must conform to the general safety and performance requirements as listed in Annex 1 of the MDR, thereby holding these devices to stricter requirements on quality, safety and performance, as well as measures such as unique device identification on packaging and devices to improve traceability.

The US FDA also categorises pen injectors and autoinjectors as combination products. They must therefore comply with the FDA's 21 CFR Part 820 and cGMP requirements. The subpart H of the 21 CFR Part 820 is attributed to acceptance activities where it mandates each manufacturer to establish and maintain procedures for finished device acceptance so as to ensure that each production run, lot or batch of finished devices meets acceptance criteria. The acceptance activities, and the documentation and review prior to release for distribution and the maintenance of acceptance records, are also specified in this section.

ISO 11608 details the applicable standards for a needle-based injection system (NIS),[1] with ISO 11608 part 5[2] specifically outlining the definitions, requirements and testing criteria pertaining to needle-based injection systems with an automated function (NIS-AUTO). Injection devices, such as pen injectors and autoinjectors, are governed by these standards. While adherence to certain ISO standards is largely voluntary for companies, regulatory authorities, such as the FDA and EMA, are increasingly referring to ISO standards for their device approval framework.[3]

Figure 2: TEAMED injector test system by teamtechnik.

> "Manufacturers can benefit from teamtechnik's fully automated testing equipment as it combines robotics, cutting-edge sensor technologies and clever software algorithms to carry out the testing process."

Global regulatory frameworks for these devices are developing and evolving constantly in response to industry, market and customer requirements. Further updates to existing regulations are also expected over the coming years – making it important for device manufacturers to work closely with expert partners so that they can be confident they have the right resources to help them meet the strict regulatory requirements and ensure that they offer a seamless experience for their end users. Manufacturers can benefit from teamtechnik's fully automated testing equipment as it combines robotics, cutting-edge sensor technologies and clever software algorithms to carry out the testing process, while guaranteeing complete traceability and accurate and consistent documentation.

AUTOINJECTOR TESTING

An autoinjector is a single-use device that consist of a triggering unit, a holder for the prefilled syringe and an integrated cannula. When the triggering unit is activated, it drives the cannula and a spring-loaded plunger helps to administer the dose in the cartridge to the user. A needle retraction or needle shielding mechanism is also usually incorporated in an autoinjector to ensure the safety of users. As an NIS with an automated function as described above, regulations specified under ISO11608 (in general) and specifically ISO11608-5 are applicable here.

The ISO 11608-5 outlines the requirements and test methods for medicinal product preparation, needle inspection, needle hiding, priming, needle extension, dose accuracy, injection time, disabling, needle retraction and needle shielding – and recommends using a risk-based approach for verifying functions such as dose setting, recording device

functions and needle removal. Of these, product preparation, dose accuracy, injection time, needle extension, retraction, disabling and shielding are relevant for autoinjectors.

Aligning with ISO11608 requirements, teamtechnik has developed and executed autoinjector tests with associated parameters, as listed in Table 1.

PEN INJECTOR TESTING

A pen injector is a multi-use, variable dosage device that consists of dosing mechanism and a cartridge holder. A rotary button on the pen injector is used to adjust the dosage to be administered and a display window shows the set dosage quantity. Pressing down the button will administer the set dosage to the user. To use a pen injector, however, the user needs to attach the injector to a pen needle. Teamtechnik's test machine for pen injector testing executes both the assembly and the testing of the complete pen injector unit. The testing machine removes the cap of the pen injector and connects it to a pen needle before the following tests are executed as per the regulations.

Aligning with ISO11608 requirements, teamtechnik has developed and executed, pen injector tests with associated parameters, as listed in Table 2.

DOSING MECHANISM TESTING

The dosing mechanism plays a crucial role in accurately delivering medication to patients through an injector pen. Testing the dosing mechanism prior to final assembly acts as the first line of defence in preventing the integration of a flawed dosing mechanism that could compromise the efficacy and reliability of the entire device. Identifying and rectifying any issues with the dosing mechanism at this early stage in the production process significantly reduces the unnecessary wastage of pharmaceutical products, as well as ensuring that only devices with impeccably functioning dosing mechanisms proceed to final assembly.

Although ISO11608 or other regulations do not mandate the testing of the dosing mechanism in itself, but rather on the complete injector pens, manufacturers are

> "Testing the dosing mechanism prior to final assembly acts as the first line of defence in preventing the integration of a flawed dosing mechanism that could compromise the efficacy and reliability of the entire device."

11608-5 requirement	teamtechnik test executed	Test type/ parameter
Product Preparation	Needle Cap Removal Force	≤30 N
Priming/Activation	Activation Force (for 2 or 3 step AI)	4–18 N
Needle Extension	Injection Depth	4–7 mm
Dose Accuracy	Dosing Volume Measurement	by weight
Injection Time	Injection Time	3–18 sec
Needle Retraction	Needle Retraction Check	Camera Check
Needle Shielding	Needle Shield Check	≤3 mm @ 75 N

Table 1: Autoinjector tests as per ISO 11608-5.

11608-5 requirement	teamtechnik test executed	Test type/ parameter
Product Preparation	Pen Needle Assembly on Pen Injector	Assembly
Priming/Activation	Dosing Force Measurement	0–45 N
Dose Accuracy	Dose Measurement	by weight
Dose Setting	Set Dosage Measurement	0–45 N By weight
Recording Device Functions	Dosing Window Inspection Corresponding to Dosing Force/Dose Measurement	Camera Check

Table 2: Pen injector tests as per ISO 11608-5.

Figure 3: 100% inline test of an injection pen.

increasingly testing the dosing mechanism pre-assemblies prior to final assembly align their principles of operational efficiency with their commitment to responsible use of pharmaceutical resources. To help them with this, teamtechnik has developed and executed both inline (Figure 3) and standalone (Figure 4) testing machines for dosing mechanism testing.

With the inline testing machines, each and every dosing mechanism is tested for its functionality as it progresses through the assembly line. This real-time assessment ensures that every device meets the required operational standards and provides immediate feedback for any necessary adjustments or interventions. This is particularly well suited for high-volume production lines where real-time quality control is essential for maintaining efficiency and precision.

Standalone testing machines, on the other hand, test a representative sample of dosing mechanisms in a separate, dedicated testing phase, in the same way that most batch release tests are executed. This allows for a more comprehensive assessment of a batch of components, offering a holistic view of their collective quality – making this a more suitable testing approach for smaller production runs where heightened scrutiny is required.

Figure 4: Standalone test system for injection systems.

CALIBRATION

To ensure the accuracy and consistency of the testing equipment to perform the highest standards of compliant testing, teamtechnik – together with its customers – develops stringent calibration protocols that cover the various equipment and instruments that need calibration and defines their corresponding frequency or intervals of calibration schedules, depending on factors such as frequency of use, required accuracy, etc.

The protocol includes both functional and metrological calibration, either by comparison with the source of known standard value or by comparison with measurement from a calibrated reference instrument. For precision-critical tests, such as dose accuracy, activation force, etc, a more frequent calibration schedule is often warranted to ensure the integrity of the test results, while less sensitive tests may require less frequent calibration. In any case, the testing machines are programmed to run automated calibration modes at defined intervals where they automate the execution of the predefined calibration processes. For example, Figure 5 shows torque measurement and Figure 6 shows weight calibration.

A comprehensive documentation of calibration activities, including the recording of calibration results and adjustments made, is also recorded by these machines –

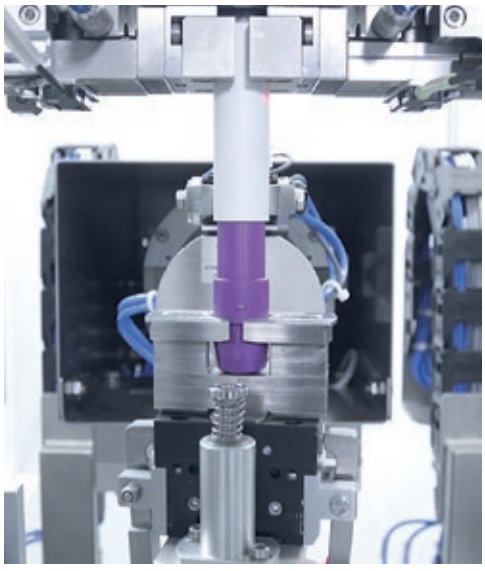

Figure 5: Torque measurement.

Figure 6: Weight calibration.

thereby providing a new level of traceability, transparency and accountability in adhering to the reference standards.

QUALIFICATION

The testing machines play a vital role in the quality control of pen and autoinjector devices and, as such, their qualification is essential to ensure the safety and efficacy of the final products they test. Teamtechnik follows a comprehensive qualification process in line with GMP compliance, satisfying relevant machine directives and ISO standards – ensuring that the testing machines are fit for their intended purpose and comply with regulatory guidelines, such as those set forth by the FDA and EMA.

It is important to note that the qualification process for these automated testing machines shares similarities with the process of assembly machines for pen injectors and autoinjectors, particularly in terms of ensuring compliance with regulatory standards and the specific requirements of the devices being tested and assembled. However, the focus and criteria for validation differ significantly, as the testing machines are primarily assessed based on their ability to accurately and reliably test the functionality and performance of finished pen injectors and autoinjectors, while assembly machines are evaluated based on their ability to consistently and accurately assemble the devices according to predefined specifications.

CONCLUSION

Teamtechnik develops high-quality and reliable testing machines in line with international standards and regulations. By doing so, the company contributes to its broader goal of enabling its customers to produce and bring consistently high-quality medical devices to the market – and thereby contributing to improving overall patient health and safety.

Drawing from its rich history in custom machine building, teamtechnik has acquired a deep understanding of the unique challenges and complexities involved in the production and testing of pen and autoinjector devices. This expertise, coupled with the company's proven track record in qualification and validation of complex automation machines, uniquely positions teamtechnik as a leading automated testing equipment manufacturer for pen injectors and autoinjectors. Combined with the company's knowledge and commitment to compliance with EMA, FDA and ISO standards, it means teamtechnik can deliver cutting-edge testing solutions that not only meet but exceed the industry's most stringent regulatory and quality demands.

Teamtechnik customers can be confident of receiving a state-of-the-art automated testing solution tailored to their specific needs, designed to uphold the highest standards of quality and regulatory compliance, and thoroughly validated and qualified to ensure the utmost precision, accuracy and reliability.

ABOUT THE COMPANY

Since 1976, teamtechnik has specialised in assembly and test systems for the e-mobility, medtech and new energy sectors of the future. Together with HEKUMA (Hallbergmoos, Germany), BBS Automation (Munich, Germany) and Kahle Automation (Caravaggio, Italy), teamtechnik is part of the Dürr Group (Stuttgart, Germany). Teamtechnik has 2,400 employees at 21 locations on three continents. In its production spaces, covering more than 125,000 m², the group develops custom automation solutions for complete production processes that set standards in terms of efficiency, safety, reliability and innovation. It is able to do so thanks to its comprehensive service portfolio of platforms and processes, and its expertise in feeder technology, palletisation and software.

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ABOUT THE AUTHORS

Hisham Jamal is a Senior Account Manager in teamtechnik's Medtech division. He has a technical and business background, with experience in diverse roles ranging from engineering consultant and application engineer to technical sales, and a wealth of international experience from Asia, the Middle East and Europe. Mr Jamal brings multidimensional expertise and perspective that helps him to understand his clients' requirements and enables him to offer innovative solutions at the forefront of medical device assembly and testing.

Carsten Köhler, DBA, is Vice-President Sales and Project Management in the Medtech division of teamtechnik. For more than 10 years, he has specialised in automation solutions for medtech devices. Before joining teamtechnik, Dr Köhler led specialised teams for medtech automation as a Director of Engineering. His expertise includes project planning, mechanical/electrical design, software, qualification and documentation.

MicroMED
Precision Drug Delivery Platform

ADVANCING SUBCUTANEOUS DELIVERY OF BIOLOGICS: A NOVEL REUSABLE MEMS-ENABLED ACTUATOR

In this article, Hong-Jun Yeh, PhD, Chief Operating Officer at MicroMED, and Jiunn-Ru Lai, PhD, Associate Professor, and Tsung-Chieh Cheng, PhD, Professor, both at Kaohsiung University of Science and Technology, explore the challenges and opportunities related to the subcutaneous delivery of biotherapeutics. They also highlight a novel reusable MEMS-enabled pneumatic actuation system designed to overcome these challenges.

The biologics drug market continues to grow rapidly, with subcutaneous (SC) administration becoming increasingly popular due to health-economic reasons and advancements in delivery technologies. Biologic therapeutics have transformed the ability to effectively treat diseases in areas such as oncology, inflammation, diabetes and cardiovascular, immunological and genetic/metabolic disorders. Unlike small-molecule drugs (oral tablets), biomacromolecules have the unique ability to bind with targeted cells during therapeutic treatment and prevent unwanted drug-to-drug interactions. However, rapid enzymatic degradation and poor absorption in the harsh environment of the gastrointestinal tract limit its administration to parenteral (mainly injectable) routes.

The discovery and development efforts of biologic therapeutics have been the focus of the biopharma industry in recent decades. As a result, the global biologics market size was valued at US$512 billion (£405 billion) in 2023 and is projected to grow at a compound annual growth rate of 10.3% from 2023 to 2030, reaching $1,009 billion.[1]

> "The discovery and development efforts of biologic therapeutics have been the focus of the biopharma industry in recent decades."

One major active area in terms of new biomacromolecule development in recent years is high-concentration antibodies, such as monoclonal antibodies (mAbs). Since their introduction as therapeutic drugs, mAbs therapies have enjoyed tremendous commercial success with continuous growing opportunities. Due to their success in treatment over the past two decades, the global therapeutic market for mAbs is projected to grow to about $300 billion by 2025.[2] As of 2023, mAbs are also the most marketed biologic, with over 4,000 mAbs undergoing preclinical or clinical development.[3] One key reason for the success of mAbs in the therapeutic sector is SC self-administration, which also helped expedite the advancement of biologics formulation and device functionality.

Injectable routes serve as alternative approaches for drug administration, distinct from the oral/digestive route. The injectable drugs market is projected to witness continued growth, with an expected market valuation of $937 billion by 2032.[4] Intravenous (IV) and SC routes are the primary administration routes within the injectable market. However, in recent years, biologics delivery has shifted noticeably from IV to SC. This trend is driven by both health-economic factors and advancements in SC drug delivery technologies.

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Spurred by technological advancements addressing the demand for high-dose delivery of biotherapeutics, emerging trends in SC drug delivery can be largely categorised into two areas. Firstly, novel formulations enable the development of higher-concentration biotherapeutics (>200 mg/mL) while also mitigating concerns related to aggregation and inherent immunogenicity. Another key formulation advancement is the incorporation of the dispersion enhancer recombinant human hyaluronidase (rHuPH20) to enhance the absorption of injection volumes in the SC space, while maintaining drug stability throughout their target shelf life.[5,6,7]

Secondly, novel device technologies facilitate the delivery of larger doses through increased volumes and/or concentration. These technologies including autoinjectors with 5 to 10 mL volume, on-body injectors/on-body delivery systems (OBIs/OBDSs) with 20 to 50 mL volume, and ambulatory infusion pumps with 10 to >250 mL volume, are all capable of handling higher drug concentrations of 120 mg/mL or above subcutaneously. Although many of these device technologies are still in development and require clinical validation and eventual approval for commercial use, the SC route of administration is expected to continue its growth trajectory in the foreseeable future.

Previously, MicroMED presented two technical papers in ONdrugDelivery to discuss the technical data and applications of the single-use microelectromechanical system (MEMS)-enabled actuator.[8,9] This article aims to provide a comprehensive review and discussion of the current landscape of the SC drug delivery system (DDS) for biotherapeutics. It will specifically focus on examining the challenges and opportunities associated with these systems, emphasising new device functionalities and capabilities. The primary focus is on device functionality aspects, therefore, the article will not take physiological and pharmacokinetic (PK) factors into consideration to avoid unnecessary complexity.

With a focus on emerging opportunities, this article introduces MicroMED's innovative reusable MEMS-enabled actuator. It presents its working principles, supported by the functional test data, and conducts a comparative analysis with other DDSs using existing drivers to demonstrate how the novel actuator is capable of fulfilling the unmet needs resulting from emerging trends in the overall DDS market.

> "Compared with IV, SC delivery of biologics eliminates the need for frequent hospital visits, reduces the risk of infections and infusion-related reactions, and provides a more convenient and flexible treatment option."

SHIFTING FROM IV TO SC

Compared with IV, SC delivery of biologics eliminates the need for frequent hospital visits, reduces the risk of infections and infusion-related reactions, and provides a more convenient and flexible treatment option.[10] Successful examples of introducing the SC route for biologics delivery after IV route approval have established compelling cases for the SC route due to health-economic advantages. These are some of the reasons why the SC route of administration is being considered more often than IV when dealing with formulation, stability evaluation and final commercialisation. SC applications can also serve as a lifecycle management strategy for a particular indication when competition is a consideration. The following are key reasons why cases of shifting from IV to SC will continue to increase:

- Easier dosing for SC than IV
- Fixed-dose regimen versus complicated bodyweight-adjusted dosing
- SC is easier to handle for combination therapy[11,12]
- Convenience: self-administration at-home setting
- Increased compliance due to patient convenience and preference
- Cost and time saving – fewer healthcare professionals, facilities and resources required
- Challenges posed by situations like covid-19 or any other pandemic, making travel for IV treatment difficult
- Remote monitoring due to Internet of Things availability
- Higher doses are possible through SC formulation advances, such as high-concentration or higher-volume SC injections by adding dispersion/absorption enhancers (sequential injection) or co-administration with rHuPH20.

Some existing examples of converting from IV to SC routes that have achieved both technical and commercial success include daratumumab, rituximab, adalimumab and trastuzumab.

OVERALL LANDSCAPE OF SC BIOLOGICS DELIVERY SYSTEMS AND NEW TRENDS

The overall SC DDS market for biologics is influenced by various factors, including the following:

- Continued growth of the biotherapeutic market
- Shift from IV to SC administration
- Maintenance of the competitive edge due to devices with similar indications and biosimilars
- Cost reduction
- Device and drug lifecycle management
- New DDS functionalities/designs to meet emerging trends and requirements.

New functionality and design considerations:

- Unique biologics formulations that require specific concentration, volume and flow rate
- Reusability (multiple injections) and recyclability (components) to address sustainability needs
- Flexible and accurate control of dosage and flow rate
- Human factors engineering (HFE), tolerability, human-machine interface (HMI) with connectivity, and digitisation to improve patient compliance and safety
- Non-traditional actuation methods for unique applications without using traditional primary containers like prefilled syringes (PFSs) or cartridges
- Addressing issues associated with traditional SC DDSs that use spring, motor, elastic material or gas cylinder-driven mechanisms.

Figure 1 illustrates the current landscape of the SC biologics DDS market.

Two main points to consider when reviewing the DDS landscape:

1. **Formulation-related factors including concentration, volume and dosage:**

a. Formulation stability evaluation, encompassing manufacturing, storage, transportation and drug delivery processes.

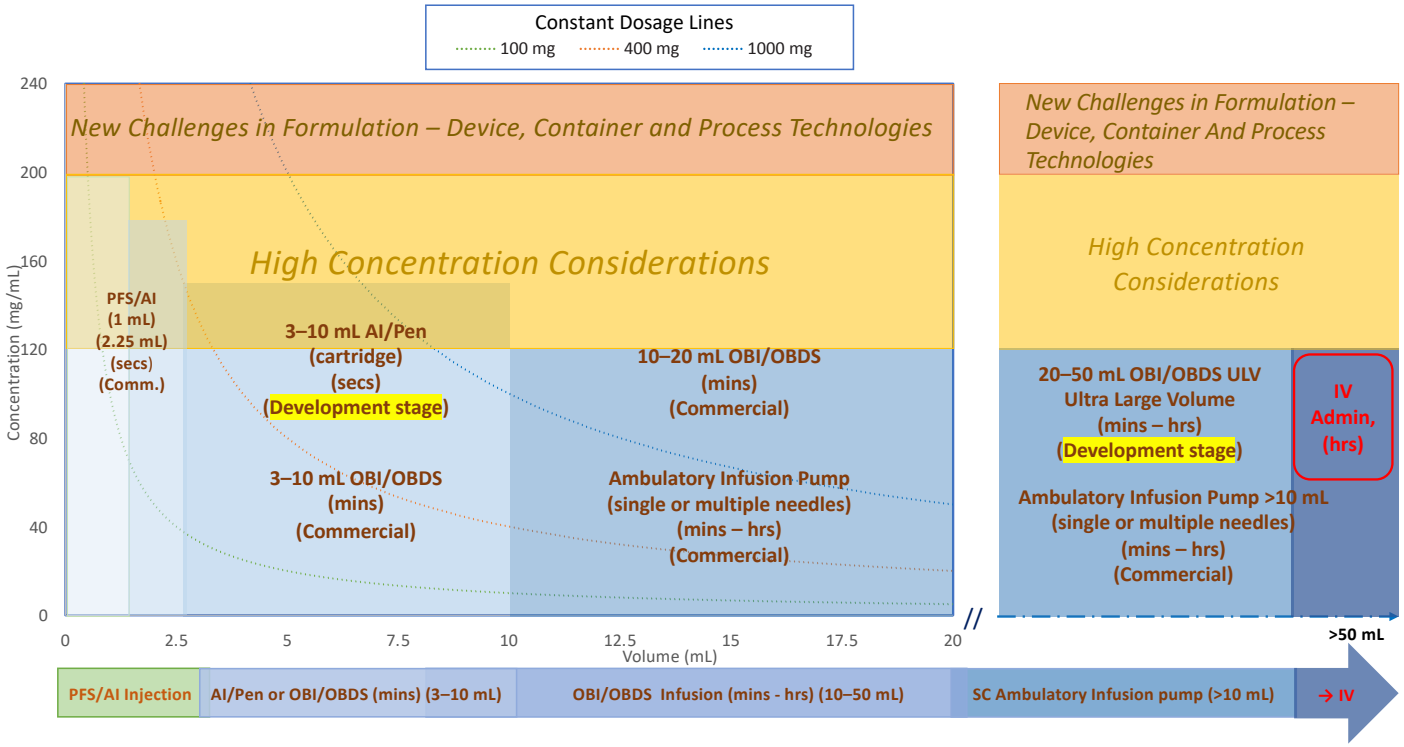

Figure 1: Overall SC delivery device design space/landscape.

> "By considering formulation-related factors and human factor/tolerability aspects, manufacturers can design and develop effective and patient-friendly delivery systems."

b. Volume, concentration and injection/infusion duration are typically considered together, determining whether a small volume at high concentration with short duration (mainly for autoinjector/pen) or a high volume at low concentration or high volume at high concentration with short or long duration (mainly for OBI or infusion pump) is preferred for the same dose. These are the main consideration factors for device selection.
c. Concentrations >120–200 mg/mL pose potential formulation development challenges and risks.
d. Concentrations exceeding 200 mg/mL are considered difficult to develop and require careful consideration.[13]
e. Constant dosage lines at 100, 400 and 1,000 mg are represented by these three curve lines (typical trend is from upper left to lower right).
f. Higher-volume formulations may leverage dispersion/absorption enhancers with rHuPH20. Either pre-injecting rHuPH20 followed by the injection of therapeutic biologics or incorporating rHuPH20 into the formulation development can enhance permeation in the SC space.
g. Additional considerations needed for fixed-dose combination therapies requirements.

2. **Human factor and tolerability considerations affecting formulation and device design:**

a. Pain and sensation associated with injection or infusion, may be influenced by factors such as viscosity, volume, speed of injection, needle size and formulation
b. Injection or infusion duration, varying from seconds to minutes or hours
c. Frequency of injection or infusion
d. Patient skin reactions, such as swelling, wheal formation and erythema
e. Impact on quality of life, evaluating injection time length, frequency, wearable (adhesive) or portable (belt, strap) options
f. Usability enhancements through HMI, connectivity (built-in or add-on) and digitisation to improve patient compliance and safety.

Review of the Current DDS Market Landscape

As indicated in Figure 1, the existing DDSs can be categorised into three main groups. These categories provide an overview of the current landscape of SC biologics DDSs. By considering formulation-related factors and human factor/tolerability aspects, manufacturers can design and develop effective and patient-friendly delivery systems.

1. **PFS with needle safety device, autoinjectors and pen injectors** (left-hand side of Figure 1):

a. This category includes 1 and 2.25 mL PFS and autoinjector devices with a wide range of concentrations.
b. Dose volumes of 1 and 2.25 mL are commercially available for PFSs, autoinjectors and pen injectors.
c. Larger-volume autoinjectors (5–10 mL),[14] (cartridge-based) are available for development studies but not yet commercially available.
d. Key characteristics include short injection times (<30 seconds)[15] to meet human factors and usability requirements, although more clinical trials and regulatory confirmation are needed.
e. Short injection time requirements limit volumes.
f. Higher concentrations (120 mg/mL or higher) are often needed to achieve the

desired dosage due to volume limitations. They require more careful stability evaluation, such as aggregation and immunogenicity.

g. Formulations for larger-volume devices (e.g. 5–10 mL) may incorporate dispersion/absorption enhancers with rHuPH20.
h. Limited number of reusable autoinjectors/pens are commercially available.
i. Spring, gas cylinder and motor-driven autoinjectors/pen injectors are available, but they all have pros and cons. The key challenges are the handling of high concentration (high viscosity) where you have to consider sufficient force output from the drivers and glass container breakage due to high initial impact.

2. **Wearable OBIs, OBDSs or large-volume injectors:**

a. Dose volumes range from 3 mL to 50 mL, although commercially available DDSs are limited to the 3–20 mL range. The upper limit for on-body wearable devices is typically 50 mL due to size and weight limitations
b. Injection or infusion times can vary from minutes to hours, depending on volume and dosing regimen requirements
c. Drive mechanism – mechanical (spring-based or elastomeric tube-based) and motor-based electromechanical OBIs are available.
d. Primary containers include PFSs, cartridges and custom-made special containers
e. Vial or PFS transfer units are available when special containers are used
f. The needle insertion unit includes a soft tube that remains in the SC tissue for the duration of the injection or infusion
g. Manual connections with infusion sets can be designed for single or multiple needle site infusion sets instead of the needle insertion unit.

3. **Infusion pumps (ambulatory)** (mainly on the right-hand side of Figure 1):

a. Dose volumes range from 10 mL to over 250 mL and can be wearable/portable using a belt or strap
b. Flow rate for infusion pumps tends to be on the lower side due to larger volume and longer infusion duration. This helps to accommodate infusion of drugs with higher concentration
c. Spring-driven mechanical pumps are typically larger in size, use standard disposable syringes and are equipped with some flow-rate controls. Their typical cost is lower compared with motor driven ones
d. Elastomeric container-driven mechanical pumps are also available for low-cost options with less flow accuracy
e. Motor-driven electromechanical pumps with more user settings and accurate controls are available. Some pumps need custom-made syringes, and they are typically reusable but more expensive
f. Infusion sets with flow-rate control allow for single or multiple needle site infusion (high total infusion rate)
g. Higher-energy driving mechanisms compared with OBI devices are needed due to the extra flow resistance from the long tubing of the infusion set.

Emerging Trends in SC Biologics DDS

To ensure effective treatment, higher doses of biotherapeutics are crucial, leading to the development of new technologies that address formulation and device functionality. On the formulation side, advancements in higher-concentration formulations and formulations incorporating absorption/dispersion enhancer rHuPH20 offer additional solutions for delivering high doses of biotherapeutics through various DDSs.

New Trends for Autoinjectors and Pen Injectors

- Expanded range of volume selection: 3–10 mL
- Wide range of viscosity selection: 1–100 cP
- Short delivery time: <30 seconds at 10 mL
- Faster flow rate range: 0.06–0.9 mL/s
- Use of rHuPH20 for high volumes (>3 mL)
- Reusability for sustainability
- Usability enhancements through HMI, connectivity and digitisation to improve patient compliance and safety.

Higher-concentration formulations enable high-dose delivery in small volumes, particularly for autoinjector and pen injector applications requiring short injection times (<30 seconds). When larger volumes (5–10 mL) are needed for autoinjector and pen injector applications, pre-injecting rHuPH20 followed by the injection of therapeutic biologics or incorporating it into the formulation can enhance permeation in the SC space. However, clinical and regulatory confirmation for autoinjector/pen injection devices with volumes exceeding 3 mL is necessary for commercial use. Currently, few commercially available autoinjector/pen devices feature reusable drive units and disposable container designs, but sustainability efforts aiming to minimise material waste have become essential. Connectivity features, including digitisation, can be built in or added as an optional feature for DDSs.

New Trends for Wearable OBIs

- Expanded range of volume selection: 3–50 mL (limited to 50 mL due to drug and device weight and size considerations for patient convenience)
- Wide range of viscosity selection: 1–80 cP
- Wide range of injection/infusion time selection: minutes to hours
- Flow rate range: 0.01–0.07 mL/s or 0.6–4 mL/min
- Option for using rHuPH20
- Exploring new driving mechanisms beyond the traditional linear actuation for space efficiency with flow control
- Single and multiple needle sites with infusion set connection for large volumes
- Solution transfer options: direct transfer from PFS or vial
- Reusability for sustainability
- Usability enhancements through HMI, connectivity and digitisation to improve patient compliance and safety.

SC OBIs and OBDSs address the need for larger-volume applications (3–50 mL). They are driven by competition in the biosimilars market and formulation challenges of higher-concentration biologics required for autoinjectors are limited to dose volumes of 1 and 2.25 mL. Currently, only a limited number of OBI/OBDS devices with volume between 3 and 20 mL are commercially available but all lack reusable drive designs. Many OBI/OBDS devices with different drivers, design approaches and specifications are still in the development stage. Motor-driven OBIs/OBDSs are mainstream in this category due to their design flexibility. But drawbacks like too many moving parts required are making higher-volume (>20 mL) OBIs/OBDSs very challenging.

New Trends for Wearable Infusion Pumps (Ambulatory)

- Expanded range of volume selection: 10 to >250 mL (patient convenience considerations)
- Wide range of viscosity selection: 1–50 cP
- Expanded range of infusion time selection: minutes to long hours
- Slower flow rate range: 0.01–0.04 mL/s or 0.6–2.5 mL/min
- Single and multiple injection/needle sites with infusion set connection
- Adjustable flow rate
- Option for using rHuPH20
- Exploring new drive mechanisms beyond the traditional linear actuation for space efficiency with accurate flow control
- Exploring better design to address rapid push SC immunoglobulin (SCIg)
- Reusability for sustainability
- Usability enhancements through HMI, connectivity and digitisation to improve patient compliance.

Infusion pumps have been used for IV delivery applications for many years. However, there is a shift towards SC delivery for infusion pump applications, such as IV immunoglobulin (IVIg) and SCIg, which are available for Ig replacement therapy for primary immunodeficiency and chronic inflammatory demyelinating polyneuropathy.[16] SCIg offers advantages such as simpler operation and shorter infusion durations.

With advancements in formulation and device technologies for larger-volume (10 to >250 mL) SC delivery, there is a need to reassess the functionalities of existing ambulatory infusion pumps to meet specific SC delivery requirements, including:

- Higher flow rates (shorter total delivery time), higher drug concentrations and volume (leveraging rHuPH20) necessitating larger driving forces
- Rapid push SCIg has gained more popularity than conventional pump infusion with shorter injection time and slightly more frequent injections[17]
- Patient convenience, achieved through pump size reduction for wearable/portable devices and ease of self-administration
- Improved convenience in terms of handling solution transfer from containers that are typically used for SC injection including lyophilised products.

Summary of the Unmet Emerging Trends for SC DDS – New and Expanding Requirements

The following high-level trends address the unmet needs and expanding requirements in SC DDSs for autoinjectors/pen injectors, OBIs/OBDSs and infusion pumps:

1. Adaptable drive platform to address wider volume, concentration and flow rate range
2. Scalable size based on different demands and applications
3. Flexible, simple and reliable in terms of design for manufacturing and assembly
4. Reusable and low energy consumption drive unit to reduce cost and address sustainability concerns
5. Flexible and accurate control of dosing regimen (dosage and flow rate)
6. Usability enhancement through HMI, connectivity and digitisation for patient compliance and safety
7. Non-traditional actuation methods for unique applications without traditional primary containers
8. Addressing performance issues and design limitations of traditional spring, motor, gas cylinder and elastomeric container driven DDSs.

NEW REUSABLE MEMS-ENABLED PNEUMATIC ACTUATOR ADDRESSING EMERGING TRENDS OF SC DELIVERY OF BIOLOGICS

As indicated in the previous summary, there is a need for a better and versatile drive mechanism platform for the DDS market that can meet the ever-evolving new requirements coming from the emerging trends. As a start-up medtech company, MicroMED has a patented MEMS-based core technology that offers a perfect drive mechanism platform for flexible DDSs focusing on – but not limited to – the SC route.

Working Principles

The MEMS-enabled actuator is a gas micropump-based system that offers a simple, small size, robust and powerful solution to address emerging unmet needs in drug delivery. The actuator leverages the unique capabilities of MEMS technology to provide a highly efficient and precise solution for SC drug delivery. MEMS technology enables the integration of mechanical and electrical components on a microscopic scale, allowing for miniaturised and high-performance systems.

Figure 2 illustrates the initial version of the form factor for the MEMS-enabled actuator. With the simplicity and few components

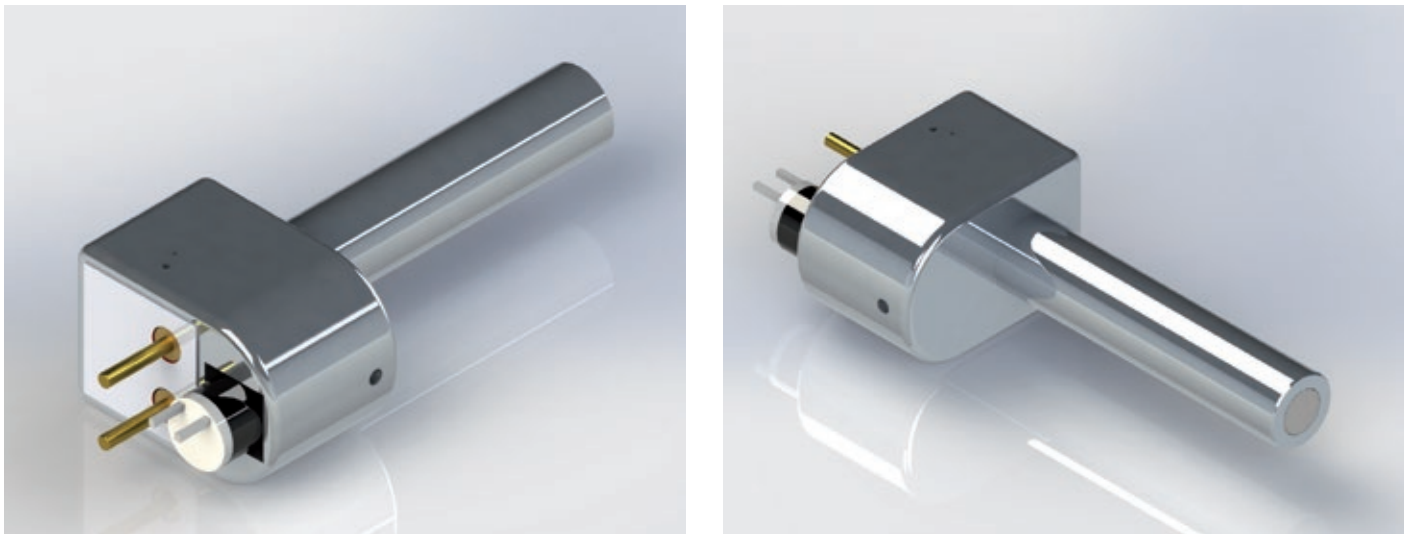

Figure 2: Reusable MEMS-enabled actuation system – MicroMED Primary Actuator®.

"The MEMS-enabled actuator is a gas micropump-based system that offers a simple, small size, robust and powerful solution to address emerging unmet needs in drug delivery."

needed to integrate the actuator into a final delivery device, MicroMED has the flexibility to adjust the form factor based on the requirements of the final device products.

As indicated in Figures 3 and 4, the actuator is a gas micropump that employs MEMS technology and electrochemical principles to convert electrolyte into gas pressure in a fast and controlled manner. In the actuator, the MEMS microelectrodes, controlled by a printed circuit board assembly, interact with the electrolyte to initiate instantaneous gas generation. This precise control over gas generation enables accurate gas pressure output, resulting in a force output from the telescopic plunger rod. The plunger rod pushes the plunger stopper forwards until it reaches the end of the syringe barrel, completing a single injection cycle as indicated in the middle diagram of Figure 4.

Figure 4 shows the key steps of the actuator operation. After the injection, when the power is turned off, the valve opens and releases the gas pressure. The stretched spring then initiates the retraction of the plunger rod, preparing it for the next injection cycle. The actuator's design allows for a high conversion ratio of electrolyte volume to gas volume, typically 1:1,000. This means that a single load of 1 mL of electrolyte can generate 1,000 mL of gas volume, enabling multiple injections with a single load of electrolyte.

Table 1 shows the existing product specifications for the primary actuator, including the new reusable actuators.

The actuator demonstrates consistent injection cycles, even without any sophisticated feedback control, as shown in Figure 5. The graph illustrates the results of 36 injections using a 2.25 mL drug-filled PFS with 60% glycerine (~10 cP). With monthly injections, the actuator can provide three years of shelf life for the final delivery device. This is the first batch of MicroMED's initial

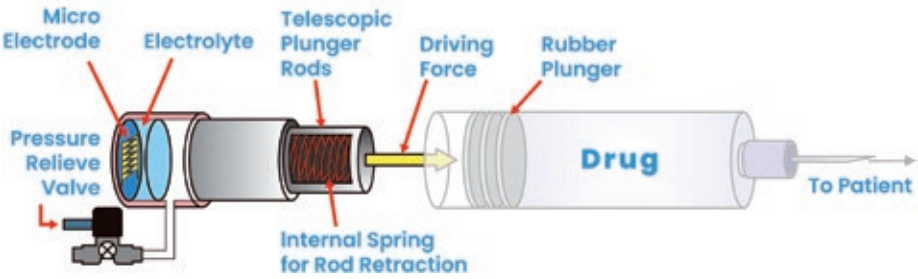

Figure 3: Reusable MEMS-enabled actuator – key components.

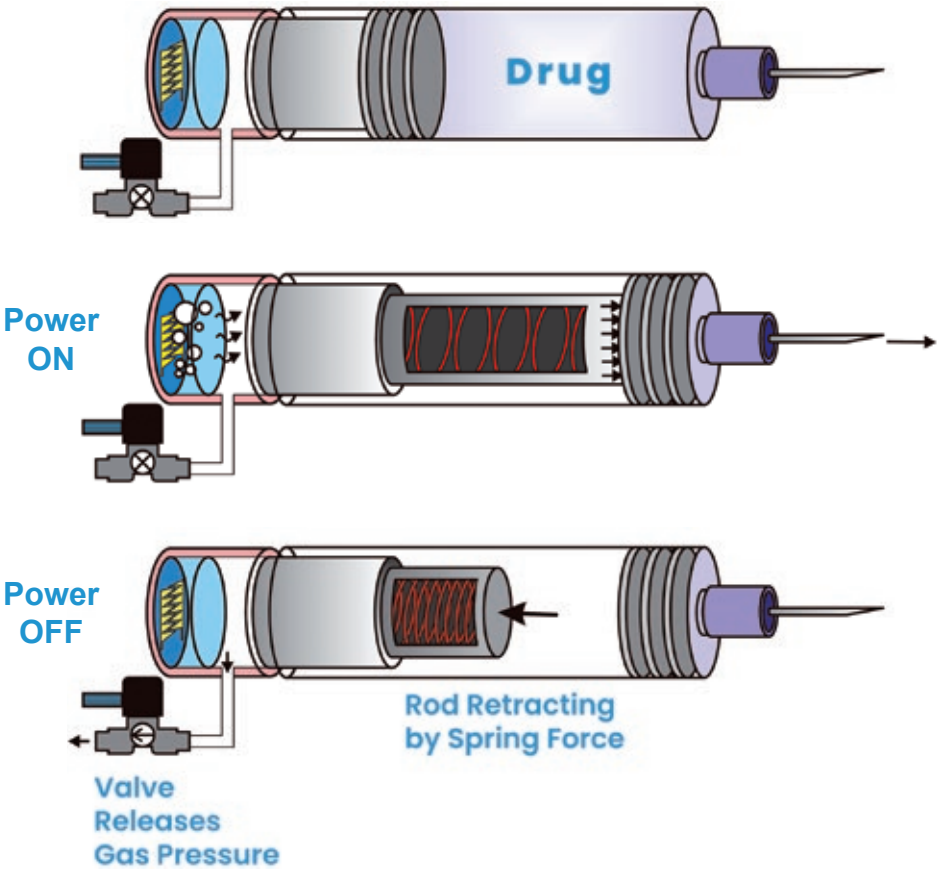

Figure 4: Operation steps.

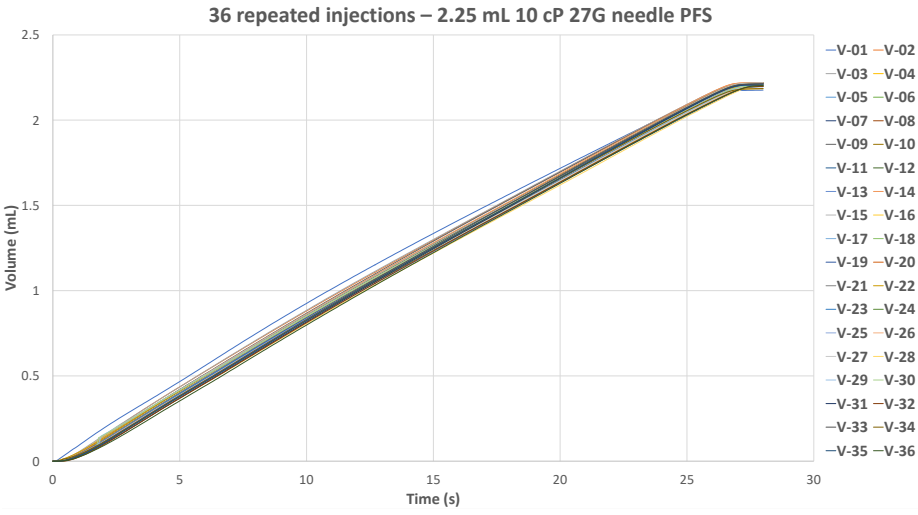

Figure 5: Reusability test data – 2.25 mL 10 cP PFS 27G needle with MEMS-enabled actuator.

Main Application	10 mL OBI	2.25 mL AI	5 mL AI	50 mL OBI/Infusion Pump
Model	PA-J Series	PA-E Series	PA-H Series	–
Container	Cartridge	PFS	PFS	Custom Syringe
ISO Certified	Yes	On-going	On-going	–
Single-use/Reuse	Single	Reuse	Single	Reuse
Injection Volume	10 mL	2.25 mL	5 mL	50 mL
Max Input Voltage (VDC)	7.5 V	10.5 V	10.5 V	7.5 V
Max Input Power	15.0 W	31.5 W	31.5 W	15.0 W
OP. CONDITIONS: **Voltage (VDC)** **Power** **Viscosity** **Needle Size** **Flow Rate** **Injection Time**	 4V 0.4W 8.5 cP 26G Up to 1 mL/min 10 min	 7.5V 15.0W 20 cP 27GTW Up to 4.5 mL/min 30 sec	 7.5V 15.0W 8.5 cP 26GTW Up to 10 mL/min 30 sec	 5V 1W 15 cP 26G Up to 1 mL/min 50 min
Stroke	39 mm	41 mm	46 mm	46 mm
Maximum Static Force	1,000 N	1,000 N	1,000 N	1,000 N
Ingress Protection*	IP66	–	–	–
Operating Temperature	0°C–60°C (32°F–140°F)	0°C–60°C (32°F–140°F)	0°C–60°C (32°F–140°F)	0°C–60°C (32°F–140°F)
Operating Noise	<30dB	<30dB	<30dB	<30dB
Pin Length	11.9 mm	11.9 mm	11.9 mm	11.9 mm
MATERIALS: **Telescopic Rods** **Actuator Housing** **Input Pins**	 Stainless Steel Polycarbonate Copper	 Aluminium Alloy Aluminium Alloy Copper	 Stainless Steel Polycarbonate Copper	 Aluminium Alloy Aluminium Alloy Copper
DIMENSION: **Housing Body** **Rod**	 23x23x16.3 mm 13(D)x16.3(L)mm	 17x25x16 mm 8.5(D)x38.8(L)mm	 18x18x16.3 mm 1.5(D)x41.8(L) mm	 21x21x11.5 mm 15(D)x53(L) mm

** IEC 60529 standard tested.*

Table 1: Existing product specifications for the primary actuator®.

reusable actuator design. The company is continuing to optimise the design to further advance the performance of the actuator. Even with the first test batch, performance remains very stable, showcasing its reliability and repeatability.

Additionally, the company is validating its actuator design to ensure the actuator's recyclability. After completing its first shelf life, the actuator can be recycled, refilled with electrolyte and recalibrated for use in a new DDS. This feature enhances sustainability and cost-effectiveness by extending the lifespan of the actuator.

The actuator can be configured as a linear actuator, where the gas pressure is transmitted through an enclosed telescopic plunger rod system, or 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.

Why Choose a MEMS-Enabled Actuator?

The following list summarises the advantages of using the MEMS-enabled actuator as a platform for the drive mechanism of different DDS needs:

1. Sustainability: reusable per single shelf life and recyclable actuator to address sustainability
2. Small but scalable size, low energy consumption and low costs
3. Precision control – dose and flow rate
4. Low impact but powerful force output
5. Adaptable to existing autoinjectors/pen injectors, OBIs/OBDSs, infusion pump DDSs and new unique gas pump applications
6. Ability to address high-volume/viscosity biologics delivery
7. Linear and nonlinear actuation to address unmet SC delivery needs and other unique applications
8. Usability enhancement by integration of HMI and connectivity for digitalisation and patient compliance and safety.

Figure 6 demonstrates the simplicity of integration of a MEMS-enabled actuator into a prototype design of an OBI or ambulatory infusion pump. The layout diagram on the right illustrates the simplicity of adapting or integrating a MEMS actuator into an existing or new DDS. This integration showcases the actuator's capacity to deliver a 50 mL 5 cP solution using a 26G four-needle site infusion set within approximately 14 minutes with 15 repeated injections, as demonstrated in Figure 7. It is important to note that this test was conducted with a four-needle site infusion set that has a long tubing length of 70 cm, resulting in higher flow resistance compared with the regular fluid path of a typical OBI.

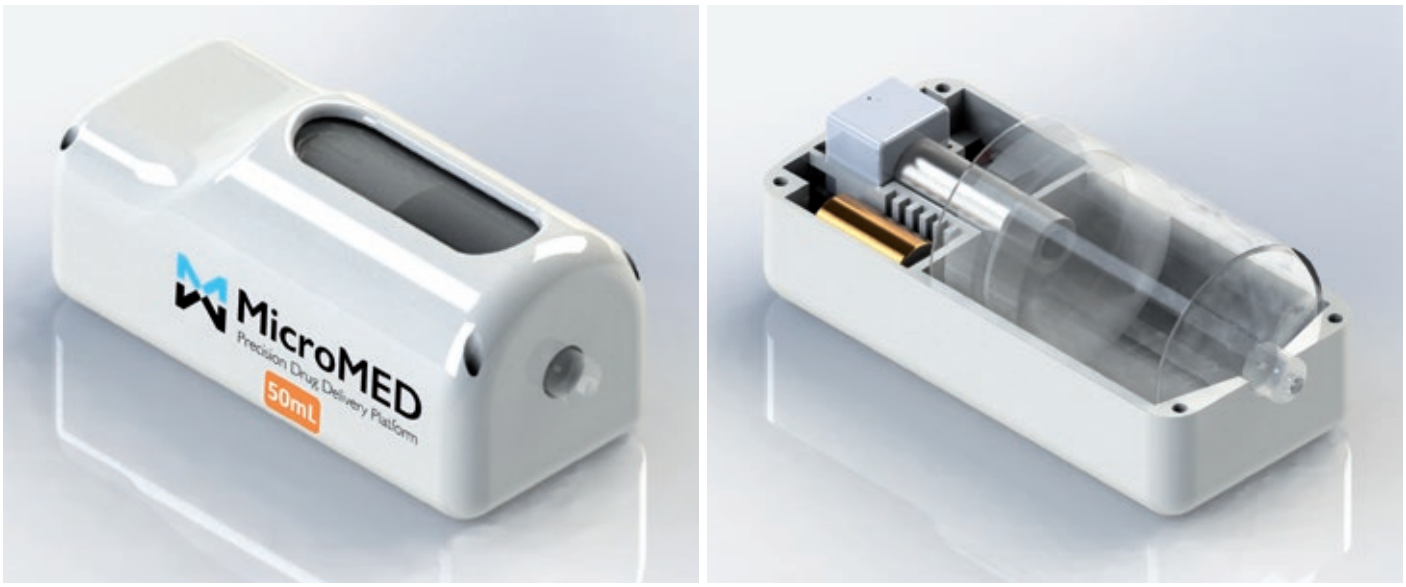

Figure 6: MEMS-actuator-driven 50 mL OBI ambulatory infusion pump – functional prototype.

"The development of a reusable and recyclable novel MEMS-enabled actuator addresses the emerging trends and unmet needs in SC delivery of biologics."

Comparison with Existing DDS Drivers

While no single driver can meet all the attributes and requirements for all DDSs, the MEMS-enabled actuator clearly stands out as the best candidate to address the emerging trends in SC biologics delivery. Table 2 (see over page) highlights the unique advantages of the MEMS-enabled actuator and underscores its suitability for the evolving requirements in SC DDSs.

When compared with existing drivers for SC DDSs, the MEMS-enabled actuator stands out due to its comprehensive capabilities and flexibility to adapt to existing delivery devices and adeptness to become a scalable platform for the overall DDSs. While other drivers may excel in specific areas, the actuator combines multiple desirable features, such as precision control, reusability, scalability, low energy consumption and integration with connectivity technologies. These advantages make it a promising solution to address the evolving trends and requirements in SC biologics delivery.

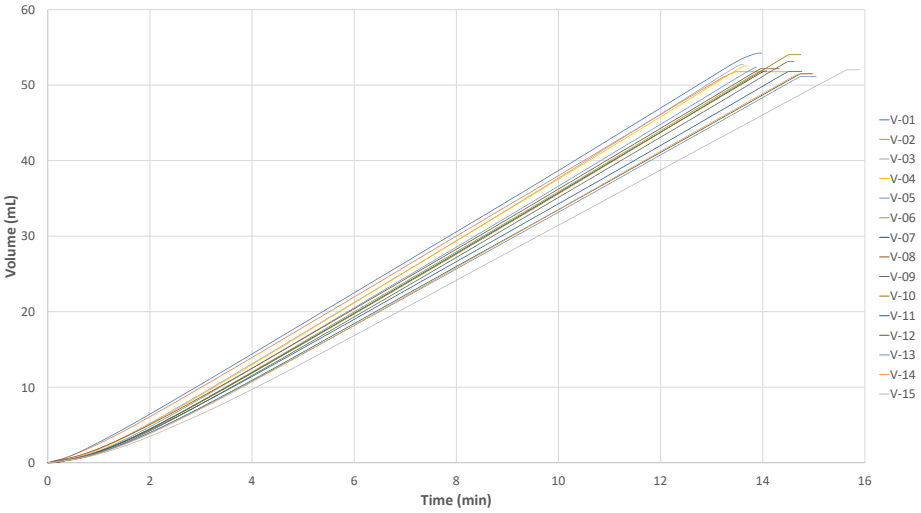

Figure 7: MEMS-actuator-driven ambulatory OBI/infusion pump (functional prototype) – delivers 15 repeatable injections of 50 mL 5 cP, 26G four-needle site infusion set in ~14 mins.

Addressing Unmet Needs and Unique Applications That Existing Traditional Driving Mechanisms Cannot Handle

The actuator's non-traditional (non-linear) actuation methods, such as gas micropump systems, offer unique advantages for specific applications. By deviating from traditional primary containers like PFSs or cartridges, the actuator opens up possibilities for innovative drug delivery approaches that require different non-linear mechanisms.

Some unique applications are listed below:

- The actuator can meet the size and power requirements of the tiny "smart pill" for oral administration of biologics applications.
- It can also provide a unique non-linear actuation mechanism for a space-efficient wearable/OBI that can deliver ~50 mL, high-viscosity biologics with reusability.
- Lastly, the gas micropump-based actuator can handle microdosing (such as intravitreal injection) applications that require µL scale volume with precision delivery control.

CONCLUSION

In summary, the development of a reusable and recyclable novel MEMS-enabled actuator addresses the emerging trends and unmet needs in SC delivery of biologics. It offers gentle, consistent and powerful performance based on simple electrochemical principles and efficient

Driver (Applications)	Spring (AI OBI IP)	Motor (AI OBI IP)	Gas cylinder (AI)	Elastomeric (OBI, IP)	MEMS Actuator (AI OBI IP)
Driving Mechanism	Spring force	Electro/mechanical Motor toque	Pneumatic	Elastic force	Electrochemical Pneumatic
Energy source	Preloaded spring induced stress	Battery	Pressurised gas Risks: leakage and high pressure gas storage	Energy transfer from user to elastic material	Battery
Container	PFS, Cartridge	PFS, Cartridge, custom built	PFS	Custom built	PFS, Cartridge, custom built
Flow rate control	No	Adjustable	Limited	No	Adjustable
Size	Small to med Size depends on force requirement	Large When large force is required Space for gear transmission	Medium	Small	Small MEMS miniaturised
Cost	Low	High	Med	Low	Med
Hardware/software	No	High	No	No	Low to med
Moving parts	Low	High	Med	Low	Low
Connectivity	Extra	Easy	Extra	Extra	Easy
Reusability	No	Yes	No	No	Yes
Platform adaption	Low	High	Low to med	Med	High
Adaptable to all existing AI, OBI, infusion pump	Low to med	High	Low to med	Low to med	High
Overall comments	Cheap Simple assembly High impact glass damage Uneven flow rate Large size spring – larger container Single use	Precision control Flexible platform adaption Connectivity HMI + display Reusability Expensive Complex assembly Complex HW/SW Many moving parts Large size & power for large torque Noise due to high revolution	Soft impact Simple assembly Long term stored pressured gas Leak risk Gas exhaust management Gas sensitive to environment Limited suppliers	Cheap Simple assembly Small size Inconsistent flow rate Limited elastic force strength Single use	Soft impact Simple assembly Precision control Flexible platform adaption Connectivity HMI + display Low energy Reusability Scalable small to big Recyclable actuator-refillable electrolyte Novel technology – development time

Table 2: Comparison of the current driving technologies for the SC DDS (autoinjector, OBI, infusion pump). Performance rating – green: pros, red: cons, blue: mediocre.

energy transfer. It allows for the precise control of flow rate and dose, while supporting both linear and nonlinear actuation for traditional and unique applications. The design is flexible and scalable, accommodating a wide range of dose volumes and viscosities. The reusable actuator also includes connectivity and digitisation features that enhance its versatility and sustainability to ensure its readiness for the eco-friendly environment and the upcoming artificial intelligence era.

ABOUT THE COMPANY

MicroMED is a MEMS-enabled drug delivery actuation systems design/manufacturing medtech company located in Taipei, Taiwan. MicroMED has developed a novel MEMS-enabled actuator that addresses emerging trends and unmet needs in SC and unique drug delivery applications. It offers gentle, consistent and powerful performance based on simple electrochemical principles and efficient energy transfer. The system allows for the precise control of flow rate and dose through either linear or non-linear actuation. The design is also flexible and scalable, accommodating a wide range of dose volumes and viscosities. In addition, it is both reusable and recyclable, while also capable of integrating connectivity features, allowing it to address emerging sustainability and digitisation/artificial intelligence trends. MicroMED welcomes partnerships across the SC drug delivery value chain, including biopharmaceutical, medical device developers and insurance payers through

the purchase of existing actuator products, co-development of advanced injector products or licensing of its micro-engine proprietary/intellectual properties.

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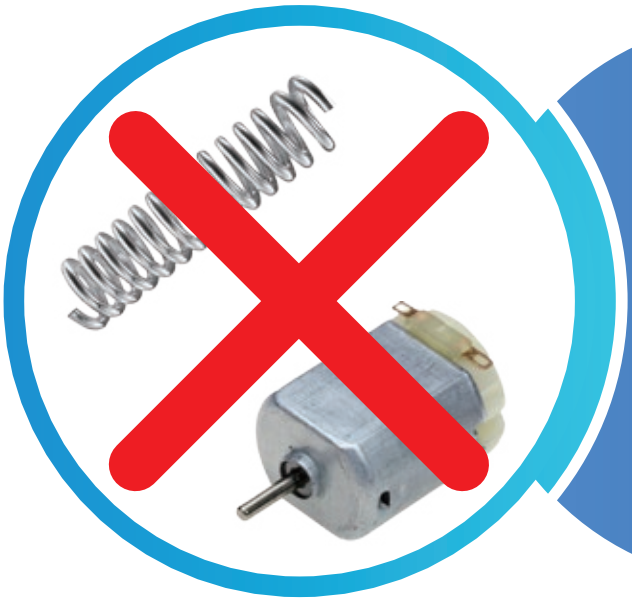
Hong-Jun Yeh, PhD, is MicroMED's Chief Operating Officer. Dr Yeh focuses on business strategic planning, client/partner development, leading and managing programmes and teams in drug/device combination product commercialisation and life cycle management through the integration of biologics process development, drug delivery device R&D, overall manufacturing processes and business development. Dr Yeh has 30+ years (post-PhD) of diversified experience across R&D, manufacturing, supplier/CMO/quality/risk management, programme management, and business development in the consumer products and biopharma/medical device industries at places like EWI, Baxter, J&J, Amgen Inc. (16+ years) and EirGenix.

Jiunn-Ru Lai, PhD, leads the microcircuitry development in MicroMED. Dr Lai is an Associate Professor with the Department of Electrical Engineering at National Kaohsiung University of Science and Technology, Taiwan. Dr Lai received the Best Paper awards from the Taiwan Academic Network Conference in 2016 and 2018. His research interests include embedded systems, mobile and wireless networking, Internet of Things and network protocol performance analysis.

Tsung-Chieh Cheng, PhD, leads MEMS microchip production in MicroMED. Dr Cheng is a Professor with the Department of Mechanical Engineering at National Kaohsiung University of Science and Technology, Taiwan, and has over 25 years of experience in the field of MEMS manufacturing, heat and mass flow, and material characteristics. Dr Cheng has published more than 130 technical papers and holds 12 patents worldwide in MEMS and materials science.

MEMS Enabled Reusable Pneumatic Actuation

MEMS:
MicroElectroMechanical Systems



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