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ONdrugDelivery Issue N° 133, May 16th, 2022

INJECTABLE DRUG DELIVERY: FORMULATIONS & DEVICES

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

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PUTTING PROCESS ENGINEERING INTO ACTION

Here, Jonathan Kearns, Head of Project Engineering, and Kevin Huang, New Product Introduction Manager, both at SHL Medical, consider how engineering competencies are being driven to the next level by leveraging process engineering and how this can transform drug-device projects.

It would be remiss not to acknowledge that, in many industries at the intersection of science and engineering, there is an integrated network of disciplines that allow us to deliver products successfully. For example, the untrained eye may think that engineering is an all-encompassing field and profession that gets the work done in any manufacturing firm. This is partly true. However, the matter at hand is not just of semantic relevance but also practical, regarding *what* and *who* successfully delivers the work and commercial products to its targets across the value chain.

The concept of engineering has existed since ancient times, as evidenced by the invention of elementary but fundamentally groundbreaking tools, such as the lever, wheel and pulley. Much like science, problem-solving is common to all engineering work, with the ultimate goal of converting natural resources for use by humankind. From ancient times, engineering has evolved to become a complex and highly specialised field, with its subdisciplines branched according to their decreasing emphasis on science (Table 1). Now, there are chemical engineers who design and develop chemical manufacturing processes in the textile, food and pharma industries. There are also biomedical engineers who focus on advancing translational work in biology and medicine for the improvement of health. As the list goes on, it becomes increasingly apparent how important engineering is towards the continuous development of society.[1,2]

PROCESS ENGINEERING IN AUTOINJECTOR DEVELOPMENT

The autoinjector industry has seen the need to harness a mix of various engineering approaches to ensure quality devices reach the hands of patients across disease areas. After all, the US National Academy of Engineering identifies "engineering of better medicines" as one of the "14 Grand Challenges for Engineering" in the 21st century. SHL Medical, with more than two decades of historical work and experience, has seen how a number of relevant industrial competencies have matured over time to take their place in the conventional device development approach. In its active pursuit of leading the industry, as well as delivering beyond what is required, SHL Medical has actively devised ways to further develop and tightly integrate such competencies into its end-to-end device development process. Here, the authors would like to present *process engineering* – an actively evolving discipline within the organisation.

> "SHL Medical has actively devised ways to further develop and tightly integrate such competencies into its end-to-end device development process."

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Engineering Function	Description
Research	Research engineers seek new principles and processes using mathematical and scientific concepts, along with experimental techniques and inductive reasoning.
Development	Using creative application of new knowledge, development engineers apply the results of research for new purposes, such as creating a working model of a new electrical circuit, clinical process or industrial machine.
Design	Methods are selected by the engineer designing a structure or product and determines shapes and performance specifications to meet safety technical requirements.
Construction	Preparation of the site is the responsibility of the construction engineer. He/she also determines procedures that result in the desired quality, economically and safely, and directs the placement and organisation of materials, personnel and equipment.
Production	Processes and tools are selected by the production engineer who is responsible for the plant layout and equipment selection. He/she also integrates the flow of materials and components and presents for testing and inspection.
Operation	Machines, plants and organisations providing power transportation and communication are all controlled by the operating engineer. Personnel supervision is also within his/her remit to ensure reliable and economic operation of complex equipment.
Management and other functions	In this category, the analysis of customer requirements falls under the engineer's responsibility. He/she also resolves problems and recommends units to satisfy economical needs.

Table 1: Engineering functions and their brief descriptions adapted from Ralph J Smith, Professor Emeritus of Electrical Engineering at Stanford University, CA.

"The importance and edge of having a well-developed process engineering function is clearly evident for SHL Medical, whose vertically integrated ecosystem allows it to design and develop its own tools and machines that produce its autoinjector devices."

One may ask, what is process engineering and what do process engineers do? As process engineering is a rather complex and continuously developing field, it would be quite difficult to formulate a textbook definition. Nonetheless, process engineering in general (as well as how it is attributed within SHL Medical) is primarily responsible for the design, implementation, control and eventual optimisation of the production process. Process engineers work as intermediaries between product design engineers and production teams – at the outset, focused on transforming raw materials into finished products via the process in question.[3]

In more practical terms, a process engineer has the know-how to make products while ultimately considering quality and cost. In a review paper on process engineering, Hartfield and Vezza (2016) interestingly describe a process engineer as one who "sees the manufacturing equipment and materials as one entity in a state of flux". Their description is, however, resonant to the fact that reducing complexity and process variation is a cornerstone of process engineering. Likewise, the importance and edge of having a well-developed process engineering function is clearly evident for SHL Medical, whose vertically integrated ecosystem allows it to design and develop its own tools and machines that produce its autoinjector devices. Having a well-defined checks and balances system within its engineering operations is thus important.[4]

PROCESS ENGINEERING IN ACTION

A critical look within SHL Medical points us to the successful practice of process engineering in the organisation's extensive disposable autoinjector (DAI) programme with one of its longstanding pharma partners. First launched commercially in 2006, the DAI is one of the world's first modern prefilled pens. The device is a button-activated, three-step autoinjector that houses prefilled syringes containing volumes of up to 1.0 mL, and its technical specifications have paved the way for how SHL Medical's device portfolio is maturing and expanding through platform modularisation.

Over the course of approximately 15 years, the DAI technology has supported the regulatory approval and commercialisation of around 20 combination products. These self-injection devices, available in varying dosage presentations, are indicated for diseases such as rheumatoid arthritis, anaemia, migraine, hyperlipidaemia and osteoporosis, to name a few. Figure 1 exemplifies the diversity of disease areas that the technology has addressed over time.

The first DAI project was developed for a multinational biopharmaceutical company headquartered in the US. The accomplishments of this partnership gave rise to successive device projects using the DAI technology, effectively creating a product range for SHL Medical's pharma partner. Given that the first project dates back to around 2006, the present-day market landscape enabled SHL Medical to evaluate, upstream and downstream, of all the concurrent device development programmes and production streams that it co-managed with its pharma partner. Both parties saw the need for a product portfolio consolidation while addressing market demands to scale up the programme.

STREAMLINED PROCESS ENGINEERING SOLUTIONS ON A MULTIVARIATE SCALE

A caveat of this programme overhaul was that it was multivariable in many aspects. Each combination product project within the programme presented its own set of manpower, machines, materials

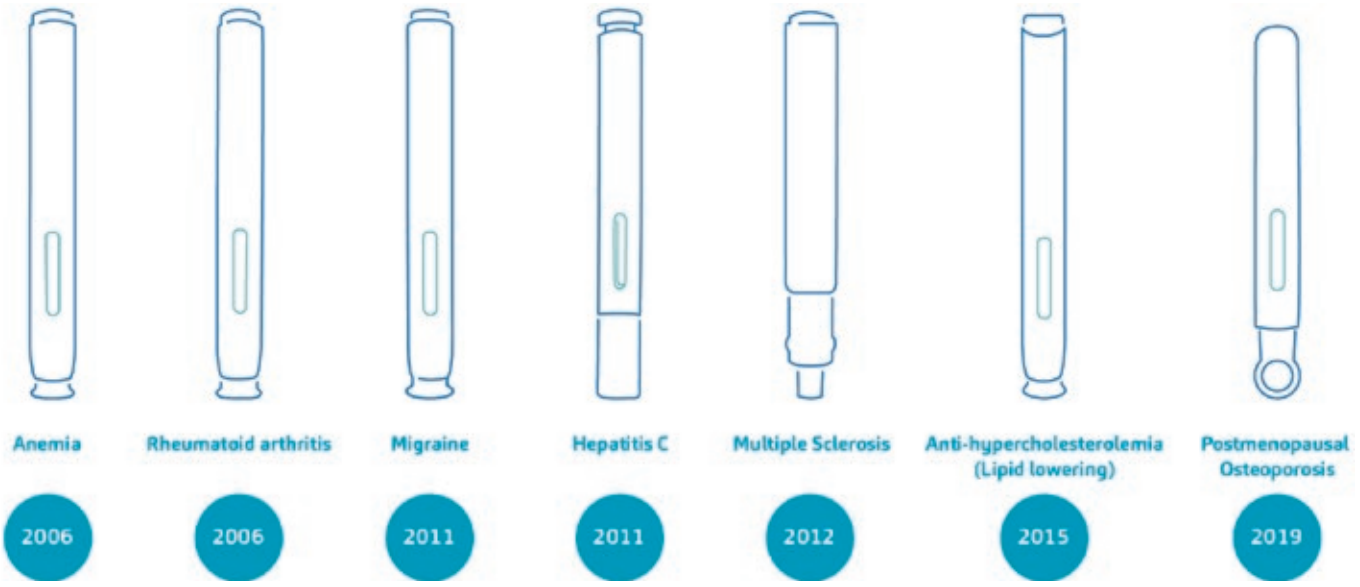

Figure 1: A non-exhaustive overview of combination products based on the DAI technology and their treatment areas; a number of these devices were part of the DAI programme.

and methods – the composite of which had to be evaluated according to both a macro- and micro-perspective. This complex yet holistic activity was addressed through a streamlined, layer-by-layer approach to programme consolidation and scaling up (Figure 2). In many ways, the solution was built upon various process engineering principles. Among many tools, part of a process engineer's arsenal is the effective use of descriptive statistics and statistical process controls, which were used as part of a larger exercise conducted to interrogate existing variables and corroborate data.

The whole process touched on all device designs, production and in-process controls, through to batch release testing, across the programme, ensuring that complexities were minimised and process variations were reduced throughout. In brief, a design for manufacturability and assembly assessment was conducted to optimise the designs from an automated and scalable process perspective. This assessment enabled the maintenance of brand recognition and colour differentiation across the industrial designs of each device within the programme. With SHL Medical moving towards automating many of its processes, this exercise also enabled centralisation of programme production flow. Now, the assembly process is automated across the programme, incorporating historical learnings and controls.

> "SHL Medical's driving force and guiding compass is to continue enabling patient independence, and the proof is in the innovative drug delivery solutions that the company has engineered over the decades."

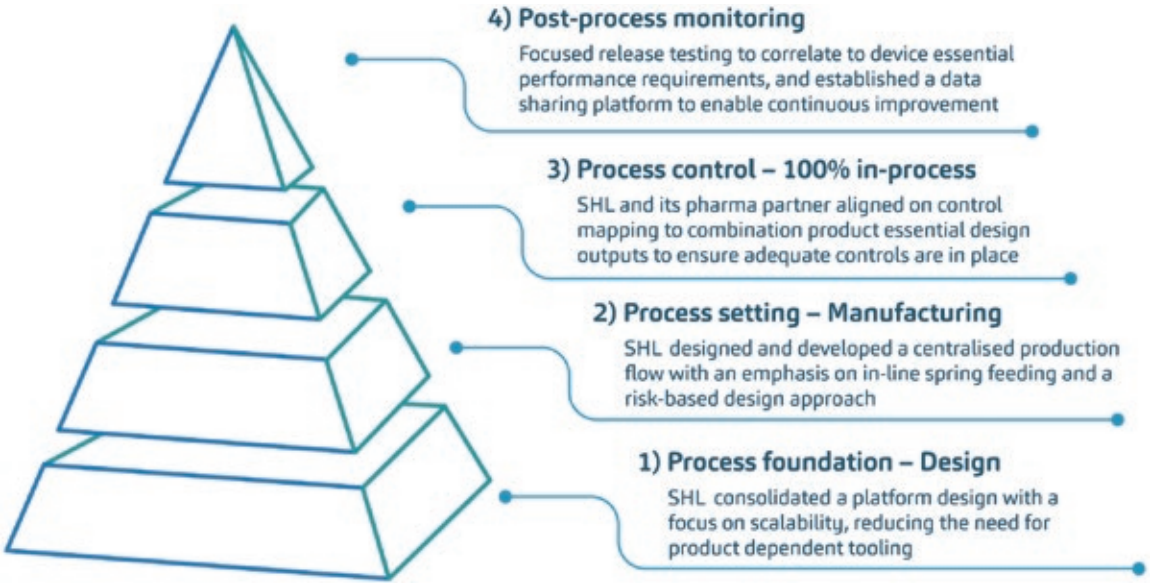

Figure 2: Diagrammatic representation of the streamlined, layer-by-layer approach to programme consolidation and ramp-up conducted by SHL Medical. The extent of this activity was large, covering five combination product projects co-developed with one of SHL Medical's long-standing pharma partners. The proceedings of this project were first presented at the 2021 PDA Universe of Pre-filled Syringes and Injection Devices conference.

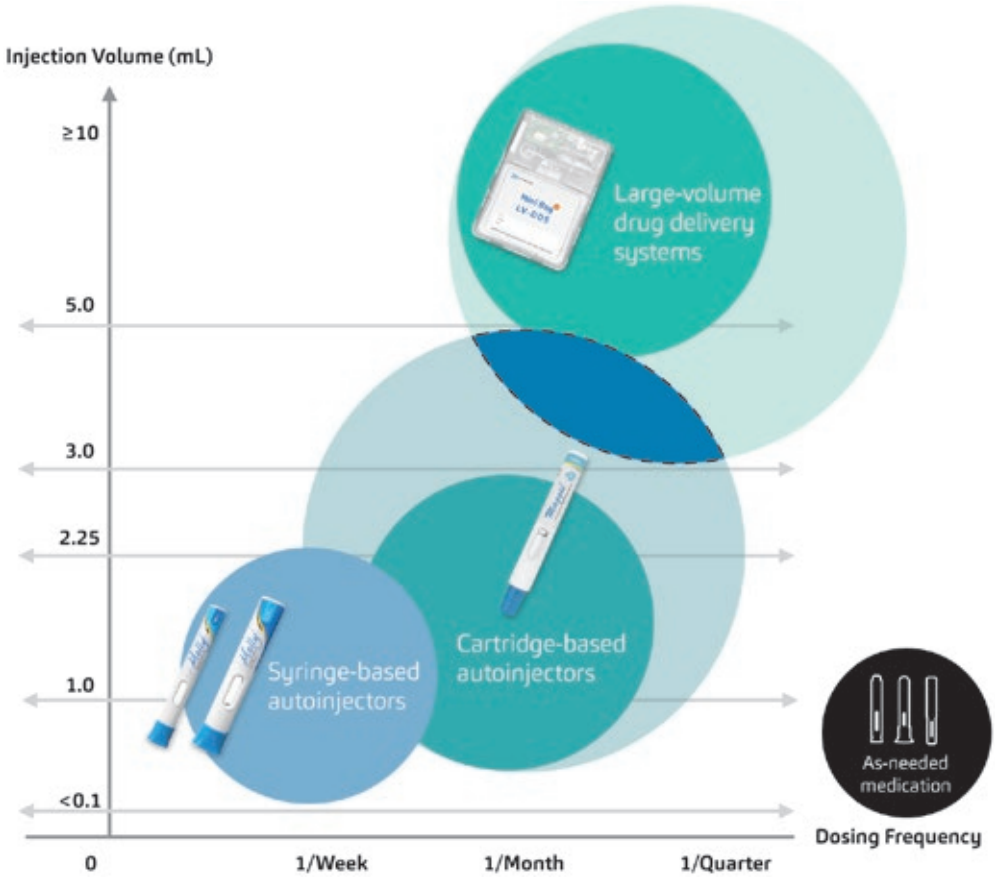

Figure 3: Towards next-generation drug delivery – SHL is constantly investing in engineering efforts to redefine what we know about autoinjectable self-injections (areas of interest marked in blue with dashed lines) and co-lead advances in the subcutaneous delivery of many formulations.

ENGINEERING THE PATH TOWARDS NEXT-GENERATION DRUG DELIVERY

The words *engineering* and *ingenious* come from the same Latin root word, *ingeniare*, which means to create or to devise. SHL Medical's driving force and guiding compass is to continue enabling patient independence, and the proof is in the innovative drug delivery solutions that the company has engineered over the decades. SHL Medical realises that part of its strength is due to the network of engineering disciplines that it has mastered over time, allowing the company to transform drug-device projects from concepts to mass production. SHL Medical's work will continue to advance its core competencies further, developing devices for various use cases and drug formulations (Figure 3) and, in parallel, meeting and exceeding its goals in the adjacent areas of digital health and sustainability.

Given the constantly evolving landscape of 21st-century medicine, SHL Medical sees a need to actively lead and innovate the development of drug delivery technologies that inspire its thinking and efforts to push the boundaries concerning subcutaneous injections, injection self-administration and adjacent domains. The pharmaceutical industry has seen recent advancements in the delivery of parenteral formulations, as evidenced by translational technologies that allow for the administration of more complex biologics through subcutaneous means. The company argues that, instead of a disconnected and independent approach between pharma and medtech, a proactive and interdependent approach is critical in the race towards engineering better medicines.

For patient-centric drug delivery, while the path remains open-ended regarding the future of syringe- and cartridge-based autoinjectors, SHL Medical will continue to extend its efforts to redefine the industry's understanding of self-injection devices, their usability and the formulations they can deliver. A proactive and interdependent approach between pharma and medtech does not necessarily require business agreements, but rather the active cognizance of developing technologies that augment the means to delivering patient therapies in a contemporary but disruptive manner.[5,6]

ABOUT THE COMPANY

SHL Medical is a world-leading solutions provider in the design, development and manufacturing of advanced delivery devices, such as autoinjectors and pen injectors. The company also provides final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe. With locations in Switzerland, Taiwan, Sweden and the US, SHL Medical has successfully built a strong international team of experts that develops breakthrough drug delivery solutions for pharma and biotech customers. These

include advanced reusable and disposable injection systems that can accommodate high-volume and high-viscosity formulations – and connected device technologies for next-generation healthcare.

REFERENCES

1. *Smith RJ, "Engineering". Britannica.com, accessed Apr 2022.*
2. *"Engineering, a Brief History". Linkengineering.org, accessed Apr 2022.*
3. *Black P, "Process Engineering – Everything You Need To Know!". Process Industry Informer, Apr 8, 2022.*
4. *Hatfield E, Vezza V, "Process Engineering". ScienceDirect, 2016, pp129–136.*
5. *Bittner B, Richter W, Schmidt J, "Subcutaneous Administration of Biotherapeutics: An Overview of Current Challenges and Opportunities". BioDrugs, 2018, Vol 32, pp 425–440.*
6. *VargasonAM, Anselmo AC, Mitragotri S, "The evolution of commercial drug delivery technologies". Nat Biomed Eng, 2021, Vol 5, pp 951–967.*

ABOUT THE AUTHORS

Jonathan Kearns leads the project engineering department as a Senior Manager. He leads a team of engineering leaders, ensuring excellent design for manufacturability and transfer of production processes to mass production for all of SHL Medical's device projects with its pharma clients. Prior to his current role, Mr Kearns was a Senior Programme Manager, leading a project portfolio for one of SHL Medical's long-standing customers. In the past, Mr Kearns worked at a pharma company as Manager of Device Engineering. He also has experience in designing and commissioning packaging lines for the pharmaceutical industry. Mr Kearns holds an MSc in Biomedical Engineering, majoring in medical device design and is currently an MBA candidate at Imperial College London, UK.

Kevin Huang leads device development through the whole process as an Engineering Leader at SHL Medical for a long-standing customer. He ensures that designs are correctly translated into a manufacturable product specification ready for mass production while being supported with stable processes. Mr Huang also leads the scale-up of a core product platform, including the transfer to automated production and higher cavitation tooling. Prior to SHL Medical, Mr Huang worked at Jabil (FL, US), based in Wuxi, China, as a Process Design Manager. In this role, he was responsible for leading the process design team to ensure that the factory could keep producing new products through efficient processes and competitive costs. Mr Huang holds a bachelor's degree in Aeronautical and Astronautical Engineering.

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RECENT TRENDS AND DEVELOPMENTS IN INJECTABLE DRUG FORMULATION AND DELIVERY

Here, Martin Gonzalez, PhD, Senior Manager, Formulation and Process Development at Pfizer CentreOne, details current trends in sterile injectable formulations and their delivery devices, and the challenges pharma and its contract development and manufacturing company partners face in bringing emerging breakthroughs to market.

An extremely broad range of increasingly advanced therapeutics are being administered via parenteral administration. Recent stars of the show are the billions of messenger RNA (mRNA) inoculations that continue to be delivered globally. Now a blockbuster technology, mRNA-based pharmaceuticals are poised to take off in the near term and are set to provide a sizeable section of the foundations for a huge growth in parenterally administered drug products.

> "Now a blockbuster technology, mRNA-based pharmaceuticals are poised to take off in the near term and are set to provide a sizeable section of the foundations for a huge growth in parenterally administered drug products."

BIOPHARMACEUTICALS TAKING CENTRE STAGE

The market for all sterile injectable (SI) drugs and their delivery devices is expanding fast. Although the number of SI therapeutics consumed globally is dwarfed by solid oral forms, more and more pharmaceuticals are being delivered to patients parenterally. The uptake of biopharmaceuticals in global healthcare for the treatment of chronic conditions, such as arthritis and diabetes, has become a significant driver of global growth. According to Precedence Research, the global biopharmaceutical market is projected to reach US$856 billion (£655 billion) by 2030 and expand at a compound annual growth rate (CAGR) of 12.5% from 2021 to 2030.[1]

THE PATIENT-FRIENDLY GORILLA IN THE ROOM

Prior to the pandemic, mRNA-based drug products were focused primarily on treating oncology indications as opposed to infectious diseases, such as covid-19. However, technical and scientific advancements have allowed researchers and drug developers to expand the use of mRNA to new therapeutic areas. During this period of R&D, carriers for mRNA were also further developed, increasing the potential of mRNA technology by prolonging antigen expression *in vivo*.[2] What is exciting is that the advances in the science proved instrumental in facilitating the success of covid-19 vaccines as well as showcasing the enormous possibilities of mRNA technology.

With mRNA-based drugs experiencing a surge in development and demand, companies supporting the technology's commercial manufacturing have had to adapt quickly to overcome the challenges involved. Virtually overnight, mRNA became the gorilla in the room for much of global pharma. The impact has been significant. Investment in mRNA's therapeutic potential has been tremendous. At the end of 2019, the combined market capitalisation of the five publicly listed companies focusing on mRNA platforms was $15 billion.[3] As of August 2021, market capitalisation was more than $300 billion.[4]

COMING ATTRACTION: ADVANCED MEDICINAL THERAPEUTIC PRODUCTS

Cell and gene therapies (C&GTs) are also transforming pharmaceutical-based healthcare and continue to demonstrate dramatic therapeutic results for patients.

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"Today's SI drugs carry a more complex profile and incorporate new thinking about ways of preserving the value of the drug while also providing additional benefits, including precise, easy-to-administer delivery systems for better dose compliance."

Now grouped as advanced therapy medicinal products (ATMPs), these modalities exhibit the potential to cure disease by addressing the root cause of the condition rather than treating it symptomatically. The science behind these therapies, as well as the means to deliver them, is advancing fast. Valued at $12.3 billion in 2021, the ATMP market is projected to reach a market value of $59.9 billion by 2031.[5]

Recent breakthroughs and approvals in the space have spurred the flow of investment, and this cash infusion is expected to accelerate the pace of development further, as life sciences developers work towards increasing patient access to these exciting modalities. The American Society of Gene and Cell Therapy noted in its *Gene, Cell, and RNA Therapy Landscape Quarterly Data Report* (Q4 2021) that, of the 3,483 C&GTs currently in development globally, 32 are in Phase III, up 10% from the previous quarter.[6]

STERILE INJECTABLES MOVING INTO THE MAINSTREAM OF PATIENT CARE

Because a third or more of all pharmaceuticals are manufactured by external partners, the pressure is on the contract development and manufacturing organisation (CDMO) community to find the capacity and new, efficient ways to speed up production and provide a shorter, surer path to market for these extremely important therapeutics. For many, it is going to be challenging to balance manufacturing capacity with demand in existing facilities, which will likely to prompt renewed capital spending on facilities. Although new ways of delivering SI formulations are being introduced, subcutaneous (SC) and intravenous (IV) delivery via needle will likely remain the dominant administration route for SI drugs.

Much of the emphasis in contemporary drug design has shifted from just preserving basic quality attributes, such as safety, efficacy and potency, in a simple container. Today's SI drugs carry a more complex profile and incorporate new thinking about ways of preserving the value of the drug while also providing additional benefits, including precise, easy-to-administer delivery systems for better dose compliance. The patient experience has influenced the development of new and creative ways to deliver sterile formulations, including patches that subcutaneously penetrate the skin, degradable implants and other innovative modalities.

IMPROVING THE PATIENT EXPERIENCE FOR BETTER COMPLIANCE AND LESS STING

According to Fortune Business Insights data, the global injectable drug delivery market was valued at $483 billion in 2019 and is projected to reach $1,251 billion in size by 2027, rising at a CAGR of 12.9%.[7] The SI market is a rapidly evolving industry. A clear example of this is the explosive creation of pharma companies devoted to developing therapies and treatments for covid-19.

For millions of patients who dose themselves daily, there is a growing preference for "smarter" and "friendlier" ways to self-administer injections. The focus on the patient has prompted broad medical device innovation over the past two decades and introduced innovations that include prefilled syringes (PFSs), prefilled pens and automated electronic injection and infusion devices. Needles have also been subject to long and continuous development and are now engineered to support less painful SC and IV delivery, as well as manage the flow of drug substance from device to patient.

Small bore, "low pain" needles (27–31G) are preferred as a way to mitigate pain and discomfort at the injection site, but usually carry the unwanted risk of clogging, rendering the administration process riskier and less predictable. Also, additional challenges exist for high concentration formulations, such as product shear or high infusion pressures, which their devices need to be able to handle. There are many pumps designs that can cope with most of these issues but there is not a one-size-fits-all answer. As mentioned prior, concurrent development of a delivery device and the drug product formulation is usually needed to address some of these challenges.

PFSs, unit-dose autoinjectors and similar delivery modalities have dominated the market for years due to their simplicity and ease of use. Among those technologies, analysts note that PFSs represent the fastest-growing segment. In 2021, the global PFS market was valued at $5.8 billion; the overall market exhibited strong growth and is expected to grow to $11.9 billion by 2028 at a CAGR of 10.7%.[8]

Although connected autoinjectors, such as infusion pumps for insulin delivery, have been on the market for a shorter time, increasingly, innovators are taking advantage of these proven technologies to increase patient-friendliness and promote better therapeutic outcomes.

OUT THERE: LONG-ACTING FORMULATIONS, MULTI-ACTIVE COMBINATIONS AND VISCOUS BIOLOGICS

Developing suitable formulations and matching them to existing and new device platforms is going to keep the industry busy in the near term. Advanced API chemistries and formulation techniques are being developed to protect these drug products from degradation, shear and other forces, including stability and storage temperature, during processing and administration. Formulators are also looking to avoid enzymatic damage upon release, and to provide a more precise delivery of the API and control attributes related to their pharmacokinetic profile (biocompatibility and bioavailability).

Reducing dosing frequency and the overall number of injections is another patient-facing challenge being addressed by the industry in formulation. Although long-acting injectables and multi-API combined formulation concepts offer workable solutions to reduce dose frequency, they can, and will, introduce additional complexity into formulation and device development.

For example, many drug substances, particularly biologics, can be highly viscous in their final commercial formulation due to their concentration and dosing requirements mandating they be kept to minimum volume. SC injections are limited to small volumes, usually 1–3 mL – even when wearable delivery devices are employed, slightly larger volumes can be delivered over time but, even then, there are limits to what patients can tolerate. Furthermore, converting a formerly IV drug formulation to one that can be delivered subcutaneously requires an increase in concentration, and likely some reformulation, to improve flow and injection pressures to reduce pain/stinging/oedema at the injection site.[9]

This can make dispensing and administration problematic because patients generally prefer SC injections of parenteral drugs instead of IV infusion in a clinical setting. This is especially true for therapeutics that require frequent dosing and is a major driver of the development of higher-concentration biologic formulations, as well as increasingly sophisticated ways to deliver doses accurately and with less pain. The adoption of SC self-administration also relieves patients from spending hours in a clinical setting to receive the drug and makes treatment less expensive for both payer and patient. Here, again, patient compliance is paramount to delivering therapeutic performance effectively and better outcomes.

PUTTING IT ALL TOGETHER FOR PATIENTS WITH EXTERNAL PARTNERS

Increasingly, the CDMO industry is being tasked to put all the pieces of this intricate puzzle together – from formulation to finished drug product – and prepare products for commercial markets and patients. In their contemporary form, SI delivery devices present several challenges to successful development. High-potency biologics come with higher viscosities, problematic shelf lives, logistics issues and other impediments to commercial development. When evaluating a drug substance's presentation and appropriateness for a delivery device, the first couple of "default options" (vial, PFS) may, ultimately, prove not to be the best path. Regardless, the chemical make-up of the drug product is prompting programme collaborators to pursue an even deeper analysis – not only of the drug's intrinsic formulation properties but also the device's technical limitations, as well as its intended use and end-user.

Depending on the enterprise, the intellectual property owner may understand what pieces of the puzzle need to come together, but not exactly how they should fit, to create the big picture of the product as early in development as possible. Experience, technical capabilities and expertise are required to commercialise and manufacture these sophisticated products successfully. That is why pharma's small and large molecule developers are increasingly turning to contract partners for help delivering their innovations to patients.

ABOUT THE COMPANY

Pfizer CentreOne is a large global CDMO within Pfizer and a leading supplier of specialty APIs. Its service offering is broad, spanning development and manufacturing services for sterile injectable and oral solid dosage forms. Pfizer CentreOne's manufacturing network includes more than 35 sites across six continents.

Pfizer CentreOne was founded in 2015 when Pfizer CentreSource, a global leader in specialty APIs, and Hospira One2One merged. Backed by Pfizer resources, the company delivers technical expertise, global regulatory support and long-term supply.

REFERENCES

1. *"Biopharmaceutical Market Size to Hit US$ 856.1 Bn by 2030". Industry Report, GlobeNewswire, Dec 22, 2021.*
2. *Pardi N et al, "mRNA vaccines - a new era in vaccinology". Nat Rev Drug Discov, 2018, Vol 17(4), pp 261–279.*
3. *Xie W, Chen B, Wong J, "Evolution of the market for mRNA technology". Nat Rev Drug Discov, 2021, 20, 880.*
4. *Stanton D, "Single-use lead times up to 12 months as COVID takes its toll". BioProcess Int, May 3, 2021.*
5. *"The Global Advanced Therapy Medicinal Products Market is projected to reach at market value of US$ 59.91 billion by 2031". Industry Report, GlobeNewswire, Jun 2, 2021.*
6. *Barrett DM, "Gene, Cell, & RNA Therapy Landscape: Q1 2021". American Society of Gene + Cell Therapy, Apr 15, 2021.*
7. *"Injectable Drug Delivery Market Size, Share and COVID-19 Impact Analysis, By Device Type (Conventional Injectable, Pre-filled Syringes, Auto-Injectors, Pen Injectors, and Wearable), By Product Type (Freeze-Dried Products, Injectable Sterile Products), By End User (Hospitals, Homecare Settings, Clinics, and Others), and Regional Forecast, 2020–2027". Industry Report, Fortune Business Insights, Jul 2020.*
8. *"Prefilled Syringes Market Size By Type (Glass, Plastic), By Design (Single-chamber, Dual-chamber), By Applications (Diabetes, Rheumatoid Arthritis, Anaphylaxis, Antithrombotic/Thrombolytic Therapy), Industry Analysis Report, Regional Outlook, Application Potential, Competitive Market Share & Forecast, 2021–2027". Industry Report, Global Market Insights, Feb 2021.*
9. *Challener CA, "Excipients for High-Concentration Biologics". BioPharm Int, 2022, Vol 35(3), pp17–20.*

ABOUT THE AUTHOR

Martin Gonzalez has a PhD in Biophysical Chemistry and over 25 years of experience in formulation development and manufacturing processes for biologics and synthetic drug products. He joined Pfizer CentreOne Contract Manufacturing Services in June 2013. Having previously worked as a scientist at the US NIH's National Heart, Lung, and Blood Institute, Dr Gonzalez has extensive expertise in plasma-derived proteins, polypeptides, enzymes, vaccines and recombinant proteins and antibodies. This expertise has made him a subject matter expert in protein formulation, product development and lyophilisation, manufacturing troubleshooting, delivery devices and final container selection.

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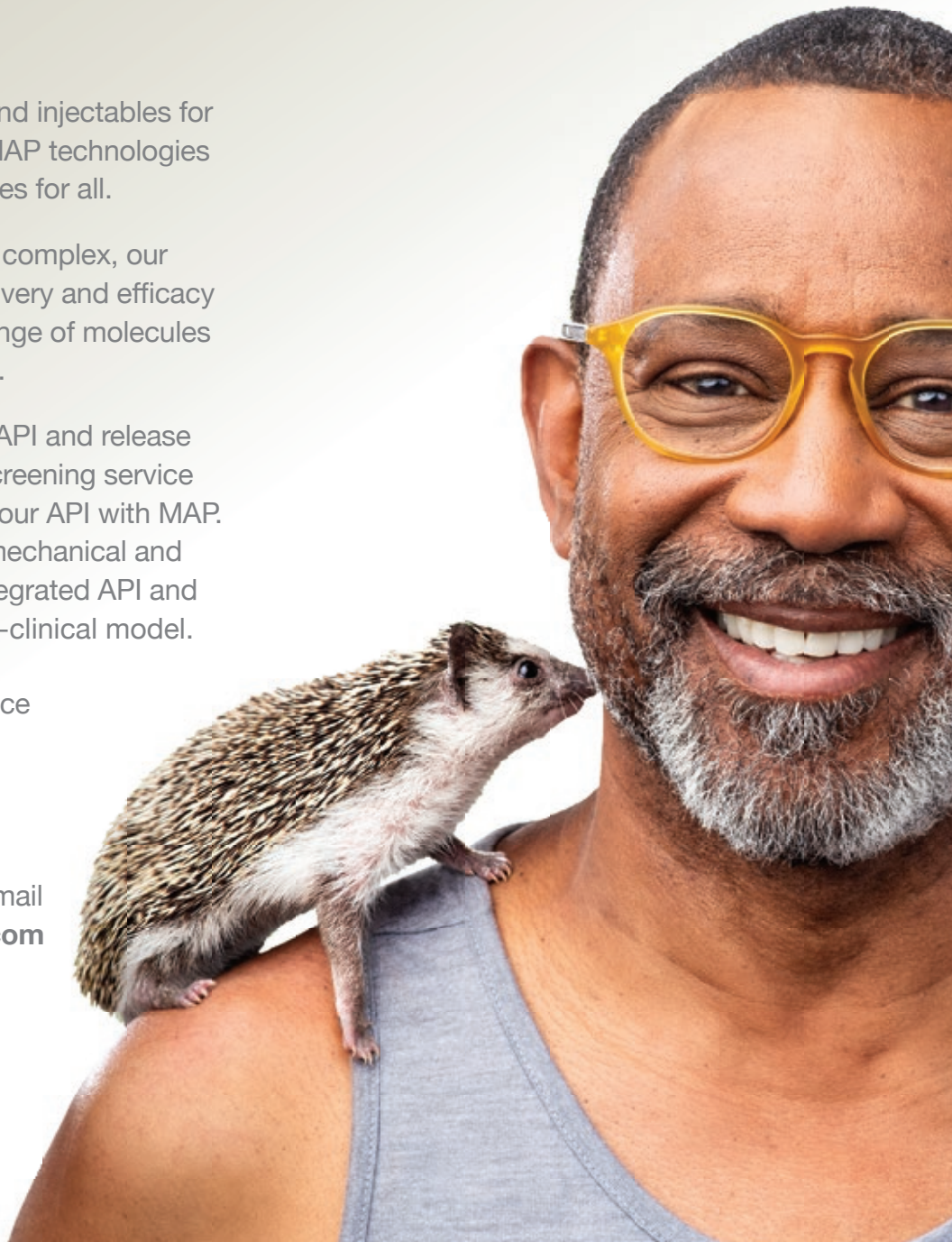

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ENABLING A NEW PARADIGM FOR PEPTIDE DRUG DEVELOPMENT

In the first of two articles in this issue from Xeris Pharmaceuticals, Michael Neely, a consultant to the company, reviews peptide formulations and introduces Xeris's XeriSol™ technology and its potential paradigm-changing capabilities.

Peptides now comprise some of the most important therapeutics in the modern pharmacopoeia. The advent of simplified and economical synthesis routes, tools for rapid laboratory synthesis, and advances in large-scale production technologies for synthetic peptides have enabled an extensive discovery and development effort across the pharmaceutical industry. Peptide drugs now account for an estimated US$28.5 billion (£21.8 billion) of worldwide pharmaceutical revenues and include hundreds of products, ranging from orphan drugs to drugs used by millions of patients on a daily basis. Growth is expected to continue at 9.6% over the next several years.[1]

Peptide molecules in traditional aqueous formulations are subject to various physical interactions that present formulation challenges. For example, they will undergo hydrolysis rather quickly in the presence of water and, in useful concentrations, will often precipitate or form aggregates that diminish or destroy their pharmacological activity while also raising immunogenicity concerns. Depending on pH requirements, peptides as aqueous solutions for injection may reach a point where they become painful due to high acid levels.

Early peptide formulations, including many that are still marketed, relied on lyophilisation of the peptide to enable packaging in vials and sufficient stability to allow distribution through the supply chain. Lyophilisation is a capital-intensive unit operation that demands both a high level of energy consumption and significant developmental effort to achieve the required process parameters. Furthermore, lyophilised products require reconstitution with a sterile diluent at the point of use, adding complexity and introducing the opportunity for dosing errors or contamination to occur.

Because peptides are labile to acids, the bases and proteases that are present in the alimentary canal mean that oral administration is not directly feasible. The simplest and most viable routes of administration have been, and will remain, parenteral; either subcutaneous, intramuscular or intravenous. Industry and academia have collectively invested billions of dollars over the past decade and a half chasing the "holy grail" of oral peptide delivery. There have been some significant successes, but they all come at a cost.

> "Science has given the pharmaceutical industry a vast and growing library of pharmacologically useful peptides, so one might ask if there is a different developmental paradigm for these potentially vital medications that might serve the cause of medicine better?"

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Typical oral formulations of peptides rely on a significant excess of the active ingredient to deliver a required dose across the gut, through the liver and into systemic circulation. Chemical modifications have been developed that help the peptide survive this gauntlet, as well as microencapsulation technologies towards the same end. Each of these approaches adds cost and complexity to clinical development, manufacturing processes and the overall cost to achieve approval and, ultimately, reach markets. In competitive markets, the cost of this kind of product differentiation effort may or may not be adequately rewarded. Much depends on the willingness of third-party payers to agree that the benefits of novel formulations merit the cost. A similar situation occurs for other routes of administration, such as pulmonary or transdermal delivery. Getting an accurate dose into the target tissues requires significant time, money and effort, as well as no small measure of good fortune.

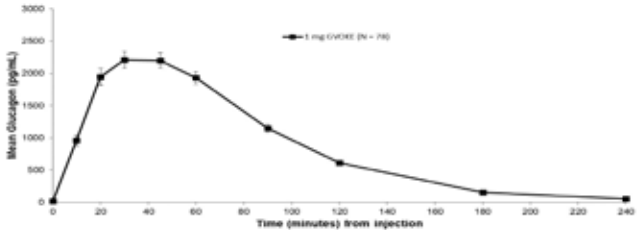
Science has given the pharmaceutical industry a vast and growing library of pharmacologically useful peptides, so one might ask if there is a different developmental paradigm for these potentially vital medications that might serve the cause of medicine better? Given that, for any therapeutic biomolecule, parenteral administration is virtually always simple and efficacious, would not a more perfect method of producing parenteral doses be of great value? The term "elegance" is used in mathematics to describe the simplest and most straightforward way of constructing a proof of a theorem. There is, in fact, a more elegant solution available to those who propose to formulate and market peptide drugs. That solution is Xerisol™, a peptide and small molecule drug formulation platform developed and made available to license through Xeris Pharmaceuticals. For those in the pharmaceutical industry focused on delivering maximum patient benefits quickly, efficiently and cost effectively, XeriSol's properties make a compelling case.

The essence of a Xerisol formulation is comprised of the active peptide molecule and appropriate molar ratios of compatible ionic species, sometimes including an excipient, all dissolved in a polar, aprotic (non-aqueous) solvent. In this context, the peptide is as free from all of the deleterious effects of water as it would be in a lyophilised state, yet, being in liquid form, it remains amenable to injection. In addition to glass, the solution has been demonstrated to be compatible with many of the alternative materials commonly used to produce vials, syringes, autoinjectors, cartridges and other primary drug containers. Virtually any of the new devices that have been developed to simplify the injection process and make it more patient friendly can be compatible with a XeriSol formulation. Clinical- and commercial-scale manufacturing is similar to that of aqueous solutions and available through multiple contract development and manufacturing company organisations. XeriSol is also supported and protected by an extensive patent estate, providing an opportunity for drug developers to achieve or maintain market exclusivity for a drug product.

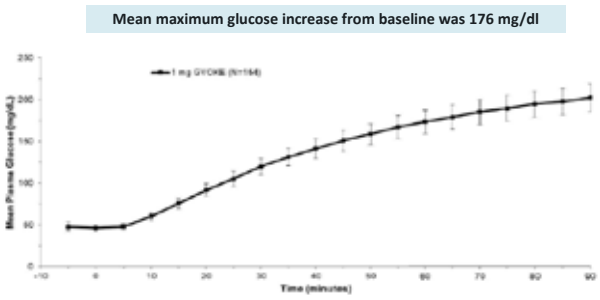
The efforts to develop non-parenteral routes of administration for peptide drugs is driven by the supposition that injection delivery is the least favourable for patient acceptance and compliant use. That may be, but as injection technologies become more refined,

> "Another benefit of Xerisol formulations is that they allow higher drug concentrations and, therefore, enable smaller injection volumes for a given dose of drug."

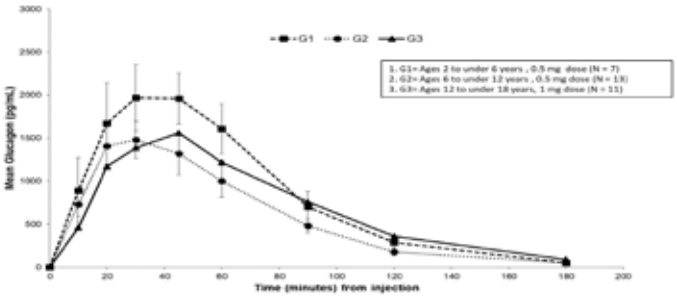
Pharmacokinetics:
Mean (± SEM) Plasma Glucagon Concentration vs. Time for 1 mg Gvoke Injection in Adults with Type 1 Diabetes Mellitus



Pharmacodynamics:
Mean (± SEM) Plasma Glucose vs. Time in Adult Subjects with Type 1 Diabetes Mellitus



Pharmacokinetics:
Mean (± SEM) Plasma Glucagon Concentration vs. Time from Gvoke Injection in Paediatrics with Type 1 Diabetes Mellitus



Pharmacodynamics:
Mean (± SEM) Plasma Glucose vs. Time in Paediatrics Subjects with Type 1 Diabetes Mellitus

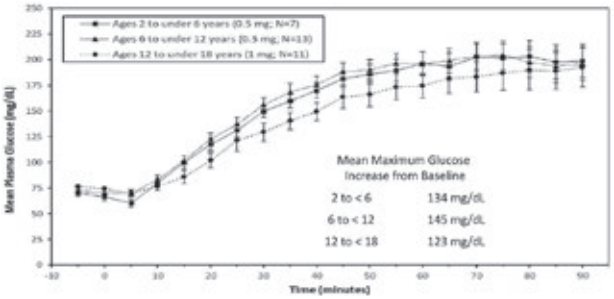


Figure 1: Pharmacodynamics of a Xerisol formulation of glucagon.

that perceived barrier almost certainly becomes lower. If a few seconds of touching a device to one's abdomen or thigh, with no perceptible pain, achieves effective delivery of a drug that provides appreciable benefits, that barrier may be less significant than currently supposed. Another benefit of Xerisol formulations is that they allow higher drug concentrations and, therefore, enable smaller injection volumes for a given dose of drug. A common complaint of injection site irritation has been demonstrated to be no more frequent with XeriSol formulations than with aqueous formulations of the same drug, and the absence of pH and reduced injected volume afforded by Xerisol might be expected to lessen such occurrences.

Not only does Xerisol afford a lower cost and faster route to an effective and marketable drug product but it is also a lower risk option. Xerisol is now a clinically proven and globally approved technology. Xeris Pharmaceuticals has launched Gvoke® and Ogluo® glucagon injections in the US and European markets, respectively, for the treatment of severe hypoglycaemia in adults and paediatric populations down to the age of two (Figure 1). The excellent stability of Gvoke and Ogluo has enabled the development of prefilled syringe and autoinjector presentations (Figures 2 & 3). Xeris Pharmaceuticals is also developing XeriSol formulations to treat additional hypoglycaemic indications that require chronic exposure and has thus developed an extensive safety database. The company has conducted several nonclinical repeat-dose toxicity studies with XeriSol, including 26 weeks' subcutaneous dosing in rats and 28 weeks' subcutaneous dosing in minipigs. No systemic or organ toxicity was observed in animals treated with XeriSol.

Figure 2: Gvoke glucagon in a Xerisol formulation pen injector, approved in 2020 for marketing in the US.

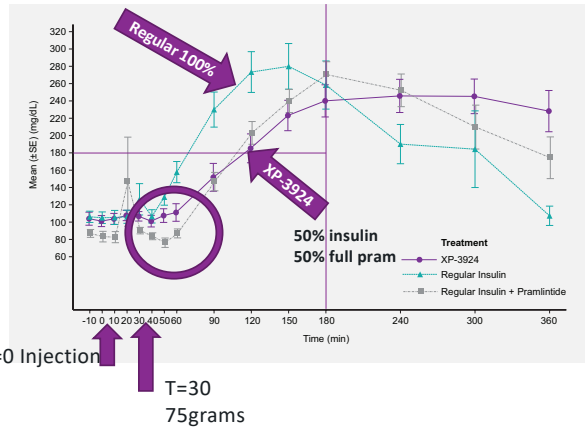
Figure 3: The Gvoke glucagon prefilled syringe product received FDA approval in 2019.

> "Molecules that require differing pH for solution in water can be solubilised together in a Xerisol formulation because pH is obviated in the aprotic environment."

XP-3924 Clinical Efficacy Results

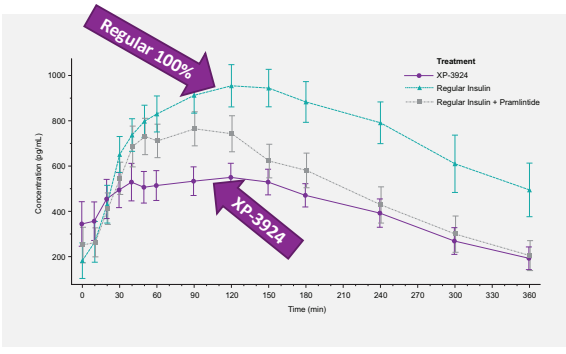
Comparative Assessments for Glucose Variability Over 360 Minutes

	Mean Absolute Change ± Standard Deviation (SD) in Blood Glucose (mg/dL)	Coefficient of Variation (%)
XP-3924	197.7 ± 70.7	53.3
Regular Insulin + Pramlintide	230.5 ± 162.4	62.1
Regular Insulin	254.2 ± 195.2	71.0

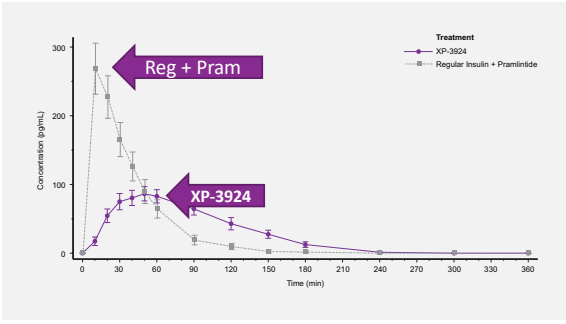


XP-3924 Clinical Phamacokinetic Results

XP-3924 Pharmacokinetics (when compared with co-administration)



Values are presented as arithmetic means +/-SE.



Values are presented as arithmetic means +/-SE.

Figure 4: Pharmacokinetics of a Xerisol formulation of insulin + pramlintide.

The ability to co-formulate two peptides with differing solubility characteristics in a single stable liquid presentation at high concentrations and with no adverse impact on clinical efficacy is another key enabling feature of Xerisol that would enable the development of single-dose peptide "cocktail" drugs for vaccines, hormonal control medicines or anticancer drugs. Molecules that require differing pH for solution in water can be solubilised together in a Xerisol formulation because pH is obviated in the aprotic environment.

A co-formulation of insulin and pramlintide (an amylin analogue) – XP-3924 – is presently in clinical development, along with several other products. Figures 4 provides information on the efficacy and pharmacokinetics of glucagon formulated in this system, as well as some early clinical results from the insulin-pramlintide development effort. It is important to note that insulin and pramlintide would not be compatible in an aqueous formulation due to their differing pH requirements for solubility.

To summarise, XeriSol enables peptide drugs to be developed, manufactured and marketed more rapidly and more efficiently – and at low risk of clinical failure due to formulation effects – all while achieving lower manufacturing cost, high efficacy and stability, greater packaging and presentation flexibility, broad compatibility with existing manufacturing equipment and compatibility with a wide array of advanced patient-friendly parenteral delivery devices that ensure precise dosing. The technology has been proven safe and effective in clinical trials and has received regulatory approvals globally.

XeriSol technology is indeed an elegant solution, and a potential paradigm-changing enabling technology for peptide therapeutics.

ABOUT THE COMPANY

Xeris Pharmaceuticals is a specialty pharmaceutical company that leverages novel formulation technology platforms to develop and commercialise ready-to-use liquid-stable injectables. The company is focused on creating medicines that are easier to use, including its Gvoke® glucagon injection, which uses Xeris's technology to deliver ready-to-use solutions for patients and caregivers alike. Xeris Pharmaceuticals is a wholly owned subsidiary of Xeris Biopharma Holdings.

REFERENCE

1. *"Peptide Therapeutics Market - Growth, Trends, covid-19 Impact, and Forecasts (2022 - 2027)". Mordor Intelligence, 2021.*

ABOUT THE AUTHOR

Michael Neely retired in 2015 after a 42-year career in the pharmaceutical industry. He currently serves in a consulting role for business development at Xeris Pharmaceuticals. His experience spans multiple disciplines, including pharmaceutical manufacturing, research and development, business development and marketing.

XERIJECT™: NON-AQUEOUS FORMULATIONS FOR SUBCUTANEOUS INJECTION OF ULTRA-HIGH CONCENTRATION BIOLOGICS

In this, the second of two articles in this issue from Xeris Pharmaceuticals, Steven Prestrelski, PhD, Chief Scientific Officer, introduces the XeriJect non-aqueous formulation technology that creates formulations with visco-elastic properties, opening the door to subcutaneous injection of difficult-to-formulate biologics, such as monoclonal antibodies, at very high concentrations.

Biopharmaceuticals are increasingly making up a larger fraction of the overall pharma market. In fact, over the past several years, sales of monoclonal antibodies (mAbs) have grown faster than all other biopharmaceutical classes. Global sales of mAb-based products are expected to grow to US$240 billion (£192 billion) by 2023 and $315 billion by 2025.[1] Further, in recent years, multiple mAbs with similar drug targets, and biosimilars, have also entered the market. This creates a highly competitive product landscape compelling biopharmaceutical companies to differentiate their products. Since their introduction, mAb therapeutics have had tremendous impact, but have yet to reach their full potential, largely because of hurdles in product formulation and delivery.

> "Since their introduction, mAb therapeutics have had tremendous impact, but have yet to reach their full potential, largely because of hurdles in product formulation and delivery."

To achieve therapeutic efficacy, antibodies can require doses as high as 1 g. Thus, mAbs have conventionally been administered via high-volume intravenous (IV) infusions that can last several hours and require administration under clinical conditions.[2] Such infusions are inconvenient, and often financially inaccessible for the patient. Additionally, they can limit the number of patients that hospitals and infusion centres can treat. A preference for SC delivery is reflected in the market as an increasing number of mAb therapeutics have been released in as SC injections.[3]

Ready-to-use subcutaneous (SC) injections of biologics are preferable to IV infusions as they decrease the burden on healthcare providers and payers by requiring much less time and offering a lower risk of complications, such as infection and infusion reaction. For patients and caregivers, they offer the opportunity for self-administration and favourably improve the economics of drug administration. SC-administered mAbs can also be more affordable as they eliminate the high costs typical of in-clinic or at-home IV infusions.[3]

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Many mAbs, however, require high concentrations (>100 mg/mL) to administer efficacious doses within the volume limit of SC injection (1.0–2.25 mL). High concentrations in an aqueous environment are often intractable due to the high viscosity and associated syringe force or protein instability.[4] These high syringe forces and stability issues make SC delivery challenging, often virtually impossible, constraining the options for delivering mAb therapeutics to either IV infusion, or administering lower doses more frequently.

Injectable biopharmaceuticals typically rely on aqueous formulations to deliver drugs and biologics, but many drugs have low solubility in water and are not stable. There are a number of conventional approaches to address these barriers but, to date, these have been insufficient. Solving the formulation and delivery challenges associated with mAbs is key to enabling mAb therapeutics to reach their full medical and market potential.

INTRODUCING XERIJECT™

XeriJect™ is a formulation technology suited for drugs and biologics consisting of large molecules such as proteins, mAbs and vaccines. XeriJect™ formulations are innovative, ready-to-use, visco-elastic pharmaceutical suspensions for various therapeutic categories that have the potential to remove many associated treatment burdens and ultimately improve patients' lives.

Xeris has pioneered the development of injectable, visco-elastic formulations with non-Newtonian properties. These visco-elastic suspension formulations achieve maximally high drug loadings and are ready to use due to lack of particle settling on storage. Furthermore, no novel processes or excipients are required to create XeriJect™ formulations. All formulation excipients are present in currently approved formulations for SC injection.

To create XeriJect™ formulations, specialised drying and particle engineering techniques are employed first to create particles/powders with highly defined characteristics. The XeriJect™ platform uses proprietary spray-drying formulation processes to engineer particles of high density and a particle-size distribution amenable to highly concentrated suspensions (see Figure 1).

Spray-drying is an oft used and well understood pharmaceutical process and, in particular, aseptic spray-drying of protein therapeutics has been scaled to metric tonne quantities. Figure 2 shows an example of spray-dried particles amenable to XeriJect™ formulations.

In creating XeriJect™ formulations, spray-dried powders are then "wetted" with biocompatible diluents, creating ultra-concentrated suspension formulations (see Figure 3). At very high particle loadings, these formulations take on visco-elastic properties, allowing for maximal drug loading, but are amenable to injection via syringes and cartridges. These suspensions are highly viscous at rest, but the viscosity drops by orders of magnitude upon the application of shear.

Xeris uses commercially available filling technologies to fill syringes or cartridges. XeriJect™ formulations have been filled into several commercially available prefilled syringes and cartridges. Figure 3 also shows an example of a 1 mL "long" prefilled syringe filled with XeriJect™ formulation; an elegant pharmaceutical presentation.

"Using the XeriJect™ platform, ready-to-use visco-elastic suspensions with protein drug concentrations in excess of 400 mg/mL can be routinely formulated, far exceeding current aqueous formulation systems."

"These visco-elastic suspension formulations achieve maximally high drug loadings and are ready to use due to lack of particle settling on storage."

Figure 1: Spray-Dryer.

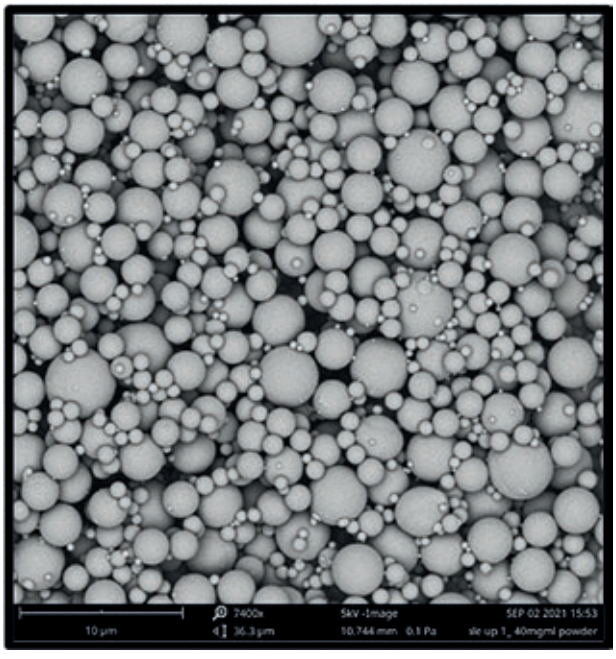

Figure 2: Electron micrograph of spray-dried particles used in XeriJect formulations.

Figure 3: Example XeriJect™ spray-dried powder, visco-elastic suspension and prefilled syringe.

Using the XeriJect™ platform, ready-to-use visco-elastic suspensions with protein drug concentrations in excess of 400 mg/mL can be routinely formulated, far exceeding current aqueous formulation systems with maximum achievable protein concentrations of 50–250 mg/mL.[4] In certain cases, the XeriJect™ technology can produce formulations in excess of 500 mg/mL of protein therapeutic. Additionally, these highly concentrated suspensions can be delivered through relatively small needles at injection forces amenable to thumb pressure. The visco-elastic properties also allow for delivery from cartridges using standard cartridge needles.

The injectability of the XeriJect™ formulations is measured using a texture analyser. During this analysis, the break-loose force and the mean glide force of prefilled syringes or syringe cartridges are evaluated at different volumetric flow rates. Figure 4 shows an injection force profile for a XeriJect™ formulation administered using a prefilled syringe with a 27-gauge needle. The injection force of the XeriJect™ formulations is dictated by the powder-to-oil ratios, geometry of the syringe, needle gauge, and injection speed. Various syringe and needle combinations are possible with XeriJect™ depending on the application and requirements. Modifications to these parameters allow Xeris to ensure injection forces do not exceed certain limits, providing safe administration to the patient.

INTELLECTUAL PROPERTY

The XeriJect™ technology platform and formulations are proprietary, and supported and protected by an extensive patent estate, trade secrets, and development and manufacturing know-how, providing an opportunity for drug developers to achieve and/or maintain market exclusivity for their products.

Xeris seeks to collaborate in the development of XeriJect™ formulations and make the technology available for licensing, allowing for lengthy patent terms.

ASEPTIC MANUFACTURING

Most biologics cannot be terminally sterilised, and the highly concentrated XeriJect™ suspensions cannot not be sterile filtered. Thus, development of XeriJect™ formulations will require processing in an aseptic environment. Incoming bulk aqueous solutions of mAbs can be sterile filtered into an aseptic isolator. All of the processes used to manufacture XeriJect™ formulations are amenable to processing in an aseptic environment.

PRECLINICAL STUDIES

XeriJect™ formulations can be administered SC (or intramuscularly) using commercially available prefilled syringes, pens and pumps. Once the injected visco-elastic suspension mixes with the physiologic, aqueous environment of the subcutaneous tissue, complete dissolution of the formulation

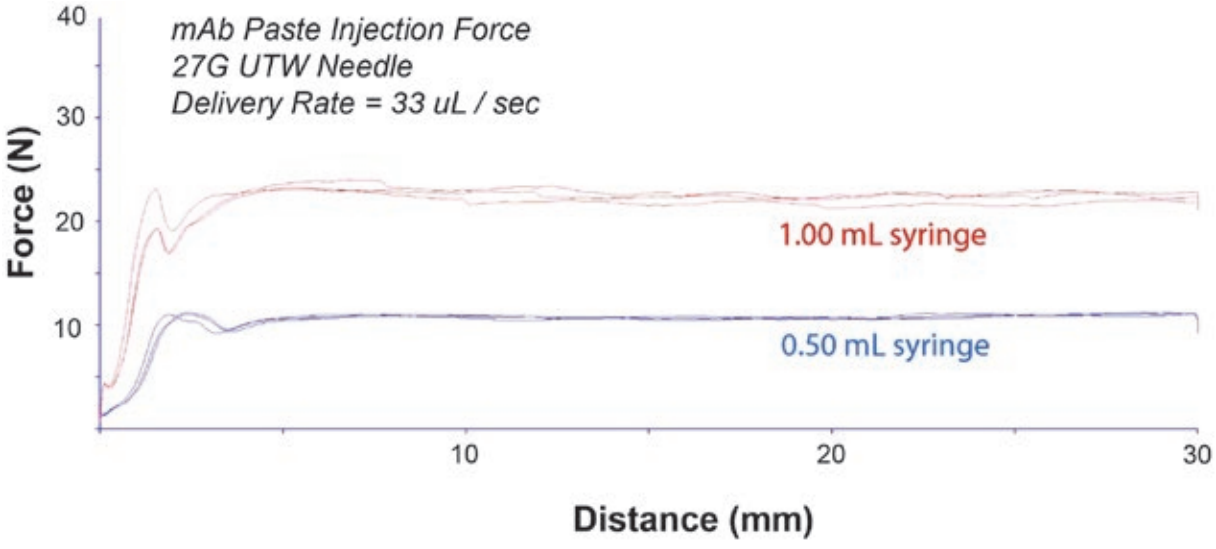

Figure 4: Injection force profile for a XeriJect™ prefilled syringe with a 27-gauge needle.

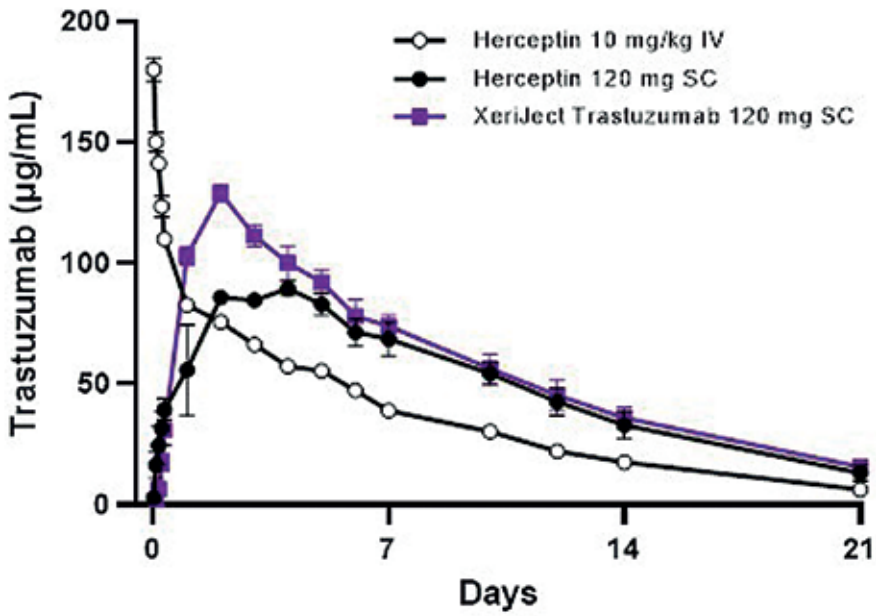

Figure 5: Mean (±SEM) Plasma Concentration–Time Curves of Trastuzumab in Yucatan Minipigs.

Treatment	Dose	N	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (µg.hr/ml)	$T_{1/2}$ (hr)
Herceptin IV	10 mg/kg	4	180 ±5	0.25 ±0	19,160 ±1,170	115 ±12
Herceptin SC	120 mg	4	92 ±2	90 ±15	27,674 ±2,759	122 ±19
XeriJect Trastuzumab SC	120 mg	4	129 ±2	48 ±0	32,118 ±2,587	140 ±5

Table 1: Pharmacokinetic Parameters of Trastuzumab in Yucatan Minipigs.

occurs rapidly, mitigating immunological risks posed by particles present in the subcutaneous space.

Figure 5 shows the pharmacokinetic profile of a XeriJect™ formulation injection compared with both an IV infusion and a SC injection of trastuzumab, in a large animal model (Yucatan minipig). Table 1 contains a list of highlighted pharmacokinetic parameters comparing injection of XeriJect™ suspensions with IV and SC administration of the approved aqueous formulation of trastuzumab drug (Herceptin®). Compared with IV infusion, XeriJect™ formulation administered SC has a longer absorption phase, though the observed elimination half-life is identical. When compared with an SC injection of aqueous trastuzumab, XeriJect™ displays similar absorption and elimination profiles with only minor differences, despite the ~20-fold higher mAb concentration in the XeriJect™ formulation. The XeriJect™ mAb formulation also shows high bioavailability, similar to aqueous IV and SC administration, indicating that, upon injection into the SC space, the XeriJect™ formulation dissolves rapidly and becomes bioavailable.

Neither a depot nor a sustained-release effect is observed. Thus, compared with an equal dose of aqueous mAb, XeriJect™ trastuzumab demonstrated similar pharmacokinetic profiles, allowing for confidence in undertaking XeriJect™ drug development programs.

CONCLUSION

Highly concentrated, ready-to-use formulations are required to optimise patient acceptance of mAb therapies. mAb therapeutics are increasingly dominating the biopharmaceutical landscape by market share, although patient acceptance remains a problem. Xeris' next-generation formulation and delivery platform, XeriJect™, can enhance acceptance and accessibility by enabling the SC delivery of protein therapeutics at high doses and high stability.

The XeriJect™ technology leads to products that are easier to use for patients and caregivers, while reducing costs for payers and the healthcare system.

ABOUT THE COMPANY

Xeris Pharmaceuticals is a specialty pharmaceutical company that leverages novel formulation technology platforms to develop and commercialise ready-to-use liquid-stable injectables. The company is focused on creating medicines that are easier to use, including its Gvoke® glucagon injection, which uses Xeris's technology to deliver ready-to-use solutions for patients and caregivers alike. Xeris Pharmaceuticals is a wholly owned subsidiary of Xeris Biopharma Holdings.

REFERENCES

1. *Ecker DM et al, "The Therapeutic Monoclonal Antibody Product Market". BioProcess International, 2020, Vol 18(10).*
2. *Janssen Biotech, "Darzalex (daratumumab) [FDA label]". 2019.*
3. *Viola M et al, "Subcutaneous delivery of monoclonal antibodies: How do we get there?". J Control Rel, 2018, Vol 286, pp 301-314.*
4. *Bussemer T et al, "Approaches in subcutaneous delivery of monoclonal antibodies". Eur Pharm Rev, 2016, Vol 4, pp 26-31.*

ABOUT THE AUTHOR

Steve Prestrelski, PhD, is the Founder and Chief Scientific Officer of Xeris Pharmaceuticals. He has been working in the area of biopharmaceutical development and innovative drug delivery. Prior to starting Xeris, Dr Prestrelski held technical and management positions at Amgen, Alza (since acquired by J&J), PowderJect Technologies (since acquired by Chiron, itself acquired by Novartis), AlgoRx Technologies and Amylin (since acquired by Bristol-Myers Squibb and AstraZeneca). He is responsible for the development of several approved drug products globally. He has more than 50 peer-reviewed publications and is an inventor on >100 patents worldwide.

EXTRACELLULAR VESICLE ENGINEERING: OPTIMISING NATURE'S NON-IMMUNOGENIC, DRUG DELIVERY PLATFORM

In this article, Anna Cifuentes-Rius, PhD, Research & Innovation Manager at Exopharm, discusses the exciting potential of extracellular vesicles to advance drug delivery, in particular their natural ability to carry API payloads across difficult-to-traverse biological barriers.

With the promise to simultaneously boost both the safety and efficacy of their medicinal cargo, nanoparticle drug delivery technologies that can transport a protected therapeutic payload to target cells are of increasing interest to pharmaceutical, biopharmaceutical and vaccine development. As such, lipid nanoparticles (LNPs) have gained recognition as a useful delivery platform.[1] Tailored LNP formulations were an enabling technology for the novel mRNA vaccines that were swiftly rolled out to help turn the tide of the covid-19 pandemic. LNPs and liposomes have also been deployed to improve the safety and pharmacokinetic profile of small molecule drugs, such as Doxil (doxorubicin – Sequus Pharmaceuticals, CA, US), and to enable *in vivo* delivery of siRNA, such as Onpattro (patisiran – Alnylam Pharmaceuticals, MA, US).

> "There remains a clear and pressing need for delivery systems that silently shepherd a therapeutic cargo to its intended target tissue."

Despite these notable successes, LNP vectors have not proven to be the therapeutic delivery panacea. Many tissues are still beyond the reach of synthetic drug delivery vectors, and concerns remain over safe and effective redosing. These significant challenges can lead to suboptimal delivery and therapeutic efficacy, as well as potentially harmful side effects. There remains a clear and pressing need for delivery systems that silently shepherd a therapeutic cargo to its intended target tissue.

Although LNP research continues to advance, the discovery and accelerated development of extracellular vesicles (EVs) suggests that these nanoparticles may be naturally suited to drug delivery.[2] EVs are nano-sized lipid vesicles secreted from living cells and present in cell culture media and other biological fluids. EVs have evolved as the body's own system for safely delivering cargo – transferring RNAs, proteins and other bioactive small molecules, for example – from cell to cell, often in a targeted fashion. By harnessing their natural capabilities and modifying them as required using EV engineering techniques, EVs offer significant promise as a valuable addition to the current suite of nanoparticle-mediated drug delivery modalities. As such, EVs are attracting increased attention from the pharmaceutical industry.[3]

EXTRACELLULAR VESICLES – A BRIEF HISTORY

EVs were first described in the early 1980s but were dismissed initially as the garbage bag of the cell.[4] The ejection of these lipid bilayer-wrapped nanoscopic particles by cells was thought to be a cellular waste disposal system, and EVs therefore received little further attention at the time.

The reappraisal of EVs' natural biological role was sparked by the 1996 discovery that EV release and uptake was a key mode by which immune cells co-ordinate their activity against pathogens. EVs' true nature as a delivery system, carrying bioactive molecules between cells was underscored in 2007 by the landmark discovery that EVs can carry an RNA cargo that can directly influence protein expression in recipient cells.

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"A range of techniques have been developed to load EVs successfully with therapeutic cargoes, including small molecule drugs, proteins and RNAs."

As the subsequent decade and a half of increasingly intense research activity has established, EVs represent a highly conserved mechanism by which cells of all types communicate with each other. Rather than jettisoned waste, EVs contain a curated cargo of biomolecules, released to deliver a particular message to other cells throughout the body.

Following this extremely exciting discovery, EVs rapidly gained attention in the sphere of stem cell regenerative medicine when it was shown that native EVs released by stem cells were the main active component of the therapy – the EV-rich supernatant collected from cultured stem cells was shown to have the same therapeutic benefit as infusions of the cells themselves. Native EVs released by stem cells and blood platelets have progressed through early phase human clinical trials and are currently under investigation for a range of applications, from wound healing to cosmetics.

More recently, the EV field has been increasingly focused towards drug delivery. A range of techniques have been developed to load EVs successfully with therapeutic cargoes, including small molecule drugs, proteins and RNAs. Overall, the more that the properties of EVs and their natural behaviours in the body have been explored, the more that EVs appear to lend themselves ideally to drug delivery. These characteristics equip EVs with advanced properties that are, in most cases, superior to their synthetic counterparts.

IMMUNOGENICITY: DRUG DELIVERY UNDER THE RADAR

Evidence suggests that EVs have an intrinsic circulatory stability, as befits their role in cell-to-cell communication.[5] EVs naturally have a negatively charged surface and can carry surface signalling proteins, such as CD47, that stave off mononuclear phagocytic system clearance. Their natural lipid bilayer structure does not trigger hypersensitivity or elicit neutralising antibodies. Critically, this immuno-quiet nature should enable ongoing and repeated dosing of EV-loaded therapeutics, in contrast to synthetic systems, such as PEGylated LNPs, where antibody recognition can compromise subsequent dosing.

In terms of toxicity and immunogenicity, decades of data from blood transfusions attest to the safety with which allogeneic EV-rich biofluids can be infused into patients. More specifically, EVs from allogeneic cell sources have been shown not to trigger a significant immunological response.

Pioneering early-stage EV clinical trials have also shown that EVs can be safely administered to humans. While EV technology is evolving rapidly, the low immunogenicity observed thus far indicates their potential in delivering therapeutics when an immune response needs to be avoided, such as with autoimmune diseases.

LEAPING BARRIERS: ENHANCED TARGETING CAPABILITIES

The body can be considered as a nested set of biological barriers, from systemic to intracellular, that keep different biosystems compartmentalised across various length scales. These barriers can be highly restrictive in what may cross, hampering drug delivery to specific cells and tissues.

Arguably, the biggest factors driving the search for new drug delivery modalities are, firstly, the significant resistance met when crossing these barriers and, secondly, the limited tissue-targeting capabilities of systemically delivered therapeutics, either alone or via viral or non-viral vehicles. For example, targeting any cell type besides hepatocytes remains a significant challenge yet to be solved for intravenously injected LNP drug formulations manufactured at clinical scale.

"EVs can natively target and deliver a cargo to highly restricted areas of the body, depending upon the type and activation status of the parental cell."

EVs naturally enjoy privileged status in the body and are actively transported across many barriers. As such, EVs can natively target and deliver a cargo to highly restricted areas of the body, depending upon the type and activation status of the parental cell. For example, EVs released by certain tumour cells show a strong tropism for other tumour cells. Other cell types shown to be targeted by specific EV populations range from epithelial cells to lung fibroblasts to pancreatic cells.

Another illustrative example would be oral drug delivery, where surviving the harsh conditions of the gastrointestinal tract before entering the body through the gut lining represents the first barrier to be crossed. EVs in milk naturally possess oral uptake characteristics and can carry a bioactive cargo from the gut into systemic circulation. During early life, the EVs present in breast milk are a key mode of biomolecular transfer from mother to baby. EVs in cow's milk also possess the necessary protein coating to enter the body through the gut. In fact, bovine milk-derived EVs are currently being developed as oral drug delivery vectors.

Once in circulation – whether by oral, intravenous or other mode of entry – the brain is a key target for many therapeutics currently under investigation, from those targeting neurodegenerative conditions, such as Alzheimer's disease, to those for central nervous system cancers, such as glioblastoma. The blood-brain barrier (BBB) represents one of the most challenging obstacles to therapeutic delivery, restricting the passage of almost 98% of small molecule drugs. EVs have been shown to be able to deliver a functional cargo to the brain. Intranasal delivery of EV therapeutics is one potential route of entry that may be able to bypass the BBB. Intravenous EV infusion has also been shown to be able to deliver a therapeutic across the BBB and into the brain. For example, in a monkey model of cortical brain injury, intravenous administration of EVs derived from stem cells led to significantly enhanced recovery of motor function.[6]

To increase cell selectivity and tissue tropism, interest in designing and engineering EVs to express select cell-targeting moieties on their surface is increasing in laboratories around the world. For example, one development in this field has been the creation of an array of fusion proteins consisting of an EV membrane protein combined with a specific

cell-surface receptor targeting component. Cell types that can be selectively targeted by drug-loaded EVs in this fashion include cardiomyocytes, neurons and tumour cells. EVs derived from readily cultured HEK293 cells are proving to be a platform well suited to the development of engineered EVs for targeted drug delivery. For synergic benefits, it is possible to co-deliver combinations of therapeutic types to target tissues within the same particle.

Further barriers present themselves once a drug delivery capsule reaches its intended cell target. EVs appear to enjoy a natural advantage when crossing the cell membrane barrier. Several studies have shown how EVs can be taken up and deliver their cargo – both small molecule drugs and RNAs – into cells faster and more efficiently than, for example, LNPs.[7,8] Although, at present, EVs may be more challenging than LNPs to load with a high concentration of RNA cargo, EVs' more efficient transfer of RNA into the target cell cytosol can more than outweigh this current shortcoming. Moreover, techniques to measure actual EV loading are still being refined and, currently, may underestimate the true loading efficiency.

Furthermore, EV RNA-loading research and development is progressing rapidly. For example, it was recently shown that cells load specific RNAs into EVs preferentially based on the presence of a particular sequence recognised by the cell. This finding potentially offers an improved way to tap into cells' own RNA-loading machinery to produce EVs that are highly and selectively enriched in a therapeutic RNA.

INNATE POTENTIAL

Understanding of EV biology has come a long way since their initial description as cellular garbage. EVs are now recognised to roam naturally throughout the body, delivering a bioactive cargo from cell to cell in a targeted fashion. As such, EVs clearly warrant thorough investigation as a drug delivery platform. EV properties are particularly attractive in the context of the known limitations of other delivery technologies.

One bottleneck to large-scale, clinical-grade production of EVs has been the isolation of EVs from cell culture media.[9] Research-scale EV purification has typically focused on ultracentrifugation, which is labour-intensive and not directly scalable, however, alternative processes are being found. EV isolation based on the combination of bespoke resins with highly scalable industry-standard ion-exchange equipment and protocols promises to alleviate this bottleneck, and has proven fit for purpose to purify EVs for human clinical trials.[10]

Inspired by their ideal behaviour as drug delivery nano-vehicles, companies specialising in EV-based therapeutics development have established a growing expertise in large-scale production and harvesting of EVs, loading EVs with a specific therapeutic cargo and decorating the EV surface with selective targeting moieties. These small, cell-derived vesicles appear to offer big potential for targeted drug delivery.

ABOUT THE COMPANY

Exopharm (ASX:EX1) is a clinical-stage biopharmaceutical company that uses EVs to deliver a new class of transformative medicines. Using Exopharm's technologies, the company provides advanced customisation of EVs to improve delivery of active ingredients, including DNA, RNA, small molecules and proteins, to selected cell types and organs. Moreover, Exopharm's LEAP manufacturing technology provides access to large quantities of high-purity EVs for research and clinical uses. Exopharm uses variations and combinations of these technologies to pursue its own product pipeline as well as to enable its biopharma partners to improve delivery of their drug candidates.

ABOUT THE AUTHOR

Anna Cifuentes-Rius, PhD, is responsible for bridging Exopharm's innovation and commercial teams, helping shape Exopharm's research and business development strategy. Before joining Exopharm, Dr Cifuentes-Rius was an academic scientist leading a research team towards the development of targeted nanoparticles for drug delivery. She has worked at world-leading universities, such as the Monash Institute of Pharmaceutical Sciences (Parkville, Australia) and Massachusetts Institute of Technology (MA, US). Dr Cifuentes-Rius's innovations have resulted in 30 publications, one patent and over AUS$1 million (£564,000) in secured funding. She has been awarded several awards in recognition of her emerging leadership, such as the 2020 MIPS Early Career Researcher Award.

REFERENCES

1. *Tenchov R et al, "Lipid Nanoparticles-From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement". ACS Nano, Jun 2021, online ahead of print.*
2. *Herrmann IK, Wood MJA, Fuhrmann G, "Extracellular Vesicles as a Next-Generation Drug Delivery Platform". Nat Nanotechnol, 2021, Vol 16(7), pp 748–759.*
3. *Zipkin M, "Big Pharma Buys into Exosomes for Drug Delivery". Nat Biotechnol, 2020, Vol 38(11), pp 1226–1228.*
4. *Elsharkasy OM et al, "Extracellular Vesicles as Drug Delivery Systems: Why and How?" Adv Drug Deliv Rev, 2020, Vol 158, pp 332–343.*
5. *Witwer KW, Wolfram J, "Extracellular Vesicles Versus Synthetic Nanoparticles for Drug Delivery". Nat Rev Mater, 2021, Vol 6, pp 103–106.*
6. *Moore TL et al, "Mesenchymal Derived Exosomes Enhance Recovery of Motor Function in a Monkey Model of Cortical Injury". Restor Neurol Neurosci, 2019, Vol 37(4), pp 347–362.*
7. *Heusermann W et al, "Exosomes Surf on Filopodia to Enter Cells at Endocytic Hot Spots, Traffic Within Endosomes, and are Targeted to the ER". J Cell Biol, 2016, Vol 213(2), pp 173–184.*
8. *Schindler C et al, "Exosomal Delivery of Doxorubicin Enables Rapid Cell Entry and Enhanced In Vitro Potency". PLoS One, 2019, Vol 14(3), e0214545.*
9. *Colao IL et al, "Manufacturing Exosomes: A Promising Therapeutic Platform". Trends Mol Med, 2018, Vol 24(3), pp 242–246.*
10. *Law S et al, "Ligand-based Exosome Affinity Purification: A Scalable Solution to Extracellular Vesicle Downstream Bottlenecks". Bioprocess Int, 2021, Vol 19, pp 28–34.*

THE DIFFERENCE OF ONE DRUG DELIVERED

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GLASS-FILLED CELANEX® MT® PBT HITS SWEET SPOT FOR BIOLOGICS AND REUSABLE DEVICES

In this article, Bryan Deacon, Global Marketing Manager, Marnik Vaes, Principal Field Development Engineer, and Peter Burke, Business Development Manager, all of Celanese, introduce Celanex® MT® PBT 2406MT GF20, a medical-grade glass-filled engineering polymer that fills a gap in the materials market between standard engineering thermoplastics and expensive high-performance polymers.

Two major driving forces in modern injectable drug delivery include the rise of biologics and the increasing push towards industry-wide sustainability. Both these forces exert their own pressures and present their own challenges to drug delivery device design. A breadth of discussion has taken place within the drug delivery device design community on how best to approach these challenges but sometimes overlooked is the question of what engineering materials are available to make these approaches reality.

When it comes to biologics, the key factor is viscosity – a category of drug that has become more prevalent in the pharmaceutical pipeline. As such, delivery device designers have had to grapple with the challenges that high-viscosity drugs present to traditional autoinjectors. In many cases, this means dealing with greater injection forces so as not to necessitate a larger needle and therefore increased pain for the patient – forces that must be stored in the device, usually as a compressed spring, prior to its actuation.

On the other hand, the industry's drive towards sustainability has invigorated interest in reusable devices. For designers developing reusable drug delivery devices, two key concerns are the longevity and reliability of the device – a reusable pen injector must deliver its last dose as accurately as its first, which requires the device be resistant to wear and creep over its lifetime, and therefore better materials will facilitate longer-lasting devices.

CELANEX® MT® PBT 2406MT GF20

Both sets of challenges expose a current gap in the materials market. New-generation delivery devices may place their components under substantially higher loads than their predecessors and, in such cases, standard engineering thermoplastics currently widely used across the drug delivery sector, such as polyoxymethylene (POM) and polybutylene terephthalate (PBT), may not be up to the task of reliably containing the stored forces required for biologic-containing

> "A clear and present need exists for a middle ground between regular thermoplastics and high-performance polymers that is at present only met by expensive custom-made compounds."

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Property	Unit	Test Method	Celanex MT PBT 2406MT GF20
Density	kg/m³	ISO 1183	1470
Melting temperature, 10°C/min	°C	ISO 11357-1/3	255
MVR, 265°C/2.16 kg	%	ISO 1133	17
Moulding shrinkage, parallel	%	ISO 294-4, 2577	0.3–0.5
Moulding shrinkage, normal	%	ISO 294-4, 2577	0.7–0.9
Water absorption, 23°C-sat	%	ISO 62	0.4
Humidity absorption, 23°C/50% RH	%	ISO 62	0.15
Tensile modulus	MPa	ISO 527-2/1A (Test speed 1 mm/min)	7800
Tensile stress at break	MPa	ISO 527-2/1A (Test speed 5 mm/min)	125
Tensile strain at break	%	ISO 527-2/1A (Test speed 5 mm/min)	3
Charpy notched impact strength, 23°C	kJ/m²	ISO 179/1eA	10
Izod impact (notched), 23°C	kJ/m²	ISO 180/1A	10
Izod impact (unnotched), 23°C	kJ/m²	ISO 180/1U	47

Table 1: Material properties of Celanex MT PBT 2406MT GF20.

autoinjectors or engineering reliable, long-lasting reusable devices. However, using available high-performance polymers would result in an overly expensive and likely over-engineered end product. A clear and present need exists for a middle ground between regular thermoplastics and high-performance polymers that is at present only met by expensive custom-made compounds.

To meet this need, Celanese has developed Celanex® MT® PBT 2406MT GF20 (Table 1), a medical-grade glass-filled PBT with polyethylene terephthalate (PET). Celanex MT PBT 2406MT GF20 is a tribologically modified PBT+PET grade polymer that is reinforced with 20% glass fibre for additional strength and stiffness. The PET improves the outer shell, reducing the material's coefficient of friction and providing an appealing high-quality finish. Furthermore, Celanex MT PBT is readily available to order in quantities suitable for large-scale production. As part of Celanese's MT® line of polymers, glass-filled Celanex MT PBT is suitable for Class I, II and III medical devices and comes with the full support of Celanese's technical expertise (Figure 1).

Glass-filled Celanex MT PBT fits in the sweet spot between standard engineering thermoplastics and high-performance polymers, achieving improved strength, stiffness, creep resistance and tensile modulus compared with unfilled POMs and PBTs and providing a more affordable, general-use option than specialist performance polymers. At present, glass-filled Celanex MT PBT is unique in this category within the medical-grade space, offering:

- Low friction with multiple materials
- Excellent creep resistance
- Retention of elongation suitable for snap-fit assembly
- High strength and stiffness
- Excellent suitability for gamma sterilisation
- High wear-resistance with no running-in required
- Low breakaway force
- Soundless sliding and elimination of stick-slip for improved patient comfort during delivery
- Good chemical resistance
- Smooth, appealing surface finish
- Full technical support from Celanese, including full 3D Moldflow® characterisation.

DESIGN FOR CREEP

Creep, or cold flow, refers to the tendency of materials to slowly deform when held under high stress for extended periods. As such, creep becomes a serious consideration when designing autoinjectors for biologics. In order to deliver these viscous formulations without increasing the size of the needle, these autoinjectors require greater force to push the drug through the needle than is typically required. As such, greater force needs to be stored within the device prior to actuation, usually in the form of a compressed spring. This means that the device components are going to be under greater stress and

Figure 1: Glass-filled Celanex MT PBT provides a broad range of advantages to drug delivery device design, including the full support of Celanese's MT polymers service package.

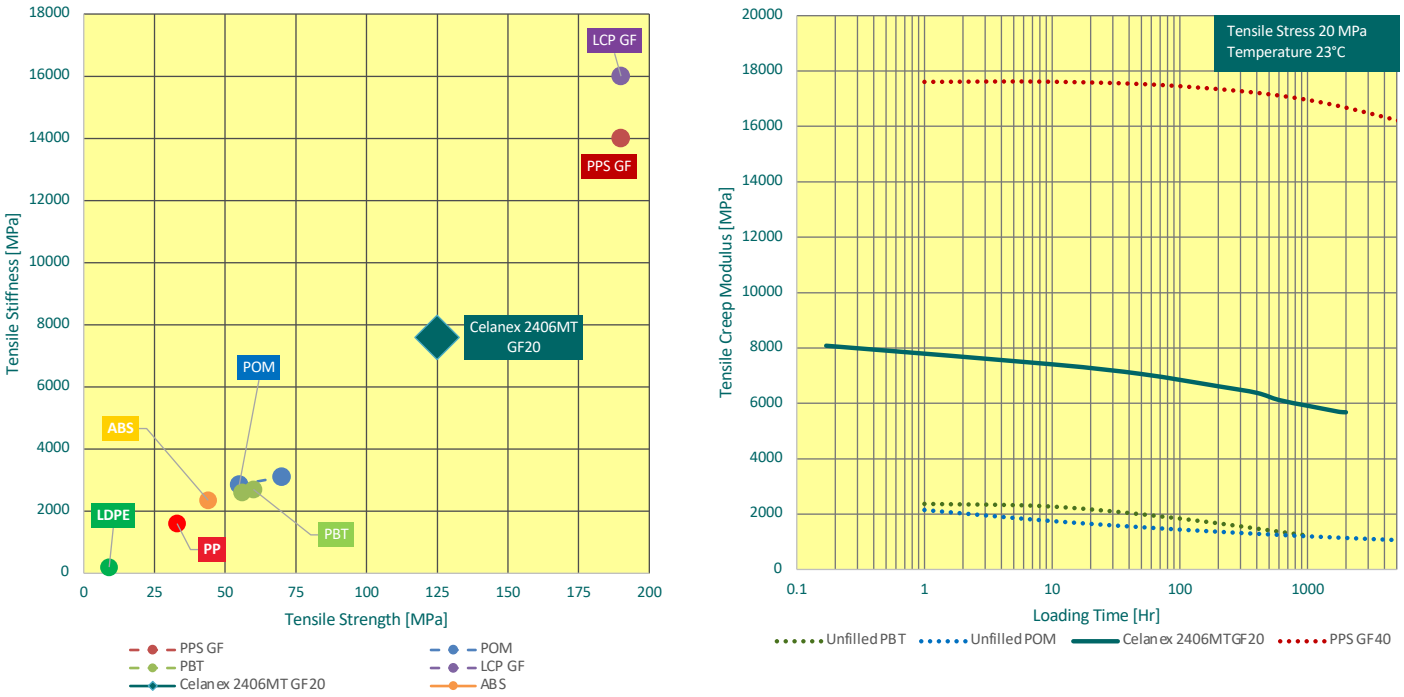

Figure 2: Glass-filled Celanex MT PBT provides a significant increase in tensile creep performance compared with commonly used engineering thermoplastics, bridging the gap between those and high-performance materials.

> "The requirements for stored force are pushing the limits of standard POMs and PBTs. Glass-filled Celanex MT PBT, on the other hand, has been specifically designed with this consideration in mind."

therefore more susceptible to creep and the loss of some of that stored force, which can compromise device reliability and potentially patient safety.

In practice, the requirements for stored force are pushing the limits of standard POMs and PBTs. Glass-filled Celanex MT PBT, on the other hand, has been specifically designed with this consideration in mind, and as such is a significantly stronger material that is much better able to resist creep when exposed to the stored force required to deliver biologics (Figure 2). Because of this resistance to creep, glass-filled Celanex MT PBT enables designers to confidently include high stored forces in their designs and minimise any force requirement on the device's user, and therefore design devices that are easier to use and more patient friendly – a key consideration when taking ageing populations into account.

FRICTION CHARACTERISTICS

When designing any mechanical device with moving parts, friction is going to be a major factor.[1] In injection devices, the primary source of friction will be the slide of the plunger during delivery – a function that should be as smooth as possible to ensure that injection speed is consistent across devices and to minimise pain for the patient.

Glass-filled Celanex MT PBT is tribologically modified to guarantee smooth low-friction sliding. This key material property results in a number of benefits, including reliability, wear resistance and noise reduction. For single-use disposable autoinjectors, consistency in first-time actuation across devices is highly desirable; a material that needs to be run-in to achieve consistent actuation is inherently less suitable, as its first-time use will be less predictable. Glass-filled Celanex MT PBT is designed so that no run-in is required – the first actuation is as smooth as any other, making it an ideal material for ensuring consistency across single-use devices.

Of course, this property is even more valuable for reusable devices. Whether a reusable injector is refillable or designed with a replaceable cartridge, device reliability is critical – a worn-out device could potentially pose a risk to patient safety. The low friction of glass-filled Celanex MT PBT is a twofold advantage for reusable devices, providing the aforementioned lack of run-in and consistent smoothness from the first actuation to the 1,000th, as well as leading to decreased wear and degradation of the device as it is used, resulting in increased reliability and longevity. Furthermore, the low friction of glass-filled Celanex MT PBT eliminates the slip-stick phenomenon, meaning that actuation and sliding is silent, improving the experience of using the device.

Only One Component Required to Reduce Friction

Investigation by Celanese has demonstrated that glass-filled Celanex MT PBT has as consistently low coefficient of friction in interactions with other materials, often significantly lower than those other materials have with themselves (Figure 3). This means that the benefits of glass-filled Celanex MT PBT can be achieved by using a single component rather than needing to make the whole device out of it. As such, glass-filled Celanex MT PBT is ideal as a tool in the design toolkit and doesn't mandate a wholesale rethinking of materials and parts to incorporate.

MANUFACTURING WITH GLASS-FILLED CELANEX MT

Glass-filled Celanex MT PBT is well suited to medical device manufacturing. The material is suitable for injection moulding and for various sterilisation methods, including

"Another advantage of glass-filled Celanex MT PBT is that it is backed by Celanese's wealth of technical expertise, which the company makes readily available to partners to assist them in getting the most out of their materials."

gamma sterilisation. Another significant factor is that glass-filled Celanex MT PBT has an ideal retention of elongation for snap-fit design for convenient assembly.

It is important to note that working with glass-filled polymers is not equivalent to working with standard thermoplastics – you can't simply switch one for the other with no change to processes. As such, another advantage of glass-filled Celanex MT PBT is that it is backed by Celanese's wealth of technical expertise, which the company makes readily available to partners to assist them in getting the most out of their materials.

Sustainability Advantages

Glass-filled Celanex MT PBT can be used as part of a more sustainable approach to drug delivery device development and manufacturing. Due to the material's higher strength and stiffness compared with standard thermoplastics, components can be designed to be thinner and more lightweight whilst maintaining structural integrity, meaning that less material is required overall. Furthermore, because only a single component in contact needs to be made of glass-filled Celanex MT PBT to take advantage of its low coefficient of friction, it is ideal for use in combination with other low-carbon footprint materials, such as Celanese's ECO-B polymers,[2] as part of a broader move towards sustainable devices.

FULL MT SUPPORT

Celanese offers global support to partners working with the company's MT-grade products. The company has extensive data available for Celanex MT PBT 2406MT GF20, including full 3D Moldflow characterisation, creep tests, friction tests up to 1,000 cycles and sterilisation tests. Celanese offers the expertise to enable partners to optimise their transition to glass-filled Celanex MT PBT and take full advantage of the benefits it can provide.

Celanese's MT-grade polymer services package includes consulting and support services, from initial concept, through part design, all the way past commercial launch of a device or combination product. The package details Celanese's commitment to the medical device industry, with the highest levels of quality assurance, regulatory data and support, notification of change, supply security and manufacturing controls, including:

- Long-term supply assurance
- Change notification commitment
- Certified biocompatibility (USP Class VI / ISO 10993)
- Food contact compliance (US FDA and EU)
- Animal- and latex-free formulations
- FDA Drug & Device Master File listing
- Production aligned with GMP principles
- Additional analytical and individual batch testing
- Expanded certificate of inspection
- Support in regulatory approval process.

CONCLUSION

The current gap between standard thermoplastics and high-performance polymers naturally leads to devices using materials that result in them being either over- or under-engineered. Until now, designers seeking a material in this space have had to rely on expensive custom compounds. To meet the need for a mid-range material in the medical-grade space, Celanese has developed Celanex MT PBT 2406MT GF20, a tribologically modified PBT+PET polymer with 20% glass filling, providing an excellent balance of properties for use across the medical sector.

Glass-filled Celanex MT PBT offers excellent creep resistance, low friction against itself and a diverse range of other materials for superior lubricant-free slide

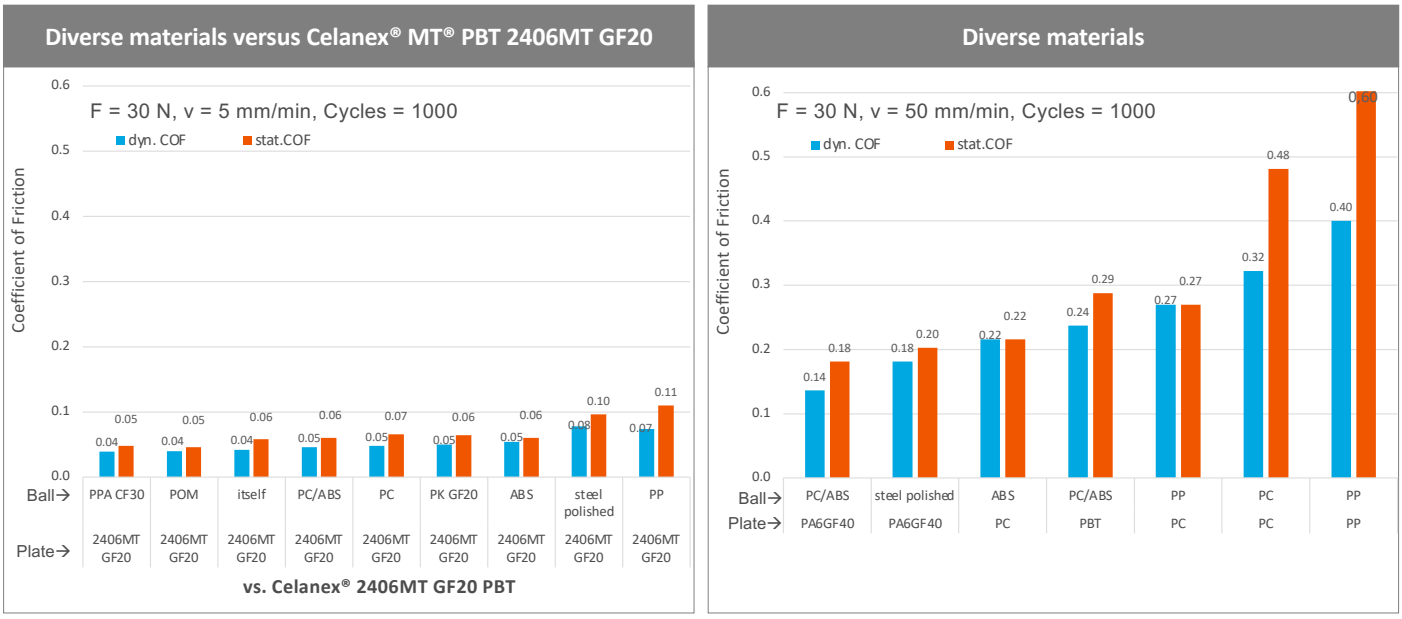

Figure 3: Glass-filled Celanex MT PBT has a reduced coefficient of friction for a diverse range of materials, meaning that only one component needs to be made of glass-filled Celanex MT PBT to achieve its low-friction advantages.

characteristics and no running-in so that the first actuation is as smooth and quick as the 1,000th. The material is ideal for handling the stored forces required to deliver viscous biologic formulations, as well as offering the wear resistance and consistency desirable for long-lasting reusable devices, all while remaining suitable for snap-fit assembly and providing a smooth, high-quality surface finish.

Celanese offers full global support to partners to help them take full advantage of their materials. The company has a wealth of data and expertise available, including full 3D Moldflow characterisation, so that partners can make optimal use of glass-filled Celanex MT PBT in their device designs. Glass-filled Celanex MT PBT currently occupies a unique position on the market, being the only medical-grade material to hit the sweet spot between standard thermoplastics and high-performance polymers readily available for large-scale production, making it a natural choice for designing devices that are more robust, reliable and patient friendly.

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. Celanese's businesses use the full breadth of the company'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, it strives to make a positive impact on communities and the world through The Celanese Foundation. Based in Dallas (TX, US), Celanese employs approximately 8,500 employees worldwide and had 2021 net sales of US$8.5 billion.

Delivering cutting-edge advances in medical devices is hard – a fact Celanese knows because its healthcare division has been doing it for decades. With a proven track record of supporting medical device innovation with expertise, materials and support, Celanese can help turn your design vision into reality. The company's high-performance polymers and thermoplastics unlock opportunities for improving patient care. Learn how Celanese's capabilities can help you address your biggest design challenges at healthcare.celanese.com.

REFERENCES

1. *Markgraf K, Johnson W, "New Material Developments for Medical Devices: Polymers with Improved Tribology". ONdrugDelivery, Issue 57 (Apr 2015), pp 40-42.*
2. *Norfleet K, Haley R, "Hostaform® POM ECO-B – Proven, Versatile, Easy and Environmentally Sustainable". ONdrugDelivery, Issue 117 (Mar 2021), pp 12–16.*

ABOUT THE AUTHORS

Bryan Deacon is a Global Marketing Manager for Celanese specialising in the drug delivery device area. Over the past two decades, in various roles, he has supported the development of some of the world's most successful drug delivery devices, working across the value chain to help end users bring their products to market. Mr Deacon holds a BEng in Mechanical Engineering/Computer-Aided Engineering from Heriot-Watt University in Edinburgh (UK).

Marnik Vaes is Principal Field Development Engineer for the Celanese Healthcare business in Europe, collaborating along the value chain to drive innovations in medical device platforms for multinational healthcare original equipment manufacturers. He has more than 25 years of experience in a range of application development and commercial roles, delivering petrochemical solutions to customers in the healthcare industry. Mr Vaes holds a Master of Industrial Science from the University of Leuven (Belgium).

Peter Burke is a Business Development Manager for the Medical business at Celanese and has worked with various medical customers and pharma OEMs for the past 10 years. He started his career with Celanese in 1998 and during this time has held several account and key account manager roles. Mr Burke holds a BSc in Polymer Science and Technology from the University of Manchester Institute of Science and Technology (UMIST, UK) and a post-graduate Diploma in Marketing.

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Celanex® MT® PBT 2406MT GF20, is a medical-grade PBT+PET reinforced with 20% glass fiber for additional strength, stiffness and creep resistance. This versatile material incorporates a high-performance lubricant for low friction sliding on multiple other polymers and metals. As part of the Celanese MT® line of polymers, glass-filled Celanex® MT® PBT can be used for Class I, II and III medical devices and comes with the full support of Celanese's technical expertise.

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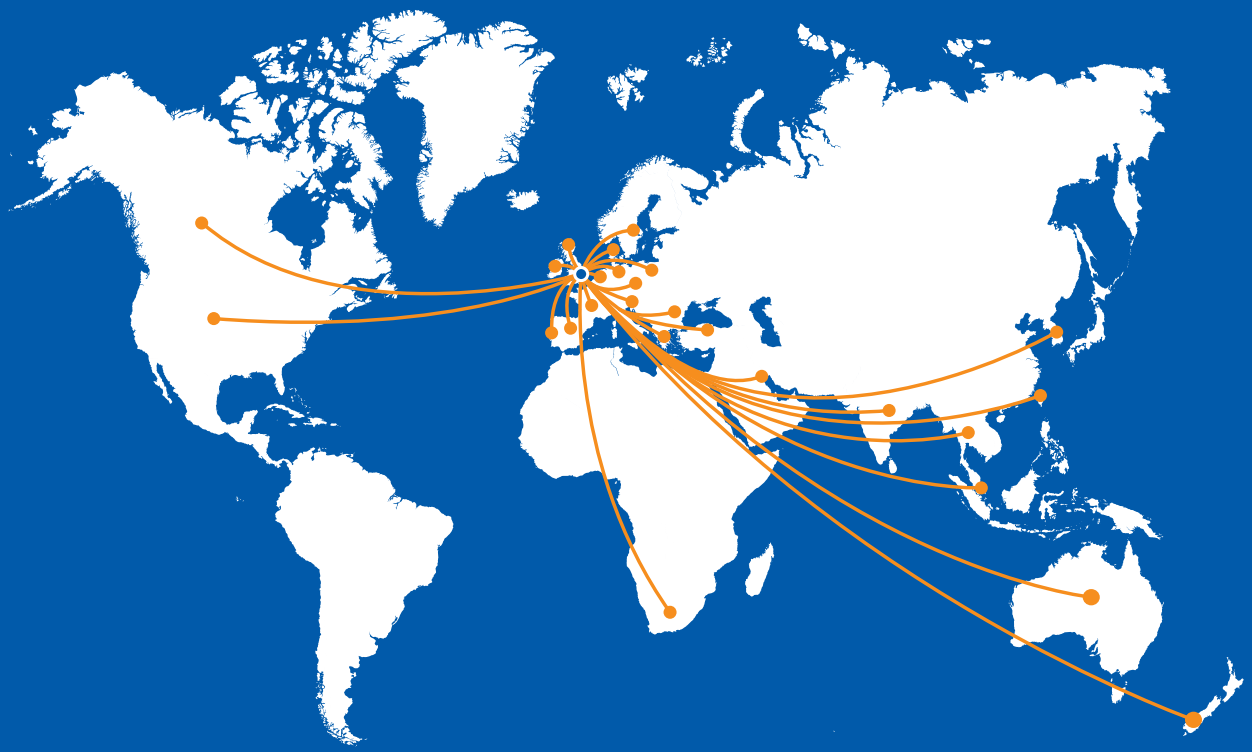

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MITSUBISHI GAS CHEMICAL

OXYCAPT™: A SUPERIOR PRIMARY CONTAINER MATERIAL FOR BIOLOGICS AND GENE AND CELL THERAPIES

In this article, Hiroki Hasegawa, Researcher, and Tomohiro Suzuki, Associate General Manager, both at Mitsubishi Gas Chemical, provide an overview of the OXYCAPT multilayer vial and syringe, along with a discussion of how OXYCAPT fares at low and very low temperatures.

In recent years, the pharmaceutical industry has expressed increasing interest in primary containers that can be used at low or very low temperatures. In particular, this interest has come from the desire for containers suitable for biologics and regenerative medicines, such as gene and cell therapies. As these drugs are sensitive to heat, oxygen, UV light and inorganic extractables, amongst other factors, and therefore have to be stored at low or very low temperatures, plastic containers are often regarded as a preferable option to the alternatives. Based on such requests, Mitsubishi Gas Chemical (MGC) has conducted stability tests on its OXYCAPT™ multilayer plastic vial at very low temperatures to ascertain its suitability for this role.

> "The carbon footprint, NO_x and SO_x emissions and water consumption associated with plastic containers for medical use are several times smaller than those of their glass equivalents."

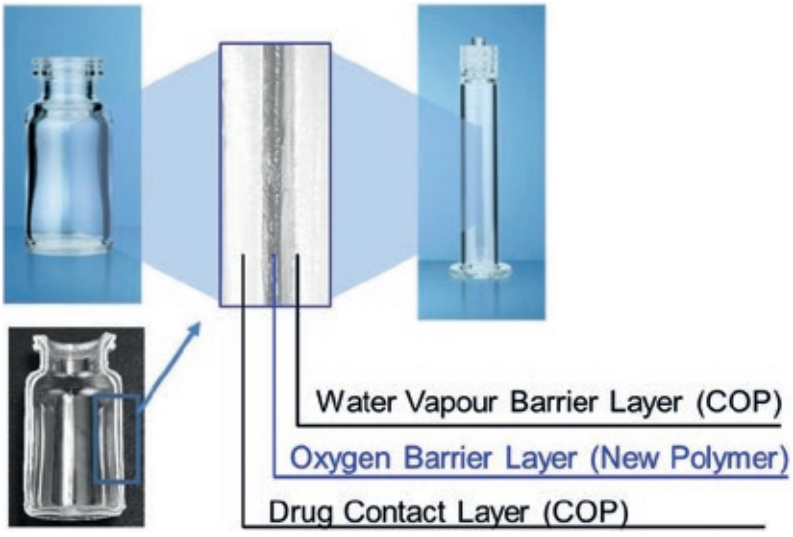

Figure 1: Multilayer structure of OXYCAPT.

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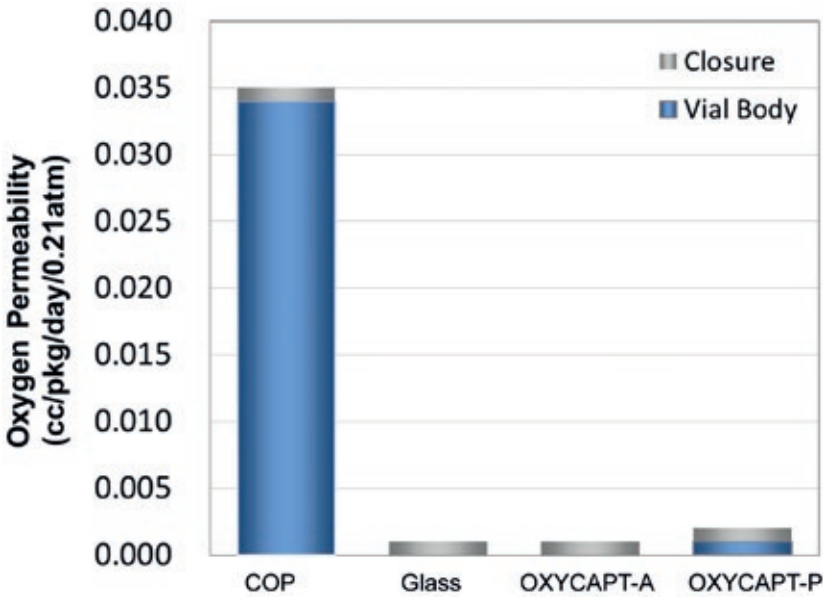


Figure 2: Oxygen permeability comparison of a typical COP, glass, OXYCAPT-A and OXYCAPT-P.

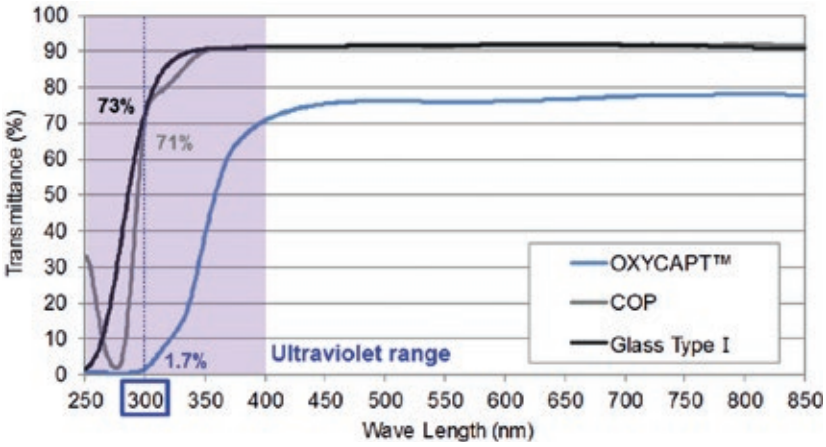


Figure 3: UV light transmittance comparison of a typical COP, Type 1 glass and OXYCAPT.

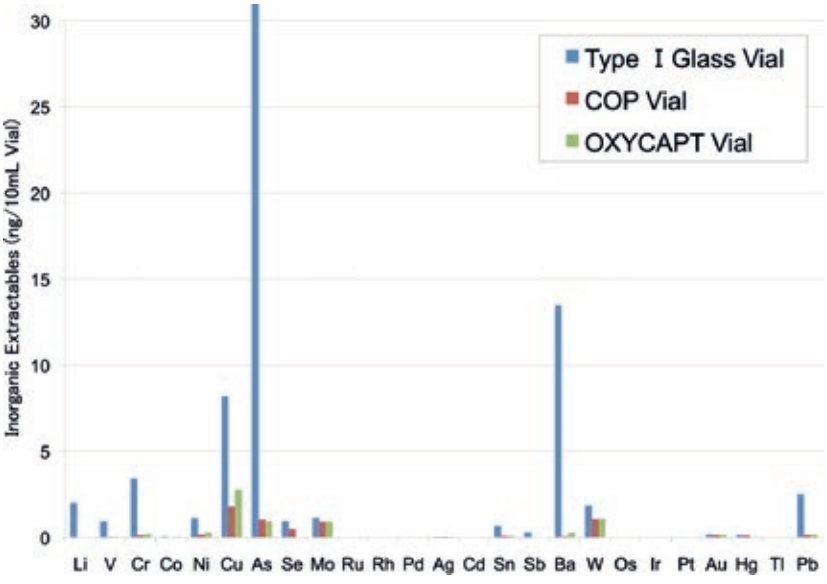


Figure 4: Comparison of inorganic extractables found in COP, Type 1 glass and OXYCAPT.

OXYCAPT consists of three layers – the drug contact layer and the outer layer are made of COP, and the oxygen barrier layer is made of MGC's novel polyester (Figure 1). OXYCAPT offers many advantageous properties, including:

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

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, NO_x and SO_x emissions and water consumption associated with plastic containers for medical use are several times smaller than those of their glass equivalents.

PROPERTIES OF OXYCAPT VIAL AND SYRINGE

There are two types of OXYCAPT multilayer plastic vial and syringe – OXYCAPT-A and OXYCAPT-P. OXYCAPT-A offers a glass-like oxygen barrier. According to internal studies, thanks to its oxygen-absorbing function, OXYCAPT-A can maintain lower oxygen concentrations in the headspace than Type 1 glass. OXYCAPT-P also provides an excellent oxygen barrier, although there is no oxygen-absorbing function. For example, the oxygen barrier of an OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial (Figure 2).

OXYCAPT also provides an excellent UV barrier. While about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT (Figure 3). MGC has confirmed that this feature contributes to the stability of biologics.

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

"MGC can offer bulk vials and RTU vials and syringes, with its RTU products provided in standard nest and tub formats."

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 (Figure 4). Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

The OXYCAPT vial and syringe are produced by co-injection moulding technology. Although this technology has been used in the production of beverage bottles for many years, MGC is the first company to succeed in applying it to the production of multilayer plastic syringes. MGC has also developed inspection methods for testing the oxygen barrier layer. All of the containers are fully inspected by state-of-the-art inspection machinery.

MGC can offer bulk vials and ready-to-use (RTU) vials and syringes, with its RTU products provided in standard nest and tub formats (Figure 5). The nest and tub are mainly sterilised using gamma rays. There are 2, 6, 10 and 20 mL variants for vials, and 1 mL long and 2.25 mL variants for syringes (Table 1). MGC is willing to provide samples for initial testing free of charge.

Each polymer meets the requirements of United States Pharmacopeia (USP) regulations USP<661>, USP<87> and USP<88>, as well as those of the European Pharmacopeia, and has been filed in the US FDA's drug master file (DMF). The vials and syringes are also compliant with each pharmacopoeia and have been filed in the DMF. The syringes are produced and controlled in accordance with ISO 13485.

The primary target market for OXCAPT 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. Additionally, MGC believes that OXYCAPT is well suited to emergency adrenaline, which is well known as an oxygen-sensitive drug, because OXYCAPT combines both an oxygen barrier equivalent to Type 1 glass and the breakage resistance of a polymer. 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.

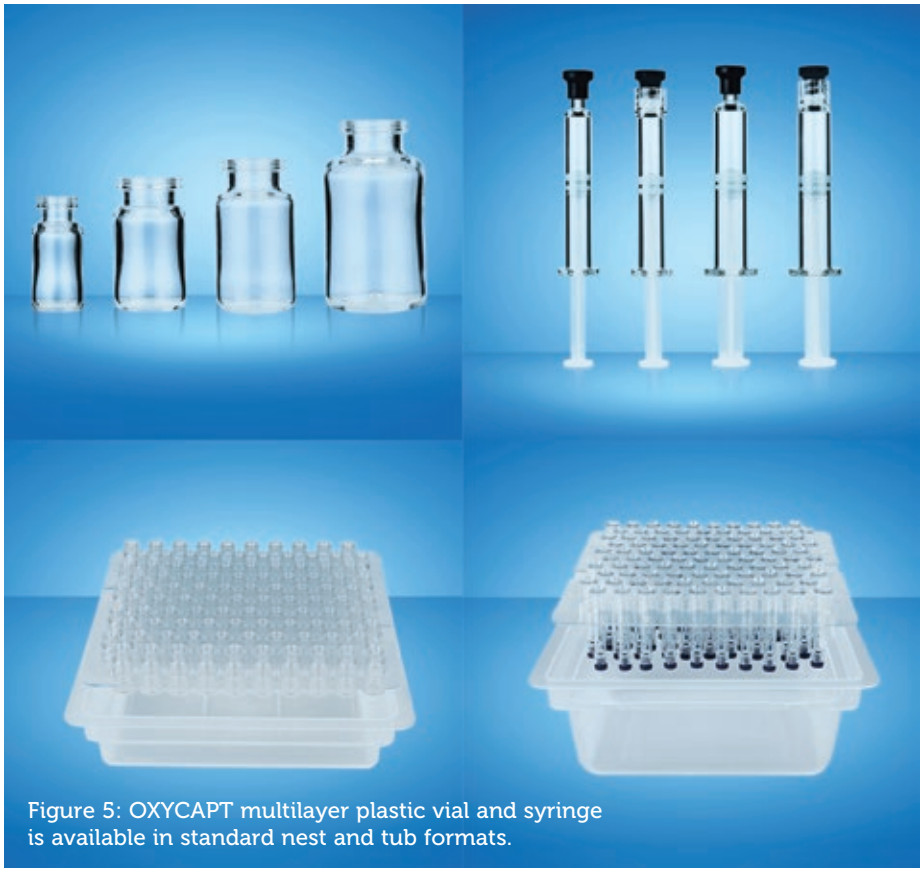


Figure 5: OXYCAPT multilayer plastic vial and syringe is available in standard nest and tub formats.

Type	Volume	ISO	Parts	Option
Vial	2 mL	ISO 8362-1	Vial	Bulk or RTU
	6 mL	ISO 8362-1	Vial	Bulk or RTU
	10 mL	ISO 8362-1	Vial	Bulk or RTU
	20 mL	ISO 8362-1	Vial	Bulk or RTU
Syringe	1 mL long	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU
	2.25 mL	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU

Table 1: MGC's OXYCAPT product portfolio.

OXYCAPT AT VERY LOW TEMPERATURES

In order to verify the suitability of OXYCAPT™ for drugs stored at very low temperatures, MGC carried out studies using OXYCAPT vials. As customers often ask about the durability of OXYCAPT at low temperatures, MGC conducted quick defrosting and dropping tests. Firstly, the vials were stored in a freezer at -80°C for one day. After being removed from the freezer, the frozen vials were immediately dipped into hot water (40°C) for 15 minutes. No breakage, leakage or layer separation was detected in any of the vials (Figure 6).

Figure 6: No breakage, leakage or layer separation was found after the quick defrosting test (-80°C to 40°C).

> "Although eight of the COP-monolayer vials were broken, no breakage or leakage was detected in any of the OXYCAPT vials."

A further test was conducted where the vials were stored in a freezer at -80°C for one-week, six-month and 24-month periods. After being removed from the freezer, the vials were immediately dropped onto a steel plate from a height of 150 cm. No breakage, leakage or layer separation was detected in any of the vials for any length of time in cold storage.

Finally, the same dropping test was conducted using OXYCAPT and COP monolayer vials that had been stored at approximately -180°C, as regenerative medicines such as gene and cell therapies are often preserved in liquid nitrogen gas phase freezers. After being removed from the liquid nitrogen gas phase freezer, the vials were immediately dropped to a steel plate from a height of 150 cm. Although eight of the COP-monolayer vials were broken (Figure 7), no breakage or leakage was detected in any of the OXYCAPT vials (Table 2). For clarification, as it was considered obvious that glass vials would shatter as a result of these tests and present a safety risk to the experimenters, glass was excluded from the test.

Figure 7: Broken COP vial after drop test following storage at -180°C.

	OXYCAPT Vial	COP Monolayer Vial
Breakage	0/20	8/20
Leakage*	0/20	8/20

** Dropped vials were stored at room temperature until the frozen water was defrosted and then leakage was observed.*

Table 2: Breakage and leakage from COP and OXYCAPT vials stored at -180°C.

In addition to the durability tests, MGC carried out a leak test, as some customers have expressed concern about leakage of liquid due to the vial and rubber stopper shrinking at ultra-low temperatures. OXYCAPT vials with 10 mL water, 0.1% polysorbate 80 and 0.05 % toluidine blue were stored sideways at -180°C for one month and then stored at 23°C for one week. After the cap and rubber stopper were detached from the vial, leakage of liquid between the lip of the vial and the rubber stopper was observed by the naked eye (Figure 8). As no leakage was detected for any of the vials (Figure 9), MGC concluded that the OXYCAPT vial can be

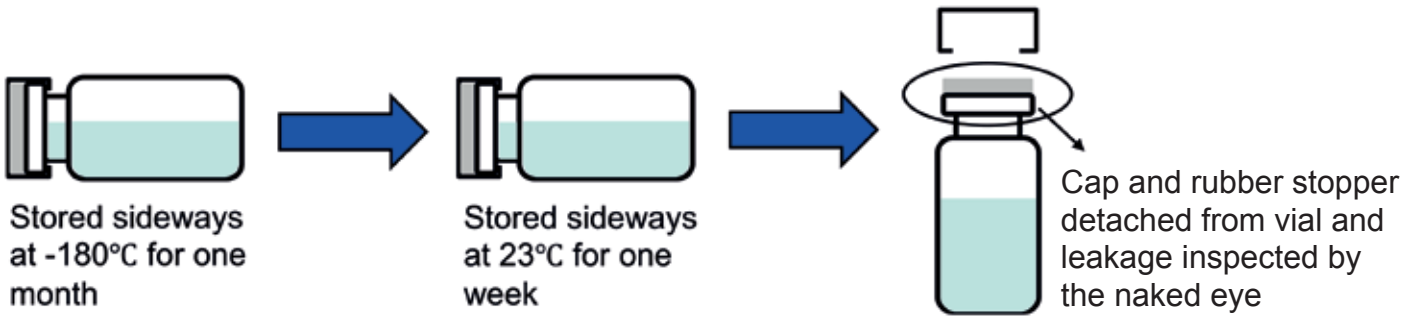


Figure 8: Procedure for the leak test.

Figure 9: Examination of OXYCAPT vial after storage at -180°C.

used to store drugs in liquid nitrogen gas phase conditions. Furthermore, since it is well established that the shrink rate between thermoplastic material and rubber is smaller than that between glass and rubber, MGC is planning to conduct additional container closure integrity tests using the oxygen-ingress method at very low temperatures.

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

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.

> "These latest results have contributed to the ongoing studies verifying OXYCAPT's superior properties for biologics and regenerative medicines."

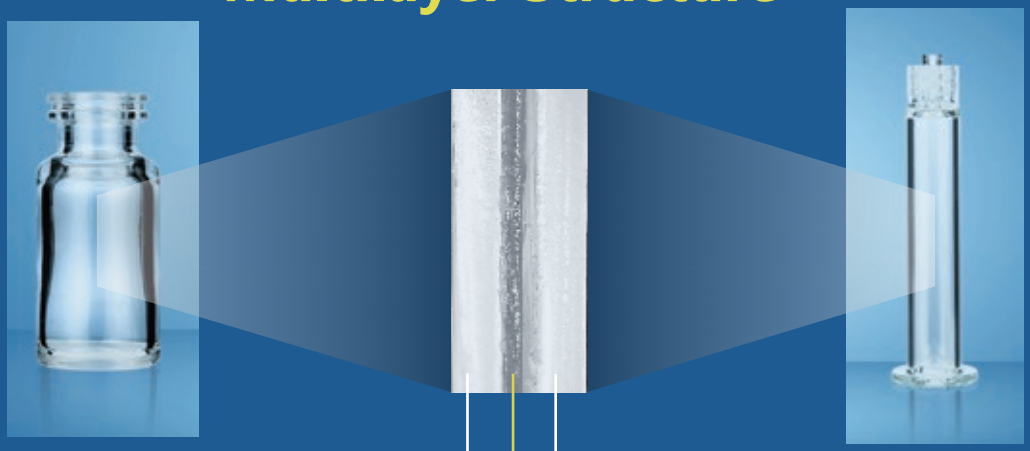
ABOUT THE AUTHORS

Hiroki Hasegawa is a researcher in the Advanced Business Development Division at MGC. He gained a diploma in science in 2013 and a master's degree in science in 2015 from Osaka University (Japan). Since April 2015 he has been working for MGC, in charge of macromolecular science, especially in the composition development of thermosetting resin. Since 2018 he has been part of the team developing multilayer plastic vials and syringes for biologics.

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™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Small Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Gene/Cell Therapy

2, 6, 10, 20mL Vial

Nest & Tub for Vial

1, 2.25mL Syringe

Nest & Tub for Syringe

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PREMIUMCOAT® SOLUTIONS: HELPING CONTROL THE LEVEL OF SILICONE TO PROTECT SENSITIVE THERAPEUTICS

Here, Sébastien Cordier, Technical Product Manager for PremiumCoat, Vincent Holterboch, Director of Research and Development, and Estelle Verger, Business Development Senior Manager for PremiumCoat®, all of Aptar Pharma, discuss how coated elastomer components, such as Aptar Pharma's PremiumCoat®, can help drug developers optimise the balance between component processability and minimising silicone migration into a drug product.

PROTECTING DRUG FORMULATIONS

From oncolytic drugs to biologics and covid-19 vaccines, injectable drug formulations undergo a long journey before their therapeutic benefits can be brought to patients around the world. A crucial aspect of success on this journey is finding the optimal primary packaging, which plays a critical role in maintaining the stability and efficiency of the drug formulation.

> "Whether a vial or PFS, primary packaging must be precisely engineered to protect the drug formulation from outside contamination and degradation throughout its shelf life."

Whether a vial or prefilled syringe (PFS), primary packaging must be precisely engineered to protect the drug formulation from outside contamination and degradation throughout its shelf life. Particulate contamination, faulty container closure integrity, extractables and leachables or other chemical contaminations are some of the many factors that may compromise the API and present a threat to patient safety. Increasing focus is therefore being placed on the importance of minimising the risks related to interaction between a drug formulation and its primary packaging. These considerations become even more acute for sensitive formulations, such as protein-based biologics, which make up a growing proportion of the injectable medicine landscape, and covid-19 vaccines, which leverage advanced formulations of biomolecules.

Aside from glass containers, the only primary packaging components in direct contact with the drug formulation are vial stoppers, PFS plungers and tip closures. In addition to protecting the drug and allowing its easy delivery, these elements must also be easily processable on filling lines, either by pharma companies or contracted manufacturers. Siliconisation, which involves lubricating rubber components with silicone oil, is a necessary process to secure the machinability of stoppers

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"PremiumCoat® high-quality components have been proven to reduce extractables and leachables."

and plungers. It is required to prevent components from sticking together and to reduce friction with filling equipment and other components, thereby limiting the potential for elastomeric particles to be generated during processing. Silicone oil also helps ease the stopper's application onto the vial and, in the case of syringe plungers, helps reduce the friction with the glass barrel. As such, siliconisation minimises break-loose and glide forces, leading to improved injection system performance when PFSs are activated by healthcare professionals, patients or within an autoinjector.

Studies have reported that the silicone oil applied to the surface of glass syringes and elastomers could migrate into the injectable solution and risk being injected into patients.[1] It is therefore important for packaging manufacturers to ensure that silicone levels are kept under control to mitigate the associated risks and help prevent the migration of silicone into the injectable solution.

Over the past few decades, the pharmaceutical packaging industry has developed advanced rubber formulations to reduce the quantity of extractables and leachables that may be transferred into the drug formulation. Furthermore, by coating the rubber with fluorinated films, such as ethylene tetrafluoroethylene (ETFE), the amount of extractables and leachables can be further reduced.

The result of such advances can be seen in PremiumCoat®, a platform of ETFE film-coated solutions for vials and PFSs developed by Aptar Pharma. These high-quality components have been proven to reduce extractables and leachables, are compatible with standard vial-neck designs, are appropriate for multipiercing applications and demonstrate excellent functional performance on filling lines and during the injection procedure.

Preliminary research conducted by Aptar Pharma, in collaboration with the Institute of Materials Science (Mulhouse, France), used X-ray photoelectron spectroscopy, a technique for analysing the atomic composition of a surface, showed that less silicon may be detected on film-coated surfaces (in the form of silicone oil) than uncoated surfaces.[2] Furthermore, Fourier transform infrared spectroscopy (FTIR), a technique for analysing the structure of proteins, demonstrated that model proteins adsorbed on the surface of coated elastomers formed fewer secondary structures (β-sheets), that are known to be associated with higher chances of aggregation.[3,4] Activity assays conjointly demonstrated that proteins adsorbed on coated components were more likely to keep their activity than proteins exposed to naked elastomers.[2] Interestingly, further FTIR assays demonstrated that higher levels of silicone were associated with increased formation of β-sheets.[2] Taken together, these results, based on model proteins, suggest that an interplay between PremiumCoat's coating and reduced amounts of silicone may promote protein stability during storage, further emphasising the need to carefully control the level of silicone oil on closure components.

Aptar Pharma uses a proprietary siliconisation process for its products, including PremiumCoat. Instead of silicone oil being applied as an emulsion during the washing process, Aptar Pharma's siliconisation process is carried out during the drying phase of manufacture. The high temperatures involved help make the silicone

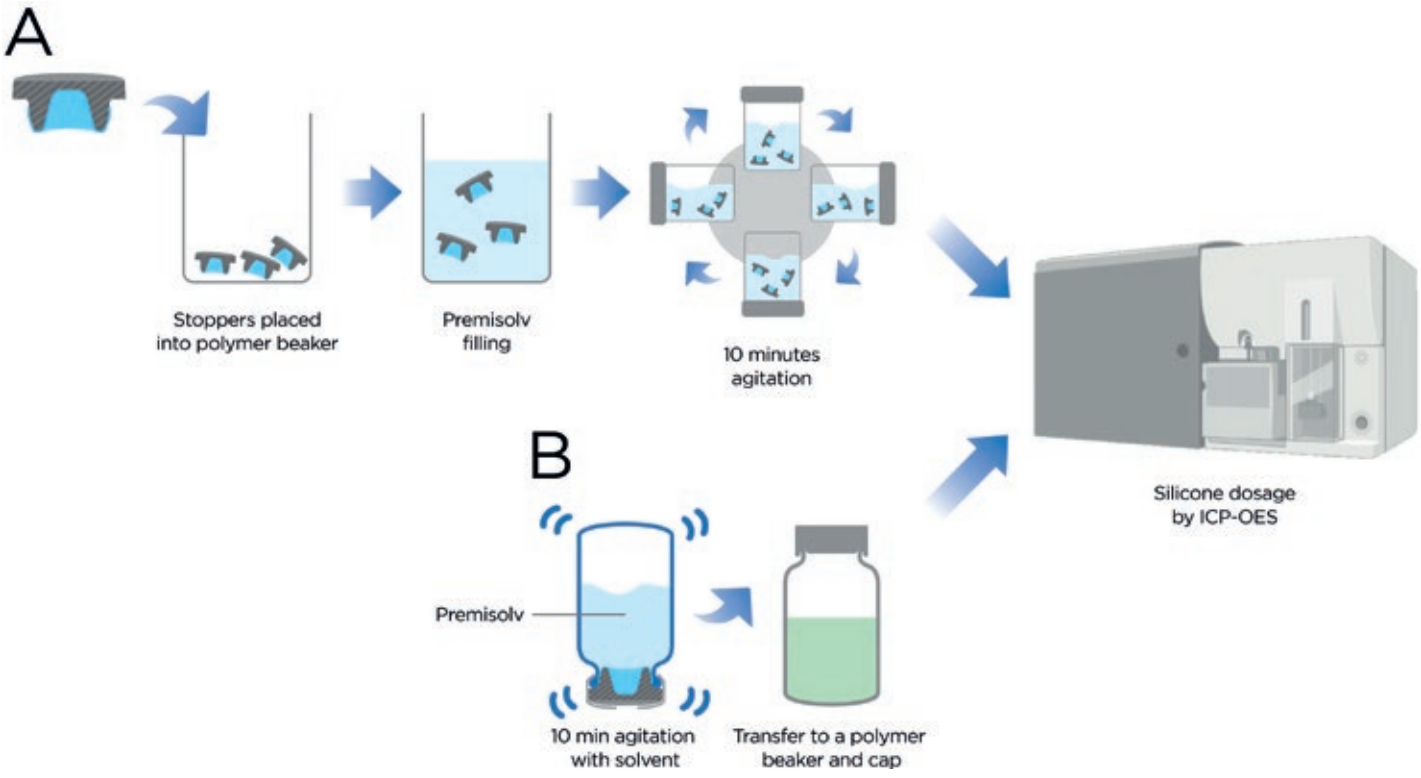

Figure 1: Protocol for measuring the quantity of silicone using ICP-OES. A) The total quantity of silicone is measured by fully immersing stoppers in PremiSolv to extract the silicone oil from the component. The solution is then submitted to ICP-OES for quantifying silicone. B) The quantity of silicone that may be in contact with the drug product is evaluated by inverting a glass vial filled with PremiSolv and closed with the stopper of interest. The solution is then transferred to a polymer vial and analysed by ICP-OES.

oil more fluid, easing its transfer onto elastomer components via contact with the wall of the dryer and contact between the products. Because the inside of the stopper cavity does not offer a point of contact, the chance for excess silicone oil to accumulate there is limited. To explore the silicone oil levels associated with PremiumCoat further, Aptar Pharma conducted a series of detailed tests evaluating the silicone distribution on its products, and comparing them with other ETFE-coated components found on the market.

ACCURATELY MEASURING THE PRESENCE OF SILICONE

Because of the small quantities involved, specialist techniques are required to measure silicone levels accurately. In the tests conducted by Aptar Pharma, the analytical method used was inductively coupled plasma optical emission spectrometry (ICP-OES). In principle, the atoms within a sample are excited by exposure to plasma and the light-emission spectrum produced as the atom recovers its unexcited state is analysed with a spectrometer. Light-emission signatures are directly related to a sample's atomic composition, thereby enabling the accurate quantification of specific elements, including the silicon atoms that form an integral part of silicone oil. The corresponding silicone quantity was calculated from the atomic mass of silicon and the molecular weight and density of silicone.

PREMIUMCOAT® STOPPERS DISPLAY MINIMAL SILICONE QUANTITIES ON DRUG CONTACT SURFACE

The PremiumCoat® manufacturing process has been optimised across all product formats so that the minimum acceptable silicone quantity is added during the drying step. To measure the amount of silicone across the entire surface of the components, the stoppers were totally immersed in Premisolv, a solvent that maximises the extraction of silicone from the component's surface as described in figure 1A. The extract was then analysed by ICP-OES and the distribution of silicone expressed as a ratio of the total quantity of silicone on the stopper with regard to the stopper surface. The quantity of silicone that may come into contact with the drug formulation is evaluated following the protocol featured in Figure 1B, and this quantity is expressed as a ratio with regard to the film-coated surface, which is by design the surface that may come in contact with the drug.

Figure 2 shows that, for both conditions analysed, PremiumCoat® stoppers displayed relatively less silicone per unit of surface at the drug contact surface than on the total surface of the stoppers. For both non-sterilised RTS and gamma-sterilised RTU stoppers, the drug contact surface displays on average 40% less silicone than the rest of the stopper.

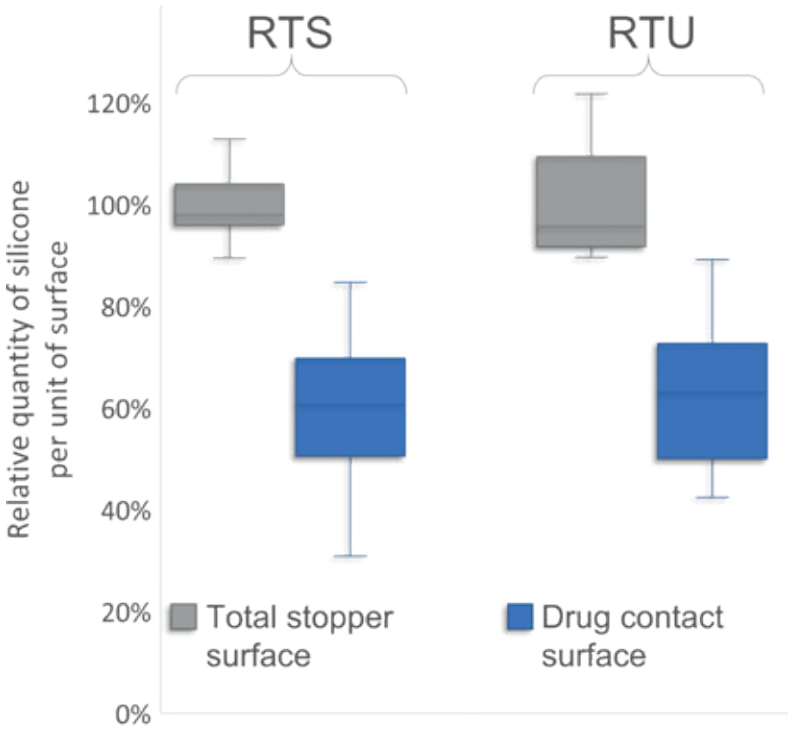

Figure 2: Comparing the distribution of silicone per unit of surface on the total stopper surface and the drug contact surface. For the total stopper surface, three batches were tested with three repetitions per batch and three stoppers per repetition (n=9, total of 27 20 mm stoppers). For the drug contact surface, three batches of 30 stoppers were tested (n=90 20 mm stoppers). Relative quantity of silicone expressed as percentage of average quantity of silicone measured on the total stopper surface. Ready-to-Sterilise (RTS) stoppers were not sterile and Ready-to-Use (RTU) stoppers were gamma-sterilised.

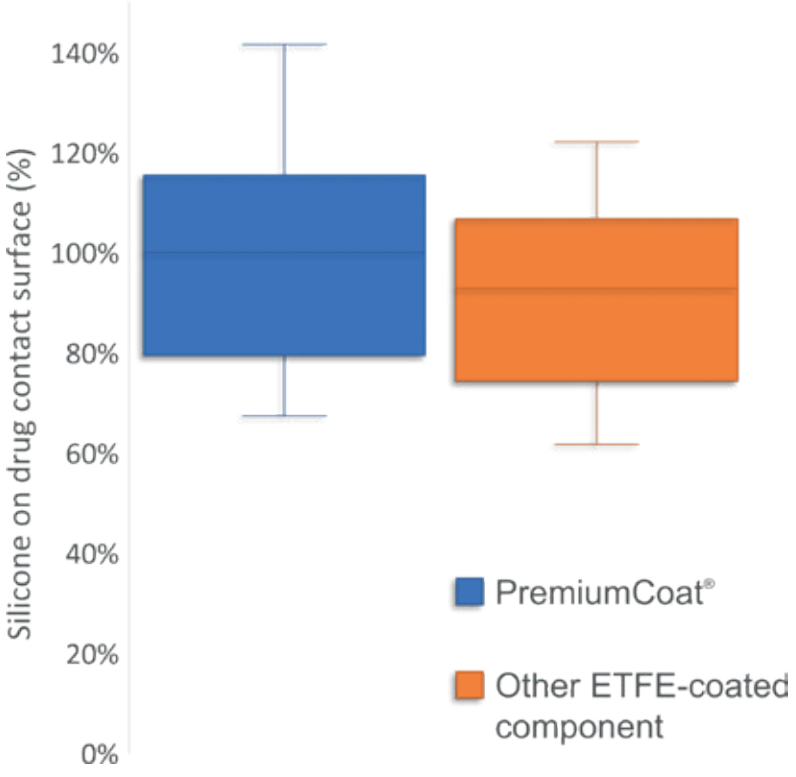

Figure 3: Comparison of the quantity of silicone that may be extracted from the stopper's drug contact surface of 20 mm, RTU gamma-sterilized PremiumCoat® (n=90) or another 20 mm RTU steam-sterilised ETFE-coated stopper (n=60) . Quantity of silicone expressed as percentage of average value for PremiumCoat® components.

"The presence of silicone oil is essential for closure components to fulfil their critical function as part of the primary packaging; however, ensuring that it is applied in the smallest possible quantity reduces the risk of silicone contamination, denaturation and aggregation for sensitive biomolecules."

This observation is a clear indication that Aptar Pharma manufacturing process optimises the distribution of silicone on the stopper's surface. The significantly lower quantity of silicone that is exposed to the drug can help preserve its integrity, while the higher quantity of silicone on the rest of the stoppers may promote optimal machinability on customers filling lines.

PREMIUMCOAT® AND OTHER COATED COMPONENTS PERFORM SIMILARLY WITH REGARD TO SILICONE

As biologics and sensitive drugs become more common on the market, other manufacturers have begun supplying ETFE-coated components. The potential issues caused by silicone oil have been raised by the market, and additional surface treatments have been developed to help mitigate the risks linked to the silicone that may be exposed to the drug product. To compare the performance of other ETFE-coated components with that of PremiumCoat, Aptar Pharma performed additional tests to evaluate the amount of silicone that may migrate into the drug solution for an alternative ETFE-coated stopper, applying the same protocol described in Figure 1B.

In Figure 3, we compare the quantity of silicone extracted from the drug contact surface of PremiumCoat® with the quantity of silicone extracted from the drug contact surface of another type of ETFE-coated stoppers for which additional surface treatments are performed. In the conditions of this test, as performed by Aptar Pharma, PremiumCoat® and the other ETFE-coated stopper displayed similar performances, with all stoppers showing comparable quantities of silicone extracted. Our results indicate that for both Aptar Pharma PremiumCoat® and the other ETFE-coated stoppers, a similar fraction of silicone may come into contact with the drug product.

In conclusion, these results demonstrate that both stoppers are susceptible to releasing very low amounts of silicone into the drug solution. It is important to note that PremiSolv is an aggressive solvent and extracts the totality of the silicone from the surfaces it touches. In practical situations, most therapeutic solutions are solubilised in non-aggressive aqueous solutions, minimising the risk of silicone migration into the drug product.

PREMIUMCOAT® HELPS MITIGATE THE RISKS LINKED TO SILICONE OIL

The findings of these tests are important to help inform decisions regarding the choice of optimal primary packaging for sensitive drug developments. Elastomeric closure components introduce several materials, including silicone oil, into the vicinity of the active drug. This opens the door to a range of possible unwanted interactions that have the potential to compromise the potency of a drug and patient safety for injections.

The presence of silicone oil is essential for closure components to fulfil their critical function as part of the primary packaging; however, ensuring that it is applied in the smallest possible quantity reduces the risk of silicone contamination, denaturation and aggregation for sensitive biomolecules. Aptar Pharma has successfully managed to fulfil this objective with its PremiumCoat solutions to allow the early de-risking of packaging concepts for drugs designers.

For manufacturers of biomolecule-based therapeutics, the complex and dynamic interplay between all the variables within the primary container highlights the need for a deeper understanding of the materials and processes involved. Being equipped with this knowledge greatly increases the chances of success when developing a drug, ensuring its long-term integrity and guaranteeing that every patient receives a safe dose.

All presented data are extracted from routine in-process quality checks and MDNFET001.

ABOUT THE COMPANY

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

REFERENCES

1. *Yu JH et al, "Silicone Oil Droplets Following Intravitreal Bevacizumab Injections". Am J Ophthalmol Case Rep, 2018, Vol 10, pp 142–144.*
2. *Huang T, "Protein Adsorption and Denaturation In Injectable Devices for Pharmaceutical Applications". PhD thesis, 2016, Institut de Science des Matériaux de Mulhouse & Aptar Pharma.*
3. *Dong A et al, "Infrared Spectroscopic Studies of Lyophilization- and Temperature-Induced Protein Aggregation". J Pharm Sci, 1995, Vol 84(4), pp 415–424.*
4. *Fink AL, "Protein Aggregation: Folding Aggregates, Inclusion Bodies and Amyloid". Fold Des, Vol 3(1), pp R9–R23.*

ABOUT THE AUTHORS

Sébastien Cordier is the Technical Product Manager for PremiumCoat projects at Aptar Pharma's injectables division. A graduate of MINES ParisTech (France) and EDHEC Business School (France). Mr Cordier spent over 15 years in the automotive industry, where he developed a strong expertise in plastics and elastomers, before joining Aptar Pharma in 2020. In his current role as Technical Product Manager, Mr Cordier is responsible for the PremiumCoat platform of vial stoppers and syringe plungers, and is dedicated to supporting customer development projects involving coated elastomeric solutions.

Vincent Holterboch is the Global R&D Director dedicated to injectable solutions for Aptar Pharma. As a graduate in mechanical engineering, Mr Holterboch has over 22 years' experience in highly technological industries. Mr Holterboch joined Aptar Pharma in 2021 with the mission to expand the company's technical capabilities further and direct its innovation strategy to secure its position as a world-class leader in the injectables drug delivery market.

Estelle Verger is the Business Development Senior Manager for PremiumCoat-coated solutions for Aptar Pharma's injectables division and is responsible for the growth of the PremiumCoat platform in the global injectables market. A graduate from ESSEC Business School (Paris, France) and Fachhochschule Dortmund (Germany), with a Master's degree in International Business Management, she joined Aptar Pharma in 2011 as a Sales Manager in the company's injectables division. Ms Verger then moved to Aptar Pharma's Consumer Healthcare division as a Product Manager, where she was responsible for airless dispensing solutions for pharmaceutical applications for a number of years, before returning to the injectables division in 2020.

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Technology Showcase: CCBio's Felice Dose

In 2018, it was reported that approximately 50% of intravenous (IV) injections failed due to inflammation of the vein or phlebitis. To combat this, the pharma and biotech industries are looking for a new solution to ease patient pain. On-body injector (OBI) devices aim to respond to this need (Figure 1).

Recently, there has been a trend within pharma towards converting drugs formulated for IV delivery to a subcutaneous (SC) format. This trend is driven by a multitude of factors, including the long-term impacts of covid-19 and the potential offered by prefilled drug delivery options. SC formulations offer patients the option to self-administrate at home and will therefore likely replace IV formulations in many cases as IV administration must be performed in a clinic regardless of injection duration. It is expected that this trend towards SC administration will be especially prevalent in new biologic drugs based on therapeutic proteins. At-home administration would reduce the time burden of treatment on patients and healthcare providers significantly, often entirely eliminating the need for travel to and from the clinic.

As part of this trend, unconcentrated high-dose wearables OBI devices are emerging as a new category in the drug delivery market. OBI devices provide notable benefits for users and drug formulators, especially regarding drug concentration. However, the SC tissue's extracellular matrix limits short-duration SC injection volumes to <2 mL in humans, according to hydrostatic and colloid osmotic pressure gradients, with delivery volumes >2 mL found to cause swelling and pain in skin if delivered too quickly. To counter this, OBI devices allow for longer injection durations; however, ensuring that patients can wear the combined weight of the high-dose drug and OBI device comfortably becomes a crucial design factor.

> "Felice Dose provides a solution to the unmet needs present in the pharma industry, with the ability to deliver large drug volumes over variable- and long-duration injections."

From the patient perspective, the most important need is receiving the correct drug volume accurately and the ability to activate the device easily. Additionally, regulatory scrutiny is increasingly important, with updates of the ISO 11608-6 series, especially those covering fluid lines and paths, meaning that meeting user needs and regulatory standards is the primary challenge faced by high-dose OBI devices.

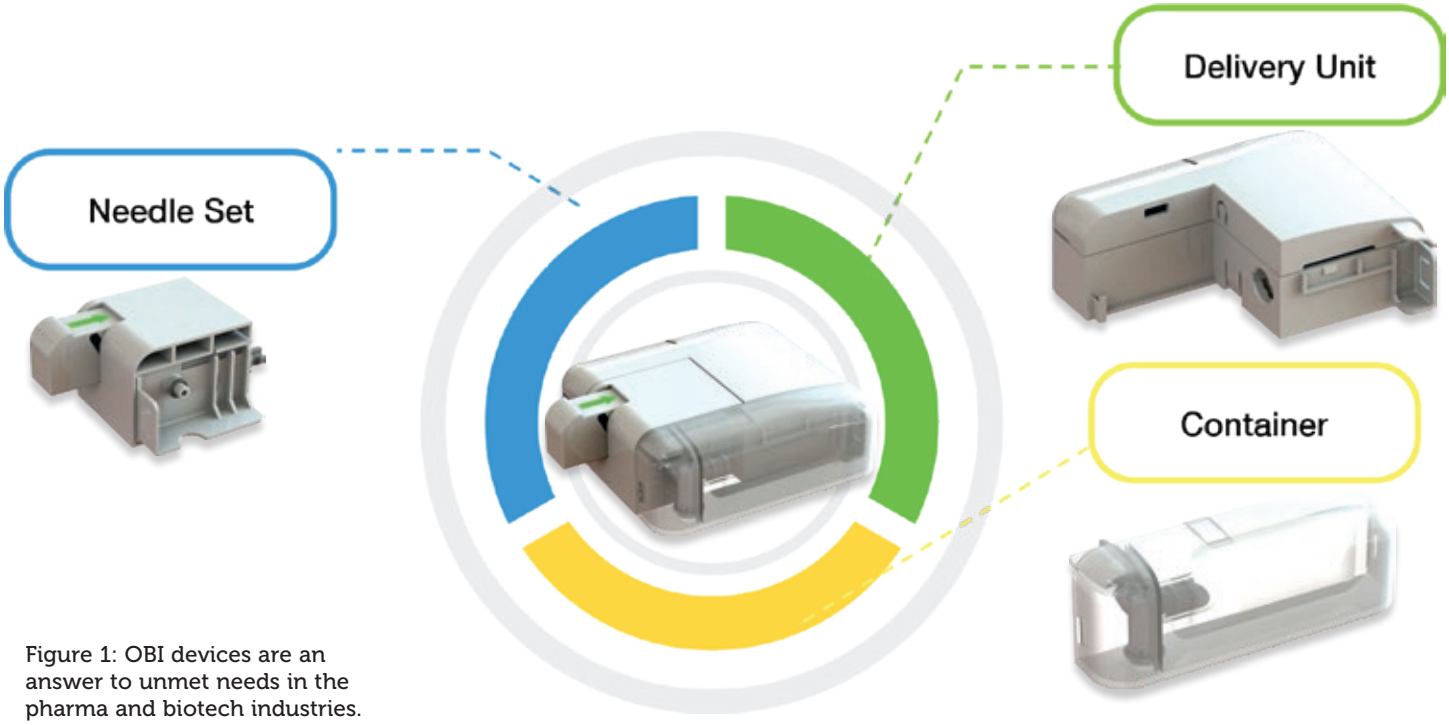

Figure 1: OBI devices are an answer to unmet needs in the pharma and biotech industries.

To meet these challenges, CCBio presents Felice Dose (Figure 2), a delivery motor system-based OBI device ready for commercialisation. Felice Dose provides a solution to the unmet needs present in the pharma industry, with the ability to deliver large drug volumes over variable- and long-duration injections. The delivery motor system can adapt to the primary drug container, providing a very stable displacement unit for the drug, and the duration for filling and delivery can be programmed to suit the drug formulation. As such, the system can deliver a stable dose of drug per unit time under discontinuous pressure, reducing the swelling underneath the skin during injection and thus decreasing patient pain. Discontinuous pressure for a high-dose container is very important because otherwise, if a drug delivery system continually places a positive linear compression pressure on the container, pressure will accumulate and contribute to increased patient pain during the injection process.

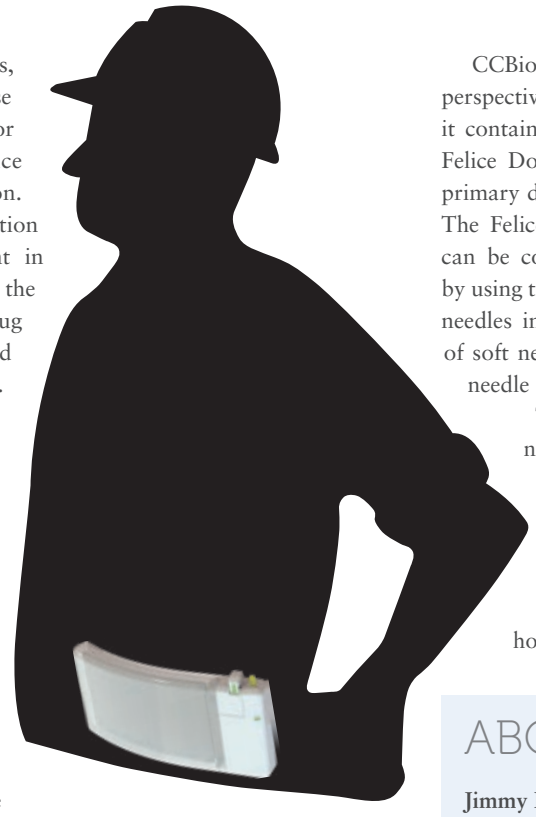

Figure 2: CCBio's Felice Dose.

Felice Dose's delivery motor system is capable of handling various drug volumes, concentrations and viscosities, as well as different injection speeds and delivery times. The delivery motor system does not require continuous power, which has enabled CCBio to reduce the size of the battery and therefore the overall weight of the device. CCBio is currently testing the Felice Dose system for a 250 mL injection lasting up to 12 hours.

CCBio's Felice Dose was successfully developed based on the perspective of both patients and pharma partners, ensuring that it contains all the necessary elements for an excellent OBI device. Felice Dose offers multiple options for customisation in terms of primary drug container, user interface and needle gauge and length. The Felice Dose primary drug container is extremely flexible – it can be configured to suit dose volumes of 5–250 mL (Figure 3) by using the mini-bag elastic polymer container system. The available needles include 6–8 mm of 29G steel needle coupled with a tube of soft needle that minimises the pain caused to the patient by the needle penetrating the skin.

The Felice Dose user interface includes options for WiFi, near-field communication (NFC) and Bluetooth connectivity, an LED display, fully-customisable programmability, a powerful delivery motor system and a lithium battery. The device's smart program functionality can help patients take control of their treatment, making their daily life easier and more comfortable, and reducing the need for hospital visits and the involvement of healthcare providers.

ABOUT THE AUTHOR

Jimmy Fan is Marketing Vice-President at CCBio, with extensive experience in biomolecules, DNA/RNA synthesis, purification and analysis, and PCR and PAGE biochemical tests and assessments. Mr Fan also has 20 years' experience of combination products for self-administration medical devices.

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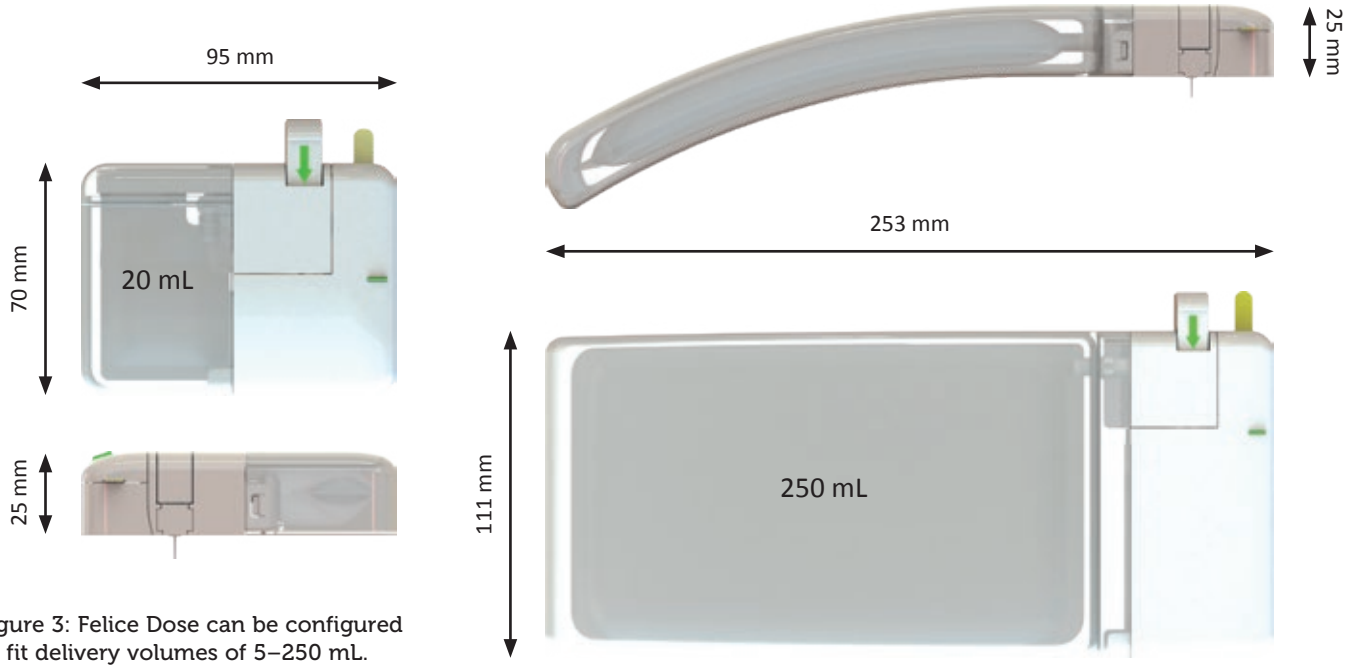

Figure 3: Felice Dose can be configured to fit delivery volumes of 5–250 mL.

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ADVANCEMENTS AND EVOLUTION OF POWER SOURCES IN DRUG DELIVERY

Here, William Welch, President and Founder of Welch Advisory Inc, Advisor to Picocyl, considers the evolution of compressed gas alternatives to spring power for single-use drug delivery devices.

The single-use autoinjector as we know it today, beginning with the US military's nerve agent antidote devices of the 1970s and the first commercial adrenaline (epinephrine) pens in the 1980s, is synonymous with compression spring-powered, needle-based drug delivery.

Compression springs offer a simple and inexpensive energy storage option. The power density is high, meaning the energy can be released very quickly. However, the energy density is very low; in other words, the more work required, the larger the spring must be. It is also difficult to control the energy release once it is activated and some potential energy is converted to kinetic energy by the spring mass, which can pose challenges such as loud noises on activation and glass syringe breakage at the end of the motion.

The continued trend towards patient-use devices has led to a projected 18.1% compound annual growth rate to 2027 for the autoinjector market.[1] As the number of drugs – especially biologics – and patient dosing regimens using autoinjectors expands, so too has the number of available options in injection platforms and power sources, all in pursuit of an improved patient experience and greater range of applications for a single platform.

One approach is to control the energy release of a compression spring, as is the case with the Controllable Force Autoinjector™ (CFAI) developed by Battelle (OH, US).[2] Presentations on the CFAI, as shown in Figure 1, have shown the ability to manage a 5 N needle insertion force and a controlled 22–30 N force during delivery of 1 mL at 125 cP

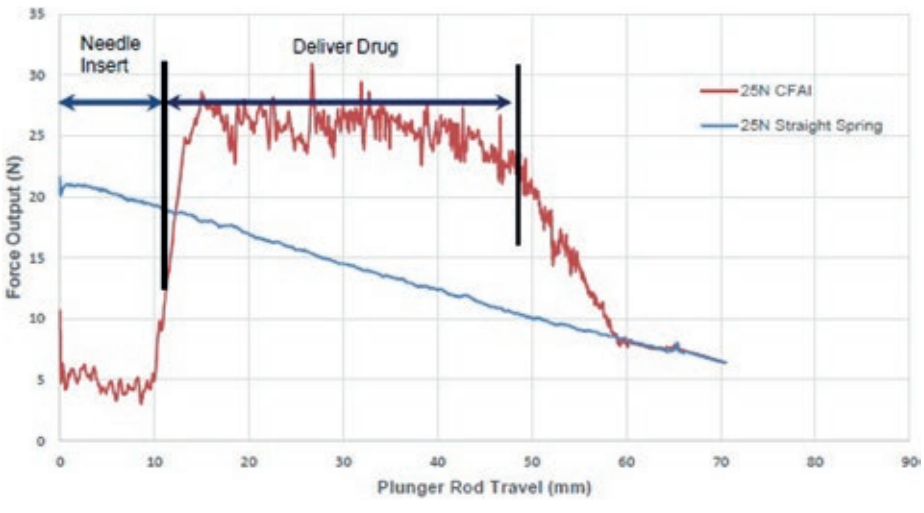

Figure 1: CFAI bench testing data, courtesy of Battelle.

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> "Ideally, a platform's functionality provides a maximum range of drug volume and viscosity capability, minimum cost and time to customise for each application."

over approximately 45 mm of plunger travel. Meanwhile, a 25 N spring in a comparable conventional autoinjector application provided approximately 20–22 N during needle insertion and declined to approximately 10 N at the end of 45mm plunger travel. The CFAI provides a much more desirable force profile during both needle insertion and drug delivery.

Another example, breaking away from the fully disposable model, is the Phillips-Medisize (WI, US) Aria reusable electronic autoinjector,[3] which is capable of delivering a range of volumes and viscosities by configuring its battery-powered reusable motor drive system, which interfaces with disposable cassettes containing a 1.0 or 2.25 mL prefilled syringe. The reusable electronic drive module changes the economics case for connected autoinjectors, and the disposable cassette reduces environmental waste versus a fully disposable autoinjector.

Similarly, in cases where an autoinjector may not be the ideal drug delivery device and an on-body injector (OBI) may be preferred, there are emerging alternatives to springs that offer benefits in long-term delivery across a range of viscosities and volumes. These options include the Subcuject (Hellebaek, Denmark) osmotic drive system,[4] which has broad flexibility in drug viscosity (as discussed in the referenced article). Another concept offered by Battelle is its compact, non-linear ChemEngine™ drive system.[5]

In addition to spring controls and the alternative drives already discussed, great strides in compressed gas innovation have resulted in another emerging option for drug delivery device power sources. In the past, industrial gas cylinders, which at present have leak, size and activation issues, were the only option. Picocyl, a medical components company, has solved these problems, producing gas cylinders with the quality and reliability necessary for medical applications. Medical-grade compressed gases have been used in precision applications, such as cataract surgery, for several years and, more recently, these gas cylinders have also been used in autoinjectors,[6] OBI transfer devices,[7] specialty oral dosages[8,9] and nasal delivery.

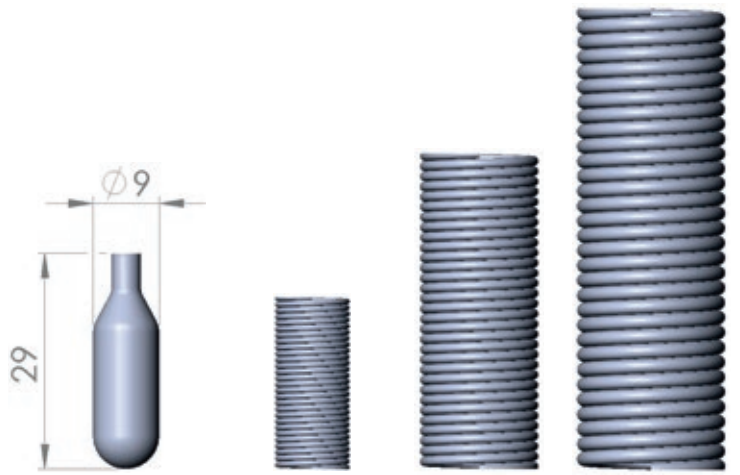
COMPRESSED GAS AND BROAD PLATFORM CAPABILITY

The primary purposes of a drug delivery platform include reuse of device design, test data, human factors and manufacturing assets across a range of drug formulations with varying properties. Commonality across platform variants and flexibility to drug-specific requirements is the balance to be achieved. A well-designed and proven platform reduces development and manufacturing costs, while providing predictable human factors and patient tolerability outcomes. These are all critical factors for reducing device risk in a drug development programme.

Ideally, a platform's functionality provides a maximum range of drug volume and viscosity capability, minimum cost and time to customise for each application, and minimum effort to manage autoinjector variants once in commercial production.

As shown in Figure 2, a compressed gas cylinder of fixed size can be manufactured to contain different pressures, customised to suit the injection force requirements. In the visual representation, a cylinder used in an autoinjector system designed for cylinders up to 276 bar delivers the same force as springs that are physically much larger while requiring more space.

It is critical to note that, while the cylinder itself may be safely loaded to 276 bar or more, the autoinjector itself does not need to withstand the same pressure. Once pierced, the gas first expands into a designed "dead space" before applying pressure to a plunger and, therefore, the device and surrounding components are never under the same pressure at the cylinder.



	cP	**10**	**100**	**100**
	mL	**0.75**	**2.0**	**2.0**
	sec	**3.3**	**23**	**8**
	Cylinder pressure (bar)	20	192	276
Compression Spring Parameters	OD (mm)	10	16	20
	Wire diameter (mm)	0.8	1.3	2.0
	Free length (mm)	131	236	246
	Installed height (mm)	23	43	63
	Rate (N/mm)	0.16	0.33	0.86
	Installed force (N)	18	64	158

Figure 2: 1.0 mL cylinder in three volume and viscosity scenarios, using 1.0, 2.25 and 2.25 mL syringes, respectively, on a Picocyl test bench, shown with comparable compression springs.

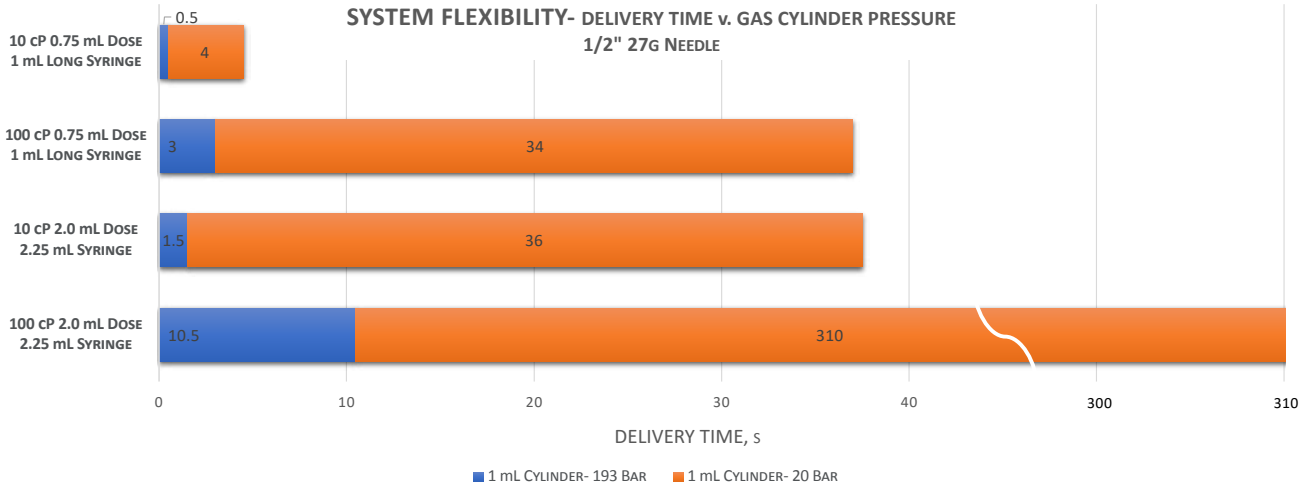


Figure 3: Potential range of delivery times for 1.0 mL cylinders with varied pressures across delivered volumes and viscosities.

Additional flexibility can be achieved by tailoring the gas type to the application. Autoinjectors, in practice, can be used across a wide range of temperatures, from refrigerated storage temperatures to high temperatures in automobiles, baggage or on-person. In this application, pure gases, such as argon or nitrogen, are appropriate as the gas pressure varies as a function of the absolute temperature. Conversely, the vapour pressure of liquified gases, such as HFC 134, vary significantly. For example, from 0–40°C, the pressure of argon will increase by 15%, while the pressure of HFC 134 will increase by 150%.

Liquified gases, however, are well suited to applications where relatively constant pressure is desired over a long stroke and the temperature does not vary widely, such as OBIs and surgical devices where the temperature is regulated by body temperature or the environmental controls of an operating room. In these applications, liquified gases, such as liquified carbon dioxide, provide higher expansion volumes at high pressures than pure gases.

High pressure gas cylinders can be filled with naturally occurring gases, such as argon and carbon dioxide, which are environmentally friendly compared with fluorinated gases.

HUMAN FACTORS

The same flexibility offered by compressed gases in generating pressure can also extend to human factors, such as noise, vibration and delivery time. Upon activation, the cylinder is opened, releasing gas into the dead space and, once sufficient pressure is achieved, starts moving the plunger. The associated noise and vibration during this process is limited to the opening of the cylinder and the movement of the plunger.

Compressed gas cylinders also offer customisation of delivery time to accommodate patient tolerability and drug absorption, adjusting to application factors such as temperature, volume, viscosity, body location and subcutaneous versus intramuscular injection. As shown in Figure 3, varying the cylinder pressure in these four volume-viscosity scenarios provides a broad range of injection times – including longer times that may be better suited to an OBI than an autoinjector – that offer customisation to patient needs.

INJECTION PLATFORM CONSIDERATIONS: DESIGN FOR THE MAXIMUM EXPECTED CYLINDER PRESSURE TO PROVIDE MAXIMUM PLATFORM FLEXIBILITY

As noted previously, an ideal platform provides a maximum range of drug volume and viscosity capability, minimum cost, time to customise for each application, and a minimum effort to manage autoinjector variants once in commercial production. Building on the first need (maximum range of drug volume and viscosity), the data modelled in Table 1 projects the dose volume that can be delivered for viscosities of 10 and 100 cP, at a minimum of 2 seconds and a maximum of 20 seconds. The intention here is not to suggest the volumes suitable for a specific drug or within the patient tolerability range but to demonstrate the very broad operating window for a compressed gas-powered autoinjector.

cP	sec	mL
10	2	3.4
10	20	12
100	2	1.3
100	20	3.5

Table 1: Range of injection volumes and viscosities in a 2–20 second time frame for a device designed for 1.0 mL 270 bar cylinder pressure. Picocyl test bench data.

The isolated pressure within the cylinder, not applied to the device until activation, also offers other benefits compared with springs, including lower stress on the assembled device, no plastic creep within the device subsystems and no energy loss due to stress relaxation in the spring resulting from long shelf-life storage under high compression.

DOWNSTREAM BENEFITS OF POWER SOURCE SIZE STANDARDISATION

The benefits of a platform with flexibility in volume and viscosity are not limited to the drug and the patient, but also the unit cost. New or modified autoinjector components must consider the following downstream impacts to cost and risk:

- Component tooling build cost and ongoing maintenance
- Component tooling validation
- Component manufacturing set-up complexity
- Component inventory management
- Assembly process equipment build cost and ongoing maintenance
- Assembly process validation
- Assembly process manufacturing set-up (i.e. changeover complexity)
- Assembly inventory management.

"In addition to bowl feeding to an assembly station, the compact gas cylinder form factor also supports bulk packing to minimise shipping and storage costs, as well as laser marking to provide traceability and assembly mistake-proofing."

The use of a platform in which a single variable (gas pressure in the selected cylinder size) provides capability across a broad range of drug volumes and viscosities provides a less complex and lower cost supply chain for both component tooling and validation and downstream assembly equipment and validation. Furthermore, there are assembly process benefits to a single cylinder size installed via a simple bowl feed to a "pick and place" robotic operation, compared with a platform with multiple spring options and the associated complexity of feeding and assembly to compress and retain the spring during subsequent assembly operations.

In addition to bowl feeding to an assembly station, the compact gas cylinder form factor also supports bulk packing to minimise shipping and storage costs, as well as laser marking to provide traceability and assembly mistake-proofing.

SUMMARY

Decades of autoinjector success have been enabled by and dependent upon compression springs. However, today, there are options to improve the spring force profile and alternatives to the use of springs altogether. Compressed gases represent the next evolution of spring alternatives, offering broad injection platform capability and flexibility, matched with minimised downstream one-time and ongoing costs of platform variants (Box 1).

BOX 1: BENEFITS OF COMPRESSED GAS-POWERED INJECTION DEVICES

- Define a broad volume-viscosity platform around a single canister size.
- Ease of gas and pressure selection in the same canister to match specific drug volumes, viscosities and human factors (i.e. platform variants).
- Low one-time development costs for platform variants.
- Laser-marked traceability, assembly error-proofing and bowl feeding enabled by canister form factor.
- Low one-time industrialisation costs for assembly of platform variants.
- Ease of production assembly changeover between platform variants.

ABOUT THE COMPANY

Picocyl enables the future of drug delivery and other specialty applications through innovative device design and gas-powered solutions for the medical and pharmaceutical markets. Every product, application and solution the company delivers is built from the ground up in its US-based, state-of-the-art, cleanroom manufacturing facilities (ISO Class 8). A pioneer in developing unique energy sources for drug delivery, the company's flagship Pico-Cylinders have become the industry standard for single use, gas-powered devices.

REFERENCES

1. *Sonar A, Sumant O, "Allied Market Research, Autoinjectors Market by Type (Disposable Autoinjectors and Reusable Autoinjectors), Application (Rheumatoid Arthritis, Anaphylaxis, Multiple Sclerosis, and Others), and End user (Homecare Settings and Hospitals & Clinics): Global Opportunity Analysis and Industry Forecast, 2020–2027". Allied Market Research, Sep 2020.*
2. *Atterbury W, "Introducing Controllable Force Autoinjector (CFAI)", presentation at Drug Delivery West Conference (PODD), May 2018.*
3. *Sørensen B, "Re-usable Electronic Autoinjector – Flexible Performance", ONdrugDelivery, May 2021, Issue 120, pp 44–46.*
4. *Schmidt Moeller C, "Subcuject WBI: Low-Cost, Larger Volume, High-Viscosity Wearable Bolus Injector – Using Standard Glass Primary Packaging", ONdrugDelivery, May 2021, Issue 120, pp 58–60.*
5. *Lafreniere A, "Enabling Reduced Size in On-Body Delivery". Presentation at Partnership Opportunities in Drug Delivery (PODD), October 2020.*
6. *Roe MJ, "Challenges in High-Viscosity, High-Volume Drug Delivery". ONdrugDelivery, Oct 2021, Issue 125, pp 40–43.*
7. *"New Utility Patent and enFuse® Vial Transfer System Technology". Enable Injections. Company web page. Retrieved Apr 6, 2020.*
8. *Progenity. (2021, October 13). "Progenity Announces Several Patents Granted by USPTO, Strengthening the Company's Intellectual Property Position in Ingestible Therapeutics Technologies". Press Release, Progenity, Oct 13, 2021.*
9. *Shimizu et al., (2021). Ingestible device for delivery of therapeutic agent to the gastrointestinal tract (US Patent No. 11,007,356). US Patent and Trademark Office.*

ABOUT THE AUTHOR

Bill Welch is President and Founder of Welch Advisory Inc, based in Wisconsin, US, and serves as an advisor to Picocyl. With more than 20 years of experience in contract development and manufacturing focused on drug delivery and diagnostics products, Mr Welch has worked across R&D, product development, quality and operations leadership roles during his career. He founded his consultancy early in 2022, serving in advisor and board member roles to companies in the healthcare product development and manufacturing space.

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ON drugDELIVERY

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August	Industrialising Drug Delivery	Jul 7, 2022
September	Wearable Injectors	Aug 4, 2022
October	Prefilled Syringes & Injection Devices	Sep 1, 2022
Oct/Nov	Drug Delivery & Environmental Sustainability	Sep 15, 2022
November	Pulmonary & Nasal Drug Delivery	Oct 6, 2022
December	Connecting Drug Delivery	Nov 3, 2022
January 2023	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 1, 2022
February	Prefilled Syringes & Injection Devices	Jan 12, 2023
March	Ophthalmic Drug Delivery	Feb 2, 2023
April	Pulmonary & Nasal Drug Delivery	Mar 2, 2023
April/May	Drug Delivery & Environmental Sustainability	Mar 16, 2023
May	Delivering Injectables: Devices & Formulations	Apr 6 2023

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EXCELLENCE THROUGH SIMPLICITY: PICCOJECT AUTOINJECTOR PLATFORM

In this article, Fred Metzmann, PhD, Senior Advisor Portfolio Management, and Chris Muenzer, Vice-President Innovation and Development, both at Haselmeier, discuss the simplicity of the PiccoJect™ autoinjector platform and the company's commitment to sustainability.

Effective self-management of chronic diseases requires healthcare solutions that are easy and convenient for patients. This is one of the key drivers for Haselmeier's patient-focused development of innovative drug delivery solutions.

The simplicity of PiccoJect, combined with the company's sustainability philosophy, is reflected in the entire supply chain to reduce waste and minimise environmental impacts. In addition to investing in green electricity and the use of sustainable feedstocks, Haselmeier focuses on the development of regional supply chains for the US and European markets. "Excellence through simplicity" sums up the company's patient-centred and sustainable philosophy.

CHRONIC DISEASES ARE ON THE RISE

The number of chronic diseases and conditions is increasing worldwide. Changing social behaviours and ageing populations are the main causes of the steady spread of these common and costly diseases. Emerging economies, with their rapid population growth, are the most affected.

The WHO estimates that non-communicable chronic diseases cause some 41 million deaths per year[1] – equivalent to 71% of all deaths globally.[2] It also predicts that the prevalence of chronic diseases will reach 49% by the year 2030.[3]

Rapid progress in the development of medicines, combined with more effective therapies, can help improve and prolong the lives of patients suffering from such diseases.

In 2021, a total of 50 new drugs were approved by the US FDA – 36 as new molecular entities (NMEs) under NDAs and 14 as new therapeutic biological products under BLAs excluding FDA approvals for generics and biosimilars.[4] The terms biologics and biosimilars refer to various substances – including antibodies, therapeutic proteins and peptides – that have a biological origin.[4-7]

Biologics will change medical practice gradually due to their distinct advantages in efficacy and selectivity, and their application will steadily expand. To date, the most considerable growth has occurred in the therapeutic areas of cancer and cancer-related diseases, rare diseases, neurological disorders and autoimmune diseases.[7] However, the specific physicochemical properties of biologics mean that delivering them as active agents into the body can be challenging. As a result, innovations in drug development today are not only limited to substances and therapies but also include the patient-centred development of delivery devices. These systems play an increasingly important role in making administration easier, faster and more efficient.

SELF-ADMINISTRATION – A KEY ELEMENT IN THE EFFECTIVE TREATMENT OF CHRONIC DISEASES

Self-administration has become increasingly important in this context. Set to surpass oral and other routes of administration, parenteral drugs are expected to see their market share grow from approximately

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Figure 1: The PiccoJect autoinjector is made up of only eight parts.

> "Injection systems for self-administration have evolved into a pivotal tool for the effective treatment of chronic diseases."

US$600 billion (£478 billion) in 2019 to approximately $1,200 billion by 2026.[8,9,10] This global growth is driven mainly by the growing importance of preventive medicine, the ageing population and the general shift towards home care.[7,8,9]

The vast majority of biologics are currently administered intravenously and subcutaneously. This applies to both biologics that are already approved and marketed and to biologics in development. However, subcutaneous self-administration is increasing in prevalence and represents a valuable alternative to intravenous administration. With a 41% share, subcutaneous bolus injection is already the preferred route of administration for biologics in the development pipeline.[6,7,14,15]

This growth is mainly due to the safety and effectiveness of subcutaneous dosing, which both patients and healthcare professionals greatly appreciate. After a short training session, patients and/or healthcare professionals can administer the drug very quickly at home. This leads to an improved quality of life, a reduction in the time spent travelling to the healthcare facility and, consequently, a reduction in costs and environmental impact. Again, this aligns strongly with Haselmeier's approach of "excellence through simplicity".

Injection systems for self-administration have evolved into a pivotal tool for the effective treatment of chronic diseases. The growing demand for such systems is driven by factors such as the convenience patients enjoy when safe and easy self-administration at home saves them the time and effort involved in trips to healthcare facilities. At the same time, autoinjectors are straightforward and safe to use by patients or their caregivers, reducing the burden on more highly skilled healthcare professionals.[5,16] Flexible care at home is not only convenient for patients but also has a positive impact on sustainability. Far fewer ambulance transports or trips to the hospital or clinic are required. In addition, the number of hospitalisations is significantly reduced.[17,18,19]

ADDRESSING THE ENTIRE VALUE CHAIN

In view of the long-term nature of chronic diseases, a favourable patient experience is paramount. However, continuous improvements in ease of administration, pain reduction, compliance and adherence are just part of the picture. Other key aspects that call for attention include the quality of the entire value chain in the drug delivery process.

With healthcare and pharmaceutical experts on the Haselmeier team, multiple interviews were conducted with customers and subject matter experts in drug delivery devices and combination products. These interviews addressed the drug delivery value chain from end to end – from the conceptual idea of the drug delivery solution, through its design and manufacture, to the packaged combination product, including its supply and use. The team also reviewed feedback and enquiries from clinicians, plus discussions with current users of existing autoinjectors. The findings identified several unmet needs that inspired the team to develop a new generation of autoinjectors that seamlessly combine functionality, convenience, user-friendliness and sustainability.

The outcome of this development is the PiccoJect autoinjector platform. Its ease of use, inherent safety and sustainability characteristics set this platform apart from existing offerings in the marketplace. It includes two variants of the highly compact PiccoJect autoinjector, supported by a rich set of services (including customisation, pre- and final assembly and packaging) along the entire value chain.

SIMPLICITY IS KEY TO EFFICIENCY

"Excellence through simplicity" sums up the key features of the PiccoJect autoinjector design. It all starts with an extremely low part count: the PiccoJect autoinjector is made up of only eight parts (Figure 1). Apart from the syringe, the highly integrated delivery mechanism consists of five injection-moulded plastic parts, two springs and one metal component.

The delivery mechanism of the PiccoJect autoinjector accommodates any standard 1 mL long and 2.25 mL prefilled glass or plastic syringe with a small round or cut flange (Figure 2). The same mechanism is available with two different cross-sections, tailored to the applicable syringe size to provide two discrete and user-friendly device form factors.

Figure 2: The dimensions of the 1.0 mL and 2.25 mL PiccoJect autoinjector.

Figure 3: Detailed view of PiccoJect features. Left – the cap must be removed before use. Right – audible clicks at the start and end of each injection, as well as visual feedback, help ensure the user holds the device in place until the full dose has been injected.

DELIVERING A BETTER USER EXPERIENCE

To help ensure adherence, the PiccoJect autoinjector is designed from the ground up for ease of use (Figure 3). It features a large wrap-around drug window for visual inspection of the drug prior to use, visual and audible feedback on the device status, and integrated needle safety. These features, plus its small size, slightly flattened (rather than circular) cross-section and intuitive feedback make this device particularly straightforward to handle.

PiccoJect is a compact, customisable and intuitive two-step autoinjector for safe and convenient self-administration, designed for subcutaneous delivery of drug products. To keep patient discomfort to a minimum, the needle guard provides a relatively large contact area that reduces pressure on the skin. Audible clicks at the start and end of each injection, as well as visual feedback, help ensure the user holds the device in place until the full dose has been injected. A dedicated status indicator provides easy-to-understand binary information about the usage status of the autoinjector. For example, upon completion of the injection procedure, the coloured status indicator notifies the user that the syringe is depleted and the device has been used.

INTELLECTUAL PROPERTY POSITIONING

Part of Haselmeier's intellectual property (IP) strategy is to constantly maximise and expand patent protection for PiccoJect technology through continuous innovation and new applications. Haselmeier has already filed several patents for the PiccoJect autoinjector, covering various innovative technologies, safety features and digitisation (Table 1).

CUSTOMISATION OPTIONS

Thanks to its versatile design, the PiccoJect autoinjector can adapt easily to a range of customer requirements. Standard customisation options include part colour, the size of the drug window and spring force. Agility is key: these customisation options are available without any detrimental impact on development timelines.

CONNECTIVITY FOR DATA-DRIVEN INSIGHT

Currently, Haselmeier is developing connectivity options that will enable the PiccoJect platform to integrate seamlessly with existing digital ecosystems, allowing injection-related data to be collected

	PiccoJect – 100	PiccoJect – 225
Part count	5 plastic components, 2 springs, 1 metal component	
Primary container	1 mL long glass or plastic syringe	2.25 mL glass or plastic syringe
Syringe flange	Small round or cut flange	Small round or cut flange
Fill volume (how to adapt the fill volumes)	0.2–1 mL	0.6–2 mL
Injection time*	<10 s	<15 s
Viscosity**	Up to 20 cP	
Needle insertion depth	6 mm (nominal); customisation possible	
User feedback	Audible click at start and end of dose; visual feedback in dose window and dedicated status indicator	
Needle safety	Automatic needle shielding with needle hidden before, during and after use	
Needle type and gauge	27G and 29G, normal wall through special thin wall	
Weight	26 g (without syringe)	34 g (without syringe)
Dimensions	H = 130 (cap on), W = 26, D = 15 mm	H = 134 (cap on), W = 30, D = 19 mm

*, ** *Injection time and viscosity capability are dependent on needle diameter and fill volume.*

Table 1: The specifications of PiccoJect.

Figure 4: Connectivity options allow injection-related data to be collected automatically at the point of care.

automatically at the point of care (Figure 4). The company draws on experience gained through its D-Flex Ecosystem and D-Flex Logbook technologies. The idea is to equip the PiccoJect autoinjector with a smart add-on that collects data and transmits it to a private cloud for clinical evaluation. Again, the guiding principle is excellence through simplicity. The company's approach to connectivity aims to minimise any impact on the injection process, reduce patient training and eliminate the need for a patient app.

> "The company's approach to connectivity aims to minimise any impact on the injection process, reduce patient training and eliminate the need for a patient app."

Smart medical devices that drive a steady increase in self-care, personalisation of treatments, predictability of outcomes or proactive intervention will help elevate the quality of care to a new level. Connected drug delivery systems in digital healthcare workflows are starting to prove their worth. For example, a clinical trial conducted by a major player in healthcare monitored the adherence patterns of 75 diabetes patients with the help of a connected drug delivery device.[20] The trial results underscored the need to gain a better understanding of patient behaviour and adherence to the prescribed therapy.

COMMITTED TO SUSTAINABILITY

At Haselmeier, sustainability is embedded in daily business and in the foundations of the corporate strategy (Figure 5).[21] The company's sustainability objectives address the rights and needs of people, profitability and the necessities of protecting our planet against severe short- and long-term impacts.

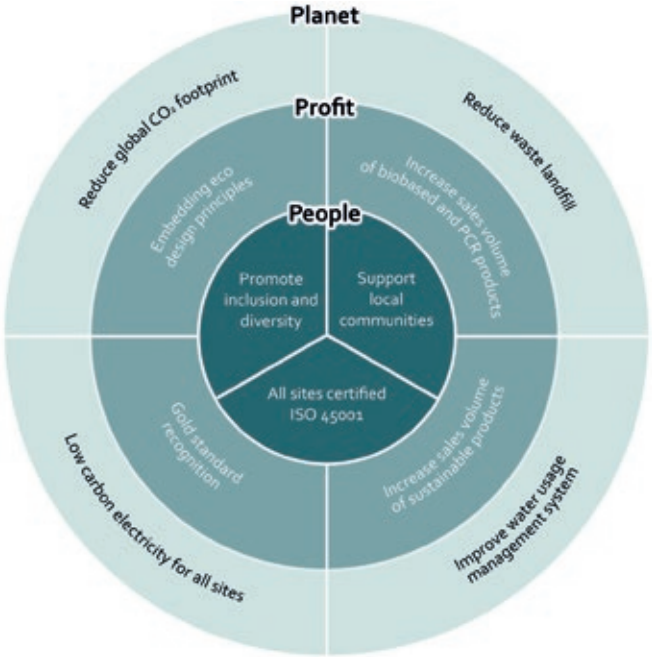

Figure 5: The sustainability goals of Haselmeier, a medmix brand.

"The underlying design concept of the PiccoJect autoinjector was driven by sustainability requirements."

In line with the global sustainability strategy pursued by medmix, Haselmeier is proactively implementing steps aimed at reducing its global carbon footprint, reducing waste landfills, improving its water usage management systems and implementing low-carbon electricity throughout its sites. Haselmeier development and design initiatives embrace sustainability during the entire lifecycle of its products.

The sustainability goals of customers and partners in the biopharmaceutical industry are equally important. The Haselmeier sustainability objectives are in line with the emission reduction goals of the pharmaceutical industry. Currently, this global industry is driving major initiatives for reducing its carbon emissions.[22] It is Haselmeier's corporate strategy to support the industry in achieving its ambitious goal of greater eco-friendliness.[23] Haselmeier proactively addresses such issues and is willing to collaborate with customers to jointly develop and implement appropriate solutions for reducing emissions and driving sustainability. It is committed to implementing specific measures along the entire value chain from conceptual design, manufacturing and packaging solutions, through to supply chain topics.

The sustainability efforts have not gone unnoticed. The Haselmeier s.r.o manufacturing site in the Czech Republic has received the prestigious silver rating from EcoVadis, one of the world's most trusted business sustainability rating entities. It achieved a score of 63/100 and performed particularly strongly within the environment, labour and human rights sectors. With the same sustainability practices incorporated throughout its sites in Europe, the company is on the right track.

The underlying design concept of the PiccoJect autoinjector was driven by sustainability requirements. Its parts were optimised to allow for the use of materials with minimal environmental impact – such as plastics based on attributed biocircular key raw materials via a mass balance approach. In line with the medmix approach to keeping shipping routes short, manufacturing and distribution facilities are located in the geographies where customers and partners are based. The PiccoJect autoinjector will be manufactured at Haselmeier sites that rely on low-carbon electricity.

HASELMEIER ECO-DESIGN PRINCIPLES

Disposable drug delivery devices still offer advantages in terms of ease of use and reimbursement over reusable products, especially for less-frequent injections. In addition, contamination and hygiene issues impose limitations on the circularity of healthcare products. Consequently, Haselmeier believes that the pharmaceutical industry and its customers will continue to request disposable products for some time to come. To offset this impact, Haselmeier's eco-design principles aim to reduce the environmental footprint of these products by:

- Optimising component wall thicknesses to minimise excess materials
- Avoiding the use of materials with high carbon intensities, such as polyamide 6
- Selecting eco-friendly materials where the supplier provides sustainable feedstock options
- Minimising the use of tray handling for individual components during assembly
- Manufacturing trays and cartons from post-consumer materials.

Haselmeier is always open to new ideas and happy to support clients from clinical studies to commercial launch of their combination products.

DISCLAIMER

The products shown in this article are under development and some of them may not yet have been approved for sale under applicable medical devices regulation. The content provides general information

about these products, their field of application and intended use, and their function, performance and specification are subject to customer specific development and may deviate from those shown herein. All information contained herein is directed at medical device manufacturers and pharmaceutical companies. This information shall not constitute a promotion for use in a way which conflicts with any applicable medical device regulations – nor is it directed at patients or intended to replace professional medical advice.

ABOUT THE COMPANY

Haselmeier, the drug delivery device business division of medmix, designs, develops and manufactures advanced drug delivery systems, such as pen injection systems and autoinjectors. Patient comfort and customers' needs are always at the heart of the company's practices. With its broad portfolio of technologies and services, Haselmeier delivers user-friendly injection systems that enable patients to self-administer their medication reliably and accurately. Haselmeier is known for its excellent and long-standing track record of providing these innovative drug delivery devices based on its proprietary IP business model. The company collaborates closely with its customers in the pharmaceutical and biopharmaceutical industries. medmix, with its precision injection moulding capabilities and expertise in liquid microdosing, plus financial strength and global footprint, helps Haselmeier accelerate innovation in healthcare.

REFERENCES

1. *"Noncommunicable diseases". Fact Sheet, WHO, Apr 13, 2021.*
2. *"Noncommunicable diseases". Health Topics, WHO, Feb 3, 2022.*
3. *"Percentage of the Population With Chronic Diseases, 1995-2030". The Silver Book, May 2009.*
4. *"Advancing Health Through Innovation: New Drug Therapy Approvals 2020". US FDA, Jan 2021.*
5. *De la Torre BG, Albericio F, "The pharmaceutical industry in 2018. An analysis of FDA drug approvals from the perspective of molecules". Molecules, 2019, Vol 24(4), p 809.*
6. *Ganesh AN et al, "Patient-centric design for peptide delivery: Trends in routes of administration and advancement in drug delivery technologies". Med Drug Discov, Mar 2021, Article 100079.*
7. *Jonaitis L et al, "Intravenous versus subcutaneous delivery of biotherapeutics in IBD: an expert's and patient's perspective". BMC Proc 15, 2021, Article 25.*
8. *"Industry Roundtable: Parenteral Drug Manufacturing". DCAT Value Chain Insights, Feb 10, 2021.*
9. *"World Preview 2020, Outlook to 2026". EvaluatePharma, Jul 2020.*
10. *"The Prospects for Biosimilars of Orphan Drugs in Europe – Current Landscape and Challenges Ahead". IQVIA, Institute Report, Jul 21, 2020.*
11. *"Global Medicines Use in 2020 – Outlook and Implications". IMS Institute for Healthcare Informatics, Nov 2016.*
12. *"The Pharma Pulse: Small Molecules and Biologics". DCAT Value Chain Insights, May 26, 2021.*
13. *"The Congruence Between Small Molecule Generic Medicine and Biosimilar Medicine Business Models". Am Pharm Rev, Featured Articles, Oct 15, 2017.*
14. *De Cock E et al, "A time and motion study of subcutaneous versus intravenous Trastuzumab in patients with HER2-positive early breast cancer". Cancer Med, 2016, Vol 5(3), pp 389–387.*
15. *Bittner B, Richter W, Schmidt J, "Subcutaneous Administration of Biotherapeutics; an overview of current challenges and opportunities". BioDrugs, 2018, Vol 32(5), pp 425–440.*
16. *"Injectables: The New Oral?". Contract Pharma, May 4, 2016.*
17. *"Health care's response to climate change: a carbon footprint assessment of the NHS in England". Lancet Planet Health, 2021, Vol 5(2), pp e84–e92.*
18. *Waller C et al, "Intravenous and subcutaneous formulations of trastuzumab Biosimilars implication for clinical practice". Br J Cancer, 2021, Vol 124(8), pp 1346–1352.*
19. *De Cock E et al, "Time savings with Rituximab subcutaneous injection versus Rituximab intravenous infusion: A time and motion study in eight countries". PLoS One, 2016, Vol 11(6), e0157957.*
20. *"Insulin Dosing Practices in Persons With Diabetes on Multiple Daily Injections". ClinicalTrials.gov, Aug 14, 2018.*
21. *"Sustainability Review". Annual Report, medmix, 2021.*
22. *"Big Pharma emits more greenhouse gases than the automotive industry". Brighter World, May 28, 2019.*
23. *"Turning Pharma Green: an Eco-Wish List for the Industry". Pharma Technology Focus, 2020.*

ABOUT THE AUTHORS

Fred Metzmann, PhD, joined Haselmeier in July 2016 as Vice-President of Sales and Marketing. Previously, he held various leadership positions in the materials and plastics processing industry at Ticona (now Celanese), Nypro (now Jabil Healthcare), Sanner, and Medisize (now Phillips-Medisize, a molex company). Based on his in-depth knowledge of the drug delivery device and combination product market, with more than 25 years of experience in the field, Dr Metzmann was appointed to the strategic role of Director Portfolio and Product Management in 2020 and assumed his current position as Senior Advisor Portfolio Management in 2021. Dr Metzmann graduated in chemistry from Johannes Gutenberg University (Mainz, Germany) and earned his doctorate at the Max Planck Institute for Polymer Research in Mainz.

Chris Muenzer is the Vice-President of Innovation and Development at Haselmeier. He leads a team of experts that creates customised drug delivery systems for pharmaceutical and biotechnology companies. He has over 15 years of experience in the pharmaceutical and medical device industry, having worked at Novartis, Roche and the Battelle Memorial Institute (OH, US). During this time, he has worked at all stages of device development from initial concept and engineering development through to clinical trials and launch. Mr Muenzer holds a BSME from Carnegie Mellon University in Pittsburgh (PA, US). He is also the inventor of several patents and is a frequent contributor to industry conferences and ISO standards.

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IMPROVING CLINICAL OUTCOMES WITH A PATIENT-CENTRIC AND REUSABLE PEN PLATFORM

Here, Cécile Gross, Global Category Manager, Parenteral, and Radosław Romańczuk, MD, Pen Platform Business Development Director, both at Nemera, discuss the company's Pendura AD pen platform and present case studies demonstrating how it can be tailored to address the user's needs and meet pharma industry constraints.

The year 2022 celebrates the 100th anniversary of the first insulin injection performed on a human being, a 14-year-old boy suffering from Type 1 diabetes. This groundbreaking scientific and clinical achievement occurred in Canada, although the disease had been identified by Aretaeus, a disciple of Hippocrates, around 100 AD. Since then, diabetes has become a chronic disease classified by the WHO as one of the four main non-communicable diseases (NCD).[1] So, have we stopped in midstream? Of course not. There have been numerous changes and evolutions in therapies and in injection.

One main revolution is the drug itself: patients now have access to human as well as analogue drugs. Another revolution is related to drug delivery devices: we have turned the corner from simple glass syringes to safe, self-administered injection devices. Both customer and patient requirements have forced manufacturers to improve their technology and provide best-in-class devices.

> "Benefiting from 10 years of experience and market presence, Nemera's Pendura AD platform encompasses all the features needed to comply with any requirement."

Nemera is no exception. The Pendura AD platform provides a multiple-use reusable pen injector that can address both the user needs and the pharma industry constraints (Figure 1).

Benefiting from 10 years of experience and market presence, Nemera's Pendura AD platform encompasses all the features needed to comply with any requirement. From the beginning of the device conception, the context of growing prevalence of chronic diseases has been central. The burden of lifelong treatment is cumbersome for patients, and treatment adherence becomes crucial in order to ensure clinical outcomes. For example, several acceptability studies have been conducted focusing on insulin-naïve individuals.[2,3] The learning curve is also at stake; it goes without saying that psychological considerations must not be underestimated. Overall, it is a question of accuracy, limited pain and discretion.

So, how does this translate into device features? First, of course, is the injection mechanism: a spring-driven movement ensures drug delivery is automatic and results in a smooth injection. There is, therefore, no need to apply manual force to perform the injection. Besides, this movement is easily triggered by a side button, which allows the user's hand to be stabilised during the injection process.[4] Second is dose checking: the cartridge containing the drug is inserted into a transparent cartridge holder, where visual inspection of the correct mixture can be performed.

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Figure 1: Pendura AD's key features designed to optimise the patient experience.

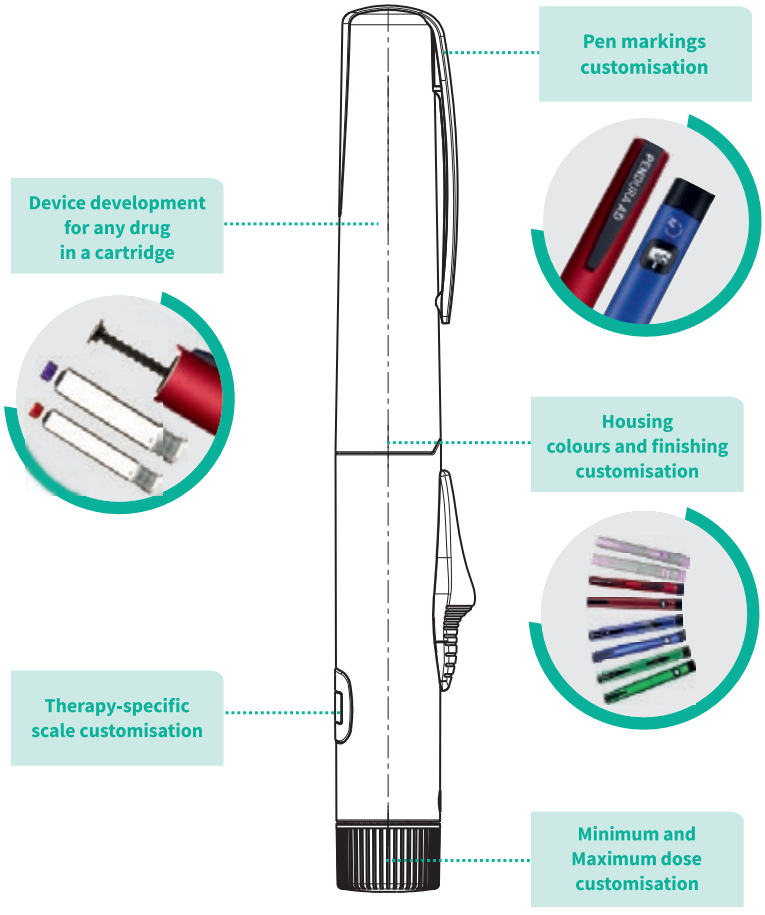

Figure 2: Highly customisable platform to fit pharmaceutical and patient needs.

By turning the dose knob with audible clicks, the user can adjust the dose, and the dose selection window clearly shows the dose in black numbers on a white background. One significant advantage is that correcting the selected dose does not result in losing drug. To be sure that the full dose has been delivered and the pen is not removed before completion, a coloured dot is made visible close to the dose knob and the thumb positioned on the side activation button. Using a new cartridge implies priming, which is also easy to perform.

FROM A HEALTHCARE PROFESSIONAL PERSPECTIVE

This article has discussed how Nemera's Pendura AD platform has been conceived from the patient's perspective, but healthcare professionals have not been forgotten. Even if the device is a self-administered device, these professionals are heavily involved in educating patients.[5] They are first to deal with adverse clinical outcomes; for them, the device must be easy to learn, easy to prepare and easy to administer. Nurses, as healthcare professionals on the frontline, allocate a great deal of attention to training time. Because their own caring time per patient is limited, so is training time. Simplicity of use is mandatory and a key concern, as a complex-to-use or non-reassuring device inevitably results in longer training or the device will, in the end, not be used at all. In the same way, the combination drug and device are part of the overall treatment protocol. If using the drug delivery device may jeopardise the clinical outcomes of the treatment, the device will not be demonstrated, recommended or prescribed. So, the same device features also provide benefits for this category of stakeholders.

Let's now have a closer look at the currently marketed applications: insulin, peptide, parathyroid hormones and human growth hormones, all of which require daily subcutaneous injections (Figure 2).

CASE STUDIES

Case Study One: Insulin and its Analogues

Thanks to Banting and Macleod who received the Nobel Prize for its discovery, insulin has been used for a long time, and insulin therapy is now well documented, especially from the drug delivery device perspective. As already mentioned, delivery devices have evolved significantly since

> "It has also been proven that using a pen device for insulin therapy improves adherence, enhances quality of life, reduces the risk of hyperglycaemia and decreases costs."

glass vials. It has also been proven that using a pen device for insulin therapy improves adherence, enhances quality of life, reduces the risk of hyperglycaemia and decreases costs. Using a reusable pen device for such therapy includes extra benefits, such as durability and flexibility; storage and carrying the mandatory doses for several days becomes easy as well. In addition, the dial-back possibility prevents loss of insulin and changing the cartridge is easy to perform.

Nemera's first partner in this field performed a series of post-market studies that showed Pendura AD was perceived as "comfortable" to use and pain severity and discomfort decreased during the assessment period.[6] A significant reduction in glycaemic level quantified by HbA1c measurements was also noted – daily-life improvement was assessed through an increase of the HRQoL score.[7]

Along with the evolution of drugs is the possibility of producing molecules identical to human ones. A good example is glargine insulin. Modifying the order of amino acids enables control of how the molecule is incorporated in the body. A small amount of the material moves into a solution in the bloodstream, while the remainder is sequestered in subcutaneous tissue for up to 24 hours, which is the reason why it is classified as a long-acting insulin. Other types of insulin are combined with short-acting insulins as part of a drug regimen targeting glycaemic control.

Biomm (Sao Paulo), a pioneer in Brazilian biotech/pharma with a facility of 12,000 square metres, combined the two, creating an innovative drug and delivery device, by offering a reusable pen for its first ANVISA (Brazilian Health Regulatory Agency) registered glargine insulin – a 3 mL cartridge containing 100 IU of drug per mL. After some technical adjustments of Nemera's technology to fit Biomm's needs, Lifepen G is now marketed, offering 60 increments and a pleasant outer shape in a grey and purple colour combination, which is a smart way to avoid confusion between insulin types.

Case Study Two: Glucagon and its Analogues

Although insulin is produced by the beta cells of the pancreas, glucagon is produced by the alpha cells. In short, whereas insulin decreases the blood sugar level, glucagon increases it. Twins, but "sister enemies". This component of pancreatic extract was identified back in 1922 and named after a portmanteau of "glucose agonist". Its properties have been fully understood since the 1970s, and it has followed the same path as its "sister" and is now available in a synthetic form.

Nemera's partner Zealand Pharma (Copenhagen, Denmark) is offering dasiglucagon, a next-generation ready-to-use glucagon analogue. Dasiglucagon is being developed for several therapies. Thanks to a constructive co-operation between the two entities, the Pendura AD platform has been selected to deliver dasiglucagon, and this combination is being investigated in clinical trials.

Case Study Three: Parathyroid Hormones and its Analogues

Teriparatide is a portion of human parathyroid hormone, a primary regulator of calcium and phosphate metabolism in bone and kidney. Aimed at treating osteoporosis, its intended use is for both men and postmenopausal women who are at risk of bone fracture. In the same way as insulin previously, it was first approved by the US FDA 20 years ago and has been extended now to biosimilar, synthetic and recombinant versions.

At stake here is the risk of fracture, which, for the patient, means input from healthcare professionals, hospital stays, rehabilitation, potential complications, etc. Several clinical studies have shown real benefits, such as an increase in both bone mineral density and bone mineral content. However, as the drug is approved for a total treatment duration limited to 24 months, the patient journey rather resembles a speed race, and treatment adherence is crucial.[8]

To secure the use of Pendura AD in this application, Nemera's partner, a leading multinational pharmaceutical company, has performed a human factors engineering study, which led to the conclusion that this reusable pen device was the solution for achieving the best clinical outcomes for patients. This choice has been confirmed with another partner, Enzene Biosciences (Pune, India), whose core values are enabling novel therapies.

Case Study Four: Human Growth Hormones (HGH)

Another therapeutic area is growth hormone deficiency (GHD) and other growth-related syndromes treated with growth hormones, which have switched in the past decade from pituitary-derived

Figure 3: In-house manufacturing capability with high flexibility for production-scale adaptation.

Figure 4: Extending Nemera's manufacturing capabilities with a new state-of-the-art facility in Szczecin, Poland.

human to biosynthetic and recombinant options. At first glance, this should be restricted to paediatric treatment only, but adults as well as children can be affected. For children with GHD, therapy would be from the age of diagnosis to early adulthood, while for adults with GHD, therapy may be for life. Needless to say, adherence is key.[9,10]

Scigen (IL, US), an integrated pharmaceutical company engaged in research and development, production and commercialisation of API and finished dosage forms, was looking for a reliable reusable pen for its somatropin. Three types of doses of SciTropin A™ (somatropin injection) are available: 2, 4 and 6 mg in cartridges of 1.5 mL. Three pens are now marketed with three different references (5, 10 and 15) and three different colours (blue, green and burgundy).[11]

Ultimately, what does it truly mean to Nemera to offer a patient-centric and reusable pen platform? It means offering the company's partners the possibility to use this reliable platform, to adapt it to their needs and to optimise the patient experience, eventually (Figure 3).

In addition to the basic features already described and tangible examples of market presence, Nemera can provide support at every step of the process, from technical adjustments according to cartridges and doses, device customisation, small-series manufacturing, clinical-batch manufacturing, high-scale manufacturing, regulatory approval and market launch.

Willing to expand its capabilities, a new plant is under construction in Poland. Gathering state-of-the-art equipment from moulding to assembly and quality control testing, this brand-new facility will be ready to operate in the fourth quarter of 2022 (Figure 4).

With 22,500m² of building overall, including an ISO 8 clean room, this digitally native plant is to become carbon neutral. Implementing BREEAM recommendations for this construction is one way to fulfil Nemera's commitment to sustainability as a company (Figure 5).[12]

A wide range of services is also available throughout the device lifecycle, in every development phase. From device strategy

Figure 5: Custom and agile services to support pen injector projects holistically.

and development, clinical trials and industrialisation to lifecycle management, Nemera's experts can help with the patient journey, human factors and user experience and regulatory dossier submission, to name but a few.

With proven records of patient acceptance and partner satisfaction, the Pendura AD reusable pen platform is robust, flexible and customisable, dedicated to optimising clinical outcomes for patients with critical long-term treatments. This platform, offering holistically state-of-the-art capabilities and services to pharma partners, is at the heart of Nemera's business.

ABOUT THE COMPANY

As a world-leading drug delivery device solutions provider, Nemera's goal of putting patients first enables it to design and manufacture devices that maximise treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market with their combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, the company works with its customers as colleagues. Together, they go the extra mile to fulfil its mission.

ABOUT THE AUTHORS

Cécile Gross is Marketing Global Category Manager at Nemera, focusing on parenteral devices. Ms Gross oversees the product portfolio strategy, development and lifecycle for safety system, pen injector and on-body injector platforms. She has more than two decades of experience in the medical device industry, marketing B2B technological products and implementing product lifecycle management for various kinds of devices. Ms Gross graduated in International Business and completed her initial training with a master's degree in Marketing and Management in the Healthcare Industry at the IMIS Institute (Lyon, France).

Radosław Romanczuk, MD, Pen Commercial Officer, has over 20 years of experience in the life-sciences industry. He is the author of the concept of a series of pen injectors, produced by Copernicus, which was acquired in 2020 by Nemera. The development and usability of medical technologies is perceived by Dr Radoslaw in three dimensions, representing his versatile experience – the perspective of a medical doctor, the perspective of the person managing marketing and business development in a biotechnological company, and the perspective of a person in charge of development of a pen injectors franchise, within a patient-centric device manufacturing organisation, which is Nemera.

REFERENCES

1. *"Noncommunicable diseases". WHO, Apr 13, 2021.*
2. *Tschiedel B et al, "Initial Experience and Evaluation of Reusable Insulin Pen Devices Among Patients with Diabetes in Emerging Countries". Diabetes Therapy, 2014, Vol 5, pp 545–555.*
3. *Wong M et al, "A randomized, cross-over comparison of preference between two reusable insulin pen devices in pen-naïve adults with diabetes". Curr Med Res Opin, 2013, Vol 29(5), pp 465–473.*
4. *Fendler W et al, "Trigger matters: an ergonomy analysis of insulin pens". Diabetes Technol Ther, 2015, Vol 17(3), pp 171–176.*
5. *Zitoun P et al, "Analysis of patient and nurse preferences for self-administered FSH injection devices in select European markets". Int J Womens Health, 2019, Vol 7(11), pp 11–21.*
6. *Gorska-Ciebiadaa M, Masierekb M, Ciebiadac M, "Improved insulin injection technique, treatment satisfaction and glycemic control: Results from a large cohort education study". J Clin Transl Endocrinol, 2020, Vol 19, 100217.*
7. *"Health-Related Quality of Life (HRQOL)". Centers for Disease Control and Prevention, Jun 16, 2021.*
8. *Lindsay R et al, "Teriparatide for osteoporosis: importance of the full course". Osteoporos Int, 2016, Vol 27(8), pp 2395–2410.*
9. *Sauer M, Abbotts C, "A new pen device for injection of recombinant human growth hormone: a convenience, functionality and usability evaluation study". Patient Prefer Adherence, 2017, Vol 27(12), pp 27–234.*
10. *Cachemaille A, Warren SE, Moss S, "A pen device for injection of recombinant human growth hormone: a European usability engineering study". Expert Opin Drug Deliv, 2020, Vol 17(7), pp 1041–1048.*
11. *"SciGen receives approval from Australian Register of Therapeutic Goods, for Nemera's reusable pen injector, for its human growth hormone". Press release, Nemera, March 17, 2022.*
12. *BREEAM Sustainability Assessment Method. www.breeam.com, accessed Apr 2022.*

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OWEN MUMFORD
Pharmaceutical Services

A CHECKLIST FOR AUTOINJECTOR DESIGN

In this article, Michael Earl, Director, Pharmaceutical Services at Owen Mumford, outlines the five key questions autoinjector designers typically ask during the development process and the choices available for tailoring autoinjector products.

In 2021, the global subcutaneous drug delivery devices market was estimated to be worth US$25.53 billion (£19.46 billion) and is expected to grow to more than $56.9 billion by 2030 – a compound annual growth rate of 9.3%.[1] This market includes devices such as prefilled syringes (PFSs), reusable and disposable pen injectors and autoinjectors. Pharmaceutical companies are increasingly moving from syringes and vials to drug delivery devices, simplifying the drug delivery process for the patient and providing more convenience with PFSs and autoinjectors.

As well as the benefits for patients, healthcare systems may see reduced pressure if more intravenous drugs – typically administered in acute care – can be reformulated for subcutaneous preparations. A notable example is the development of Neulasta (pegfilgratim) in a formulation for subcutaneous delivery. This allows cancer patients to administer their own medication outside of acute care, rather than prolong their hospital stay or return to the clinic.

Given increased demand and evolving requirements for subcutaneous administration, the design of drug delivery devices has developed to accommodate a variety of needs and patient requirements over the years. As a designer and manufacturer of these devices, Owen Mumford Pharmaceutical Services has developed a range of technologies and solutions over the past decades to help address common challenges.

> "The design of drug delivery devices has developed to accommodate a variety of needs and patient requirements over the years."

HOW WILL THE SPRING BE POSITIONED?

Compression springs are critical to the function of most autoinjectors (Figure 1). They create the "powerpack" to both insert the needle and move the plunger to deliver the drug into the patient. These springs can be positioned in a variety of ways within the autoinjector, with a rearward

Figure 1: Compression springs are critical to the function of most autoinjectors.

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Figure 2: The new disposable autoinjector platform Aidaptus® from Owen Mumford.

"With multiple regulations on the prevention of needlestick injuries globally, drug delivery devices must protect patients and carers from sharps injuries when injecting."

position being the most common design. Springs can be either external or internal to the primary container. An external spring helps to deliver variable-volume doses and more viscous drugs but creates a larger-diameter device than those with an internal spring. Constant-force springs provide flexibility in the delivery force curve and are more commonly used in reusable autoinjectors.

HOW WILL THE PATIENT ACTIVATE THE INJECTION PROCESS?

Patients can either manually insert the needle and deliver their medication or activate the injection via a button on the top or side of the autoinjector. Alternatively, the device can be automatically activated once the patient presses the autoinjector onto the selected injection site – removing a user step in the process. Once injection is activated, needle insertion and dose delivery are typically achieved in a single phase controlled by the release of a single spring. Single-phase delivery provides a consistent administration sequence for the patient and makes for a less complex device with fewer components.

The new disposable autoinjector platform Aidaptus® from Owen Mumford Pharmaceutical Services employs two-phase drug delivery (Figure 2). Needle insertion and plunger depression for dose administration are two separate, independent phases, each controlled by an individual spring with the appropriately designed force. This can help to prevent the syringe breaking, a problem that can occur when using only a single strong spring. It can also help to prevent drug spillage before injection, since the needle must be inserted before the drug is delivered.

An additional safety feature of autoinjectors is the locking and prevention of pre-activation – restricting the patient from initiating the injection and exposing the needle too early. To achieve this, some devices employ an interlock design on the cap to keep it securely in place prior to removal. An alternative safety interlock can be employed between the front and rear body of the device so that injection cannot occur until the patient depresses the safety shroud on the injection site, engaging the two sections.

HOW WILL USERS BE PROTECTED FROM INJURY?

With multiple regulations on the prevention of needlestick injuries globally, drug delivery devices must protect patients and carers from sharps injuries when injecting. There are two main options: the needle can automatically retract safely into the autoinjector following injection or the needle can be protected using a shroud that is deployed following administration. The first option results in a less-complex device with a lower component count, helping to simplify the manufacturing process; however, patients may need training to ensure that devices using this method are being used correctly.

CAN THE DEVICE ACCOMMODATE DIFFERENT FILL VOLUMES?

The maximum volume for single delivery via subcutaneous administration is typically less than 3 mL. More recent studies have shown higher volumes may be possible, especially if administered over a longer period of time.[2] The number of devices that can accommodate 2.25 mL PFSs has grown in recent years. Additionally, the industry has seen the introduction of wearable drug delivery devices specifically designed to deliver larger volumes above 3 mL. Conversely, the protein nature of biologics means that doses for these drugs are often less than 1 mL and require accurate dosing and delivery.

Fill-volume flexibility in a single autoinjector allows pharmaceutical companies to keep the same device if formulation changes are made in early drug development, through clinical trials or even later on in lifecycle management. One approach for enabling different doses in one device is to select a variable-dose autoinjector with a single-use PFS. This allows for volume variations such as weight-based dosing. However, some of the drug may potentially be wasted with this option.

Aidaptus takes a novel approach. The autoinjector has a self-adjusting plunger to accommodate multiple fill volumes – with no change parts in the device (Figure 3). The plunger is also automatically positioned to allow limited rearward movement of

Figure 3: Aidaptus® has a self-adjusting plunger to accommodate multiple fill volumes.

the stopper, without impacting container closure integrity. This is critical to maintaining sterility of the contents of the primary container in transport and storage as it travels from factory to patient.

DISPOSABLE OR REUSABLE?

The first autoinjector to come to market – the Autoject® 1 designed and produced by Owen Mumford – was designed for reuse and also featured automatic needle insertion. Since then, single-use, disposable autoinjectors have dominated the market, driven by convenience and ease of use. The annual volume of these products is currently estimated to be above 100 million.[3] Today, options for reusable autoinjectors are being seriously reviewed as the pharmaceutical industry and its suppliers increase their sustainability efforts to help meet national and international targets.

A potentially conflicting trend is the desire for more digitally connected devices to transfer key data. Adding electronics to drug delivery devices makes recycling and reuse more complex – and introduces regulatory obligations, such as compliance with the European directive on Waste Electrical and Electronic Equipment (WEEE). One solution is to add electronics to a reusable device or a reusable unit that is separate to the disposable autoinjector. Another simple option is to customise labels or wraps on the autoinjector to add radio frequency identification (RFID) tags for connectivity.

> "A patient-centric approach to product design should incorporate the aim of encouraging and improving medication adherence."

GROWTH AND INNOVATION

Autoinjectors have been in common use since the mid-1980s. Many patients have learnt to make them a part of their daily routine to treat chronic conditions. New designs of these devices offer multiple options for drug delivery, while improving ease of use for the patient. A patient-centric approach to product design should also incorporate the aim of encouraging and improving medication adherence. This is critical as healthcare demand and associated costs continue to increase, driven in part by the ageing population and a resulting rise in chronic diseases. This growing need, coupled with a growing market and advances in technology, mean that autoinjectors in a variety of designs will continue to play a key role in medication administration for years to come.

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.

REFERENCES

1. *"Subcutaneous Drug Delivery Devices Market (By Product Type: Auto-Injectors, Pen Injectors, Prefilled Syringes, Wearable Injectors, and Needle-Free Injectors; By Distribution Channel: Retail Pharmacies, Hospital Pharmacies, and Online Pharmacies) - Global Industry Analysis, Size, Share, Growth, Trends, Regional Outlook, and Forecast 2021–2030". Precedence Research.*
2. *Badkar AV et al, "Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements". Drug Des Devel Ther, 2021, Vol 2021(15), pp 159–170.*
3. *Owen Mumford internal analysis based on multiple sources.*

ABOUT THE AUTHOR

Michael Earl joined Owen Mumford as Director of Pharmaceutical Services in November 2020. He was previously the Commercial Vice-President at Bespak (now part of Recipharm), leading the commercial team there to drive growth in its substantial medical devices business. Prior to that, he worked for a number of pharma, biotech and device companies. In a career spanning 35 years, Mr Earl has been responsible for all aspects and stages of drug and device development and commercialisation. He has also completed a substantial number of commercial, licensing and mergers and acquisitions transactions.

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CONNECTED DRUG DELIVERY – MAXIMISING ACCESS BY DESIGN

Here, Oliver Eden, PhD, Business Unit Director at Jabil Healthcare, discusses the factors that drive the design and development of a reusable autoinjector solution. Foremost amongst these considerations is the patient, in terms of ease of use with the device itself and maximising access to the broadest possible population with a versatile, portfolio-enabling platform ready for the connected world.

"You've got to start with the customer experience and work back toward the technology – not the other way around." Apple founder Steve Jobs spoke these oft-quoted words as part of a Q&A at the company's 1997 Worldwide Developer Conference. It's an insightful statement but can be very challenging to do in healthcare, where an interplay of core objectives – access, quality and cost containment – can sometimes lead to conflicting priorities among the many different participants in its ecosystem.

Healthcare practitioners (HCPs) strive to improve patients' lives, regulators work towards a balance between clinical outcome and safety, whilst payers and insurance companies work to balance clinical outcome and total healthcare costs. At the same time, pharmaceutical companies seek approval and reimbursement for therapies that will be clinically successful and commercially viable. And, at the centre of it all, is the patient, seeking improved health with access to effective treatments that are as minimally disruptive to their everyday life as possible.

The key to good design for developing or improving a medical device, such as an autoinjector, is to walk in each of these stakeholders' footsteps to understand their combined perspectives, goals and challenges, and find an ideal balance between functionality, usability and cost that will benefit them all in their mutual pursuit of improving patient outcomes.

A MANUFACTURER'S PERSPECTIVE

When it comes to strategic ways to address the future needs of Jabil's customers, meaningful insights come when the team asks the right questions. What are the technical and business process opportunities that will deliver value to customers and the broader healthcare ecosystem – the patients and their care teams, the payers and providers?

The goal is to develop a partnership that goes beyond simply matching requirements with capabilities – the answer to "How do we build it?" – towards a more complete

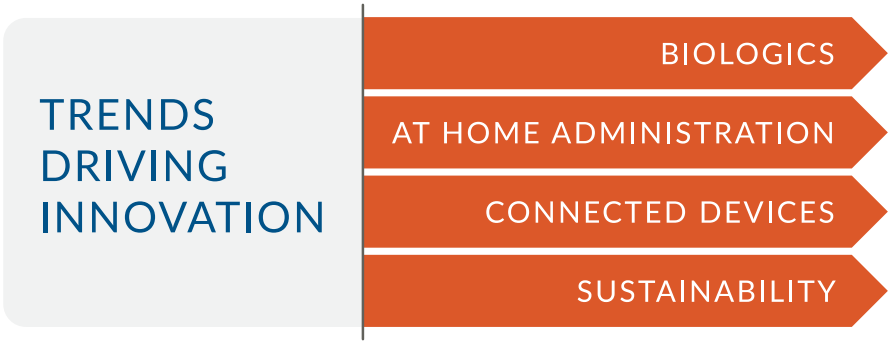

Figure 1: Industry trends driving innovation.

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solution – how to build it simply, more sustainably, with fewer supply chain nodes and a lower bill of materials, and modularly so that a product is easily upgradeable as a hedge to changing market dynamics.

How can sound product lifecycle management principles, combined with design for manufacturability (DfM) expertise, inform the development of an autoinjector device platform – whilst also aligning the solution with powerful, emergent trends in pharma delivery. Such trends include advancements in biologics; the shift to more patient self-care in the home; demand for connected, digital platform enhancements; and increasing calls to improve medical device sustainability metrics (Figure 1).

Figure 2: The Qfinity autoinjector.

QFINITY™ ANSWERS THE CALL

Qfinity is a platform for subcutaneous (SC) drug self-administration, centred on a reusable autoinjector that supports the emerging prioritisation within pharma for more sustainable drug delivery (Figure 2). Designed to help pharma customers get to market quickly, at a lower cost, Qfinity accommodates the direction of travel in portfolio characteristics, both in terms of formulation properties (e.g. viscosity) and delivery volumes.

Additionally, the system provides a low-cost pathway to digital health connectivity for all players in the healthcare ecosystem with Qfinity+™. This connected version features a home hub that provides wireless charging and seamless cellular data transfer functionality in near-real time (Figure 3), without requiring any change in drive unit form factor between the two versions – the non-connected solution, Qfinity, and the connected solution, Qfinity+.

At the centre of the platform is a simple spring-loaded reusable autoinjector with a single form factor drive unit. The use of a mechanical drive system is fit for function, negating the requirement for an alternative drive system (e.g. electromechanical) that would add unnecessary cost without significantly improving function. The drive device accommodates and operates with either of two disposable cassettes – one for each of 1 mL and 2.25 mL prefilled syringes (PFSs).

Purposefully designed to be versatile and portfolio enabling, Qfinity provides a path to connected healthcare without added complexity or additional cost in a more sustainable, competitively priced solution for use in both clinical development and commercial supply.

ADVANTAGES FOR PATIENTS

Ongoing human factors studies bear out high marks for ease of use per Qfinity's form factor, which is exactly the same for both the connected and non-connected versions, as is the user operation sequence. Precedented form factor and feature sets are well considered and validate design choices, requiring no retraining. Users report that the drive device "feels right" in terms of its shape and that it is intuitive and "easy to use".

> "Optimising the device's design to secure the greatest advantage for the largest potential user population is an acceptable and strategically sound compromise."

For users accustomed to disposable injectors, the additional step of loading a cassette is also reported as being simple and straightforward. Inclusive design principles and usability engineering have proven effective in securing Qfinity's developers' objectives for an easy-to-use, easy-to-teach disposable cassette and reusable injector experience.

Assessments bear out the inevitable trade-offs inherent in medical device design. Sustainability and other value advantages offered by a reusable device impact an autoinjector's overall size and shape. In some instances, devices that are too small or compact can be detrimental in terms of grip function. For example, as demonstrated by users with rheumatoid arthritis, a larger-diameter device is likely to be easier for them to close their hand around.

In the context of standard use for these types of products – typically at-home self-administration no more than once weekly – optimising the device's design to secure the greatest advantage for the largest potential user population is an acceptable and strategically sound compromise.

THE PLUS IN QFINITY+

As for the connected version, Qfinity+ allows medical teams to remotely monitor their patients' care and compliance via built-in sensors and electronics. This does not increase the version's complexity, as the device's drive unit form factor and the use steps are exactly the same as the non-connected

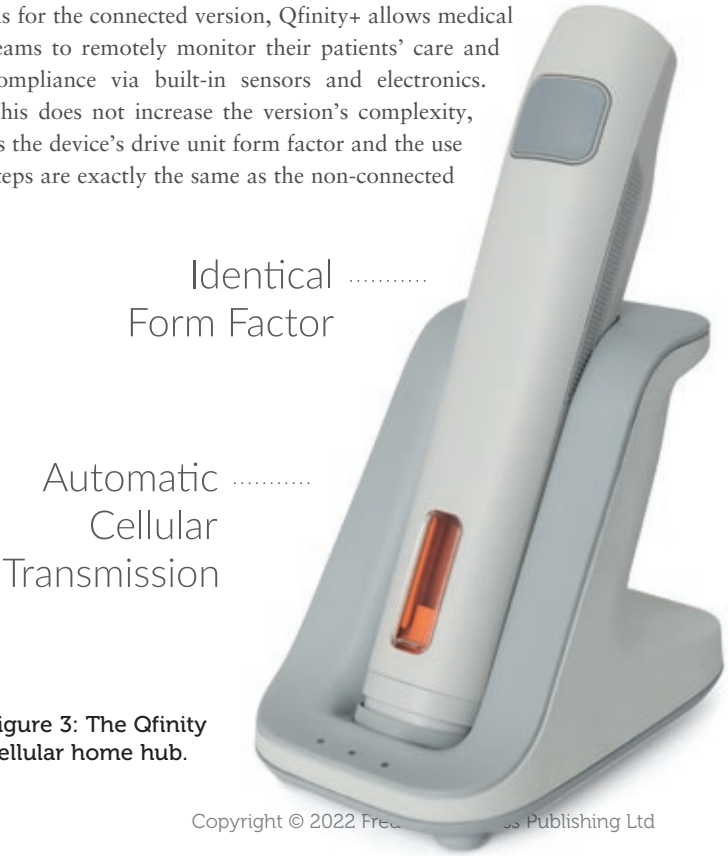


Figure 3: The Qfinity cellular home hub.

"Capture and transmission of data is delivered seamlessly by virtue of the home hub solution, which accommodates both charging and data transfer without requiring input from the patient."

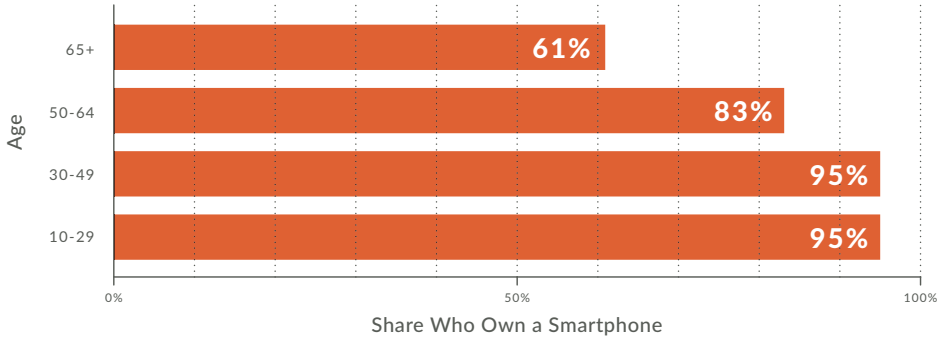


Figure 4: Smartphone ownership by age.

version. Capture and transmission of data is delivered seamlessly by virtue of the home hub solution, which accommodates both charging and data transfer without requiring input from the patient. Qfinity+ delivers this improved adherence benefit – seamless, real-time event tracking for accurately measuring compliance – at a cost 20% lower than current market-leading non-connected disposable autoinjectors.

DEEPER DIVE ON THE QFINITY+ CONNECTIVITY SOLUTION

Within the disposable mechanical autoinjector market, a common route for delivering connectivity is a "sleeve" that fits over the autoinjector and captures adherence and/or compliance data and communicates it to the user's smartphone via Bluetooth Low Energy (BLE) protocols. Jabil's decision to design a cellular home hub solution for Qfinity+ instead goes back to the company's primary objective: maximise access.

The sleeve solution adds user steps and complicates a patient's therapy rather than simplifying it. Sleeves require attaching and detaching, pairing the injector device with a smartphone, downloading and maintaining an app and co-locating the injector and the smartphone. There are several assumptions inherent in this model, for example that the patient has some technical know-how and can learn how to perform the necessary steps. Of course, a patient must also have a smartphone in the first place!

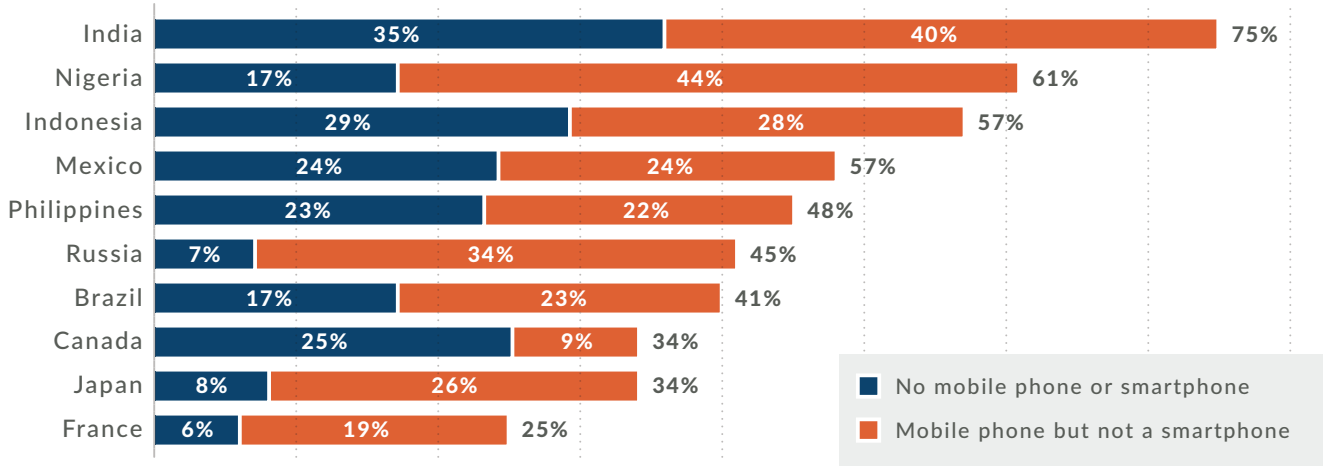
For broad populations in the developing world, as well as in more advanced markets, ownership of smartphones is not guaranteed. Nor is the physical ability to manage these variables something that can be assured in what are often older or infirm patient populations.

Analysis of smartphone ownership by age, socio-economic status and level of education provides critical insight. Even in a technologically advanced country like the US, smartphone ownership amongst people over 65 years old – a key demographic for healthcare – is only 61% (Figure 4). Throughout the developed and developing world, coverage gaps exist and must be considered. The home hub for Qfinity+ was conceived to negate the accessibility issues inherent in requiring a smartphone, as its connectivity solution is based on cellular communications coverage, which is typically greater than 95% worldwide and delivered seamlessly without the requirement for any additional devices.

BENEFITS WITHIN CLINICAL DEVELOPMENT

Within clinical development, the integration of digital technology is transforming how studies are conducted. However, all the benefits connectivity provides for personalising and strengthening patient engagement for the emerging practice of decentralised trials are dependent on trial participants actually using their device's connectivity features.

Communication platforms dependent on a study participant having access to a smartphone means that either pharma companies need to provide a smartphone for the participants or listing a smartphone as a criterion for participation in the study. Both options are challenging for studies conducted in regions with low smartphone ownership (Figure 5), and the latter option is simply not acceptable, as it would bias the study population and potentially impact study timelines.



Source: © 2019 Pew Research Center

Figure 5: Smartphone and mobile phone ownership by region.

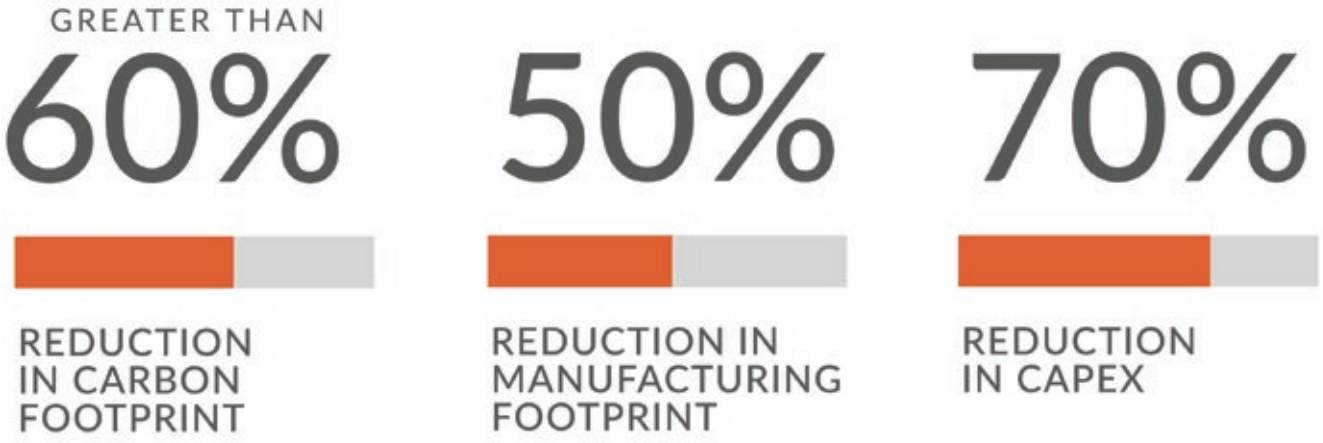


Figure 6: Sustainability improvements delivered by Qfinity compared with market-leading disposable autoinjectors.

> "Qfinity's reusable mechanical drive unit consists of 19 components and the disposable cassette assembly consists of only four moulded components, plus the PFS."

The combined design requirements of Qfinity+, revolving around access, quality and cost, provided a clear challenge for its designers – one which catalysed the team's inspiration for the home hub. The resulting solution became another emblem of versatility-driven design, enabling both connectivity and charging by virtue of more universal cellular communications, being independent of smartphones, and requiring no additional user steps or training for a truly patient-centric product platform. Data is captured seamlessly without requiring action from the patient, potentially driving better adherence by simplifying correct usage and enabling more proactive management of studies by their sponsors.

REUSABLE IS MORE SUSTAINABLE

One of the human factors participants stated things quite simply: "Sustainability affects us all." Another said: "You're doing something to stay healthy and then also making your planet healthy."

The disposable autoinjectors available today have several different form factors and share very few components. From a pharma company perspective, while these simple mechanical solutions are portfolio enabling, they increase manufacturing footprint requirements, drive additional capital expenditure, result in more medical waste and increase supply chain complexity – all of which have an impact on the cost of goods produced.

Qfinity's reusable mechanical drive unit consists of 19 components and the disposable cassette assembly consists of only four moulded components (plus the PFS). The Qfinity 1 mL and 2.25 mL design variants share up to 80% of their components in a common form factor. In contrast, the market-leading disposable 1 mL and 2.25 mL disposable autoinjectors both feature 15–20 components, and then the device is only used once before being thrown away.

In other words, Qfinity delivers the equivalent portfolio-enabling functionality as the market-leading 1 mL and 2.25 mL disposable autoinjectors combined at a lower cost of goods and in a more sustainable solution.

Jabil's designers conducted a lifecycle assessment to determine the cost benefits captured within Qfinity's platform design, with a particular focus on the benefits of the reusable drive unit. Due in large part to the fact that the design requires less material, it is estimated that Qfinity delivers a 65% reduction in cost per injection compared with market-leading disposable autoinjectors, as well as delivering improved sustainability metrics (Figure 6).

This assessment considered the carbon footprint from sourcing, manufacturing and supply to a pharma partner but did not take into account the savings in transportation afforded by the greater packaging density possible due to Qfinity's compact cassette or cold chain storage costs.

QFINITY – INSIGHT DELIVERED

Qfinity comes to market as one of the most versatile autoinjector platforms available today. Sustainable, accessible and inclusive, both in terms of ease of use and the seamless connectivity option it provides for enhanced digital health, Qfinity is deftly positioned at the intersection of converging value trends within pharma. Accommodating the fullest range of requirements from across the healthcare ecosystem, Qfinity is a simple and insightful solution to meet the industry's current and future needs.

ABOUT THE COMPANY

Jabil Inc. is comprised of over 260,000 people in more than 100 facilities around the globe working every day to be the pharmaceutical industry's most technologically advanced and trusted manufacturing solutions provider. Jabil Healthcare works with customers to design, develop and manufacture some of the most complex and innovative drug delivery devices in the market.

ABOUT THE AUTHOR

Oliver Eden is a Business Unit Director at Jabil Healthcare, focused on the development and commercialisation of drug delivery devices for the division's pharmaceutical delivery systems business. Operating from the UK, Dr Eden earned his Master's in Mechanical Engineering and PhD in Biomaterials Engineering from the University of Exeter (UK).

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JABIL HEALTHCARE

INJECTING THE FUTURE

In this article, Simone Farina, Engineering Systems Manager at Flex, discusses the company's new smart autoinjector platform for the healthcare market. The platform is designed to enable original equipment manufacturers to accelerate time-to-market, reduce costs and boost reliability, while ensuring patient compliance.

The global covid-19 vaccination rollout brought into sharp focus the importance of speed when bringing new drugs to market. It has highlighted the complexity of administering drugs and keeping track of patient drug dosing and timing of doses. Even at a personal level, if you have had the vaccine, that recent experience may have surfaced some of your own concerns about being injected. The fact is that injections are a day-to-day reality for millions of chronic disease patients who feel the same. The market has been ready for low-cost, smart autoinjection devices that are easier to use.

> "The Flex design team engineered and created a new autoinjector platform in response to the growing adoption of autoinjector devices and the corresponding increase in the diverse demands placed upon them."

SMART AUTOINJECTOR PLATFORM

The Flex design team engineered and created a new autoinjector platform in response to the growing adoption of autoinjector devices and the corresponding increase in the diverse demands placed upon them. The platform is designed to help medical device original equipment manufacturers (OEMs) overcome design delays and costs and to facilitate a smoother path from production to patient.

The Flex autoinjector platform features:

- **A drug delivery engine** capable of managing multiple drugs, as it can identify a cassette and the type of drug inserted.
- **Temperature monitoring** for the management of less painful injections.
- **A skin sensor** for optimal placement of the autoinjector on the injection site.
- **Voice control** through an advanced touchless user interface able to recognise sequences of human speech and translate them into operative commands for the device.
- **Support for low-power Bluetooth and CatM1/NB-IoT** connectivity to mobile phones or the cloud for managing information about drugs delivered and related therapy.
- **Modular firmware** composed of an application layer, allowing for customisation to meet unique medical device OEM requirements, and built on top to a predeveloped and tested standard part.

ADVANCED DRUG DELIVERY ENGINE

Motor Regulation for Drug Delivery and Needle Insertion Speed Control

At the core of the platform are two motors: one to manage the needle insertion, the other to manage drug delivery. Needle insertion is performed via a direct current motor connected to a syringe. A leadscrew transforms the rotational movement of the motor into a linear one and a proportional-

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integral-derivate (PID) algorithm is used to control speed during needle movements. The end of needle insertion and its retraction are defined by stall conditions that are detected by the encoder movement. This design protects patients from accidentally puncturing themselves and can reinforce confidence when using the device. Patients can also control the variable needle insertion speed, optimising it to deliver less painful injections.

The drug delivery motor subsystem moves a prefilled syringe (PFS) of 1 mL/vial plunger at a constant speed, selected by the user. The speed of the injection and speed of drug delivery can affect the patient's perception of pain – which, of course, varies from person to person. The speed selected is kept constant by a PID algorithm. If a full dose is delivered, the end of the injection is detected by a stall condition. If only a portion is provided to the patient, a fine position control is used to monitor the end of the dose delivered.

Another benefit from the motor-driven systems in the platform is that different kinds of drugs can be used. Identification details on the cassette mean the drug and dose are recognised immediately by the device. The PID parameters are adjusted to meet the viscosity characteristics of that specific drug and a constant speed is set for drug delivery.

Identification of the Cassette and Type of Drug

The autoinjector is equipped with a near field communication (NFC) reader that can communicate with the NFC tags of the drug cartridges (Figure 1). This assures the authenticity of the cartridge, identifies the type of drug and checks its validity (i.e. expiry date). It also reads delivery parameters and stores logs about injections completed. All of these processes can be encrypted. Additionally, the passive NFC tags can harvest energy from the same electromagnetic field used for communication, so power is not needed – offering a cost-effective solution.

Temperature Monitoring to Improve the Injection Experience

Multiple temperature sensors are integrated into the platform. These sensors monitor various components, including the autoinjector itself, to ensure the unit is only used within the defined operating conditions. The rechargeable battery temperature is also monitored to verify the battery is only charged within its defined operating temperature range. Temperature monitoring also checks for drug degradation or unacceptable levels of drug viscosity, both of which can lead to more painful injections.

Figure 1: The autoinjector is equipped with an NFC reader that communicates with the drug cartridge tags.

Figure 2: The skin sensor helps deliver an optimal injection.

"Temperature monitoring checks for drug degradation or unacceptable levels of drug viscosity, both of which can lead to more painful injections."

Skin Sensor Detector for Correct Device Placement

To help deliver an optimal injection, a sensor in the apical part of the device detects the presence of skin and the angle of the autoinjector (Figure 2). The skin sensor is

a capacitive model embedded in the printed circuit board and can precisely distinguish skin from other surfaces. The unit can also detect the autoinjector's tilt angle to perfectly position over the ideal injection zone; if contact with the skin is lost, the delivery of the drug is interrupted. This sensor essentially self-regulates to compensate for changes in environmental conditions.

VOICE CONTROL/ TOUCHLESS USER INTERFACE

As medical devices move towards consumerisation, particularly in the drug delivery space, both usability and user interface have grown in importance. Voice control in smart consumer products has paved the way for voice-enabled injection devices. Through a more natural human-machine interaction, the patient can issue commands directly to the autoinjector, instructing it to start or suspend the injection or to adjust speed settings.

Machine-learning algorithms have allowed the platform to implement a speech recognition model optimised to run on low-power and low-memory-size microcontrollers. This also ensures an increased level of data privacy because the information is exclusively processed on the device, with no connection to the cloud.

"Providing family members, caregivers or clinicians with drug delivery data can save time and worry for all concerned."

The effectiveness of speech recognition depends on a unit's ability to operate in noisy conditions. The Flex platform uses an on-board voice solution where sensors capture motor and ambient background sounds and, with real-time edge processing, mutes those sounds from the recognition software. This enables the embedded speech recognition engine to recognise the user's voice commands easily.

AN INTEGRAL PART OF DIGITAL HEALTH ECOSYSTEMS

Providing family members, caregivers or clinicians with drug delivery data can save time and worry for all concerned. The Flex platform transfers data to mobile phones or clouds.

Data Transfer to Smartphone via Low-Power Bluetooth

The platform can send data via low-power Bluetooth directly to a smartphone or equivalent media. This inexpensive short-range communication technology has evolved to be transformational in the world of drug delivery. As smartphone ownership becomes increasingly common, patients can access a colourful and interactive user interface where data measurements sets, with the corresponding time stamps (i.e. complete data sets), can be stored or shared.

Data collected can be uploaded to a cloud-hosted database, where algorithms instruct data processing to extract patterns and inform, for example, therapy changes. In this sense, smartphones are used as a communication gateway between the medical device and the data backend. The Bluetooth interface supported by the platform is an ideal technology to enable data to reach smartphones. This solution optimises battery life and ensures enough data throughput and physical connectivity at less cost.

Figure 3: Cat-M1/NB-IoT cellular connectivity allows automatic and direct access to the cloud.

Data Transfer Directly to Cloud via Cat-M1/NB-IoT

Flex's expertise in cloud and communications infrastructure enables it to deliver a solution ready for the data-driven, 5G smart and connected future (Box 1). The Flex autoinjector platform is equipped with low-power wide-area Cat-M1/NB-IoT cellular connectivity (Figure 3). This emerging technology for Internet of Things (IoT) applications allows automatic and direct access to the cloud via an integrated SIM card. There is no need for the patient to initiate the communication.

BOX 1: STANDARDS AND REGULATIONS

Flex designs needle-based injection systems containing electronics (NIS-Es) that are compliant to international standards required to demonstrate conformity to the essential requirements of the Medical Devices Regulations (Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices), US FDA regulations and other national requirements.

Flex leads product development according to several standards – ISO 10993 to guarantee the biocompatibility of the materials, REACH regulation to improve the protection of human health and the environment from the risks that can be posed by chemicals, the RoHS Directive related to the restriction of hazardous substances in electrical and electronic equipment and the Waste Electric and Electronic Equipment Regulations.

Flex designs medical devices in line with the IEC 62366-1 usability standard, the IEC62304 software lifecycle requirements and the standards related to electromagnetic compatibility, wireless communication and cybersecurity.

With a patient-safety-first approach, Flex designs NIS-Es with features designed to reduce risk for the patient and meet the IEC 60601 standard related to basic safety and essential performance and the ISO 11608 standard focused on accuracy of delivered doses. The Flex Milan Design Center is one of the few ISO 17025-certified test laboratories to verify requirements for the ISO 11608-1 standard, and a Flex Milan representative is a member of the technical committee appointed to develop these standards. Flex actively collaborates with the most important international certification agencies, offering its customers a support service for a smooth and straightforward certification of their products.

Figure 4: The autoinjector platform is modular to accommodate features such as multiple drug delivery speeds.

"The Flex autoinjector platform is equipped with modular firmware created by reusable and customisable building blocks designed to speed up the process of firmware development and test in relation to the final customer product."

Cat-M1 and NB-IoT leverage existing 5G network infrastructure, so they do not require additional deployment of an antenna, radio or other hardware. They use smaller bandwidth than standard long-term evolution, which is convenient for battery-operated IoT application needs.

FIRMWARE FRAMEWORK

The Flex autoinjector platform is equipped with modular firmware created by reusable and customisable building blocks designed to speed up the process of firmware development and testing in relation to the final customer product (Figure 4). Flex offers pharmaceutical companies a software development service for the application layer, which creates the unique solution based on a customer's requirements.

The software is created using building blocks, similar to how a house is built with prefabricated bricks. The blocks are Flex's intellectual property (IP), while the customised parts are the OEM's IP.

The firmware is compliant with the IEC 62304 standard, which specifies lifecycle requirements for the development of medical software and software within medical devices.

SUMMARY

The demand for effective homecare and remote monitoring has increased the relevance of autoinjectors for patients looking to manage chronic illnesses and allergies conveniently without visiting hospital. This has been especially true in the case of diabetes, Crohn's disease and rheumatoid arthritis patients relying on PFSs and autoinjectors to manage their condition at home. Pharmaceutical companies looking to meet these rising at-home needs are going to require flexibility, faster time to market, cost efficiencies and reliability in their autoinjector products, while ensuring patient compliance.

The Flex autoinjector platform offers a modular approach that addresses these needs:

1. An efficient drug delivery system
2. An advanced touchless user interface
3. A complete set of connectivity solutions that places the autoinjector at the heart of a digital health ecosystem
4. A flexible firmware framework able to implement the customer's requests on top of a robust preconstituted stack.

ABOUT THE COMPANY

Flex is a manufacturing partner of choice that helps a diverse customer base design and build products that improve the world. Through the collective strength of a global workforce across 30 countries and responsible, sustainable operations, Flex delivers technology innovation and supply chain and manufacturing solutions to diverse industries and markets. Through its Health Solutions business, Flex partners with pharmaceutical and medical technology companies to provide comprehensive design and quality manufacturing through a highly regionalised global network. Its experience includes the design and commercialisation of more than 75 regulated medical devices, from pens and autoinjectors to pumps and inhalers. It also partners with medical equipment and device companies, producing critical-care equipment, such as infusion pumps and ventilators, and a wide range of diagnostic machines and surgical tools. Its approach is supported by FDA-registered and ISO 13485 compliant facilities and a world-class quality system.

ABOUT THE AUTHOR

Simone Farina is Systems Engineering Manager at the Flex Milan Design Center, where he oversees the systems engineering team responsible for leading the development process of medical devices from a technical point of view – from the concept phase to mass production. He has more than 20 years of experience in industries ranging from medical to information technology, consumer electronics, IoT and telecommunications.

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