PREFILLED SYRINGES & INJECTION DEVICES

ON drugDELIVERY

MARCH 22ND 2021 • ISSUE N° 117

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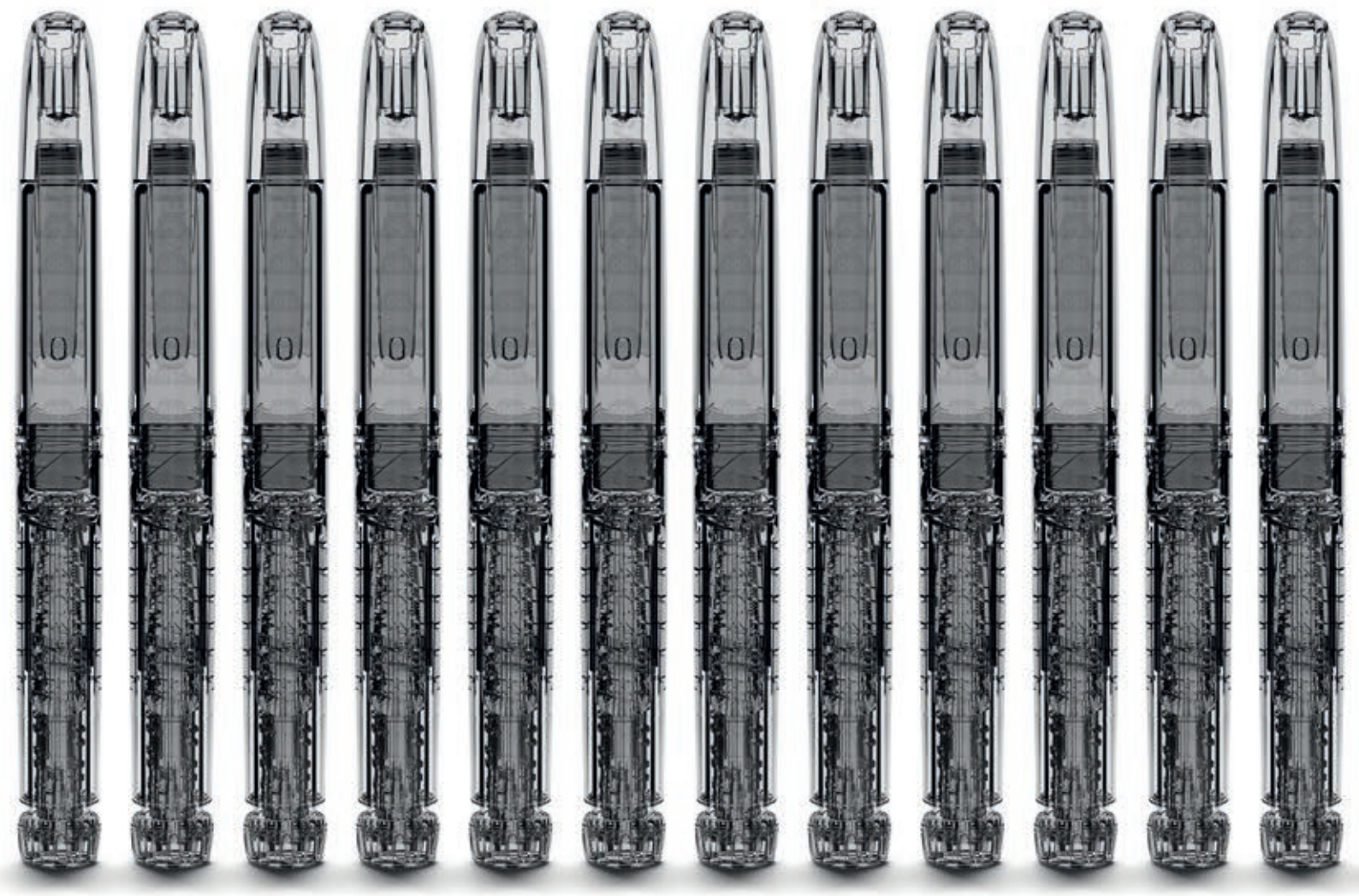

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PREFILLED SYRINGES & INJECTION DEVICES

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. 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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Feb	Prefilled Syringes & Injection Devices

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Front cover image, "Customised syringe barrel with threaded sealing closure, comprising tip cap, rigid cap and Luer lock adapter. Components are steam sterilisable, medical grade, and biocompatible per ISO 10993-1 and USP Class VI (see Page 18). Reproduced with kind permission.

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TOP FIVE DRUG DELIVERY TRENDS FOR 2021

Here, Tom Oakley, Director of Drug Delivery Device Development at Springboard, provides an overview of the top five trends to expect in drug delivery in 2021.

Drug delivery devices are evolving rapidly, and Springboard is in the privileged position of being at the centre of development of many of them. Often, we get asked about trends and hot topics in drug delivery device development so, based on our experience, here are our top five trends to watch for in 2021.

THE COVID-19 DIVIDEND

Among all of the disruption, confinement and loss caused by covid-19, there have been some unexpected positive effects on human life.

The business case for vaccine development was difficult before covid-19; it takes years of development with all the failure risks common to drug development, and the financial return can be limited because each patient might receive only one or two doses during their life, or, at most, once per year. Compare that with chronic diseases, such as diabetes, where each patient receives multiple doses per day.

However, many governments have now realised that vaccines are necessary for economic security, if nothing else. They have accepted that they must invest in vaccines at risk, and sometimes in advance, to ensure that research, development and supply are possible. It seems inconceivable that governments and philanthropic funds will stop vaccine funding in the near future.

We should also expect to see strong investment from both public and private funds in autoimmune drugs (the first drugs known to help treat severe covid-19), diagnostics, critical care infrastructure and personal protective equipment.

"Many governments have now realised that vaccines are necessary for economic security, if nothing else. They have accepted that they must invest in vaccines at risk, and sometimes in advance, to ensure that research, development and supply are possible."

REDUCED ENVIRONMENTAL IMPACT

The pharmaceutical and medical device industries have long prioritised safety, efficacy, regulatory compliance, usability and economics when developing drugs and devices. In addition to these, we have seen a marked increase in the importance of reducing environmental impact in new device developments.

Part of this is driven by corporate environmental goals. Springboard has worked on multiple projects to reduce environmental impact, for example:

- Assessing the CO_2 equivalent of metered dose inhalers compared with dry powder inhalers and soft mist inhalers
- Working out better global supply chains to reduce air miles and other carbon-intensive operations
- Designing devices to be reusable, or to have significant reusable subassemblies
- Reducing the mass of plastic used.

Device manufacturers are already implementing more sustainable devices too, such as the YpsoMate Zero (Ypsomed, Burgdorf, Switzerland) (Figure 1).

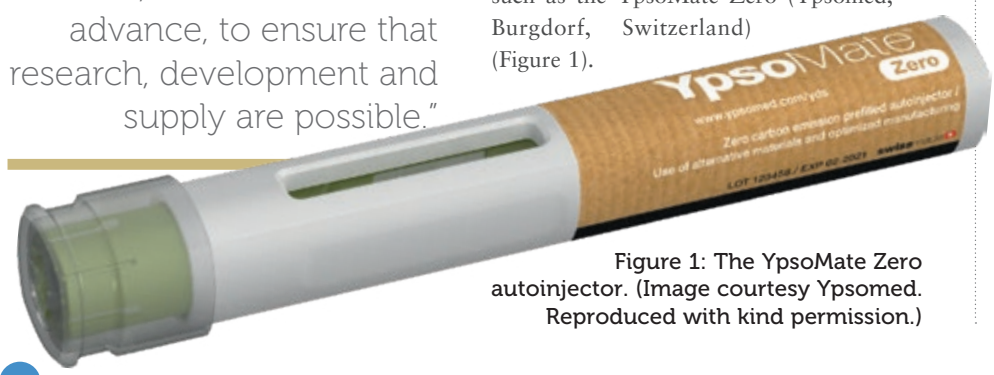

Figure 1: The YpsoMate Zero autoinjector. (Image courtesy Ypsomed. Reproduced with kind permission.)

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"Springboard has been developing connected drug delivery devices for its clients, some of which have new abilities that have not yet been seen on the market."

CONNECTED DEVICES

Connected devices have been the darling of conferences in recent years and are a big area of development – all of the main pharma companies and drug delivery device manufacturers are working on them.

The general technological hurdles have been overcome and the first connected drug delivery devices have reached the market, such as the Bayer (Leverkusen, Germany) BETACONNECT.

Springboard has been developing connected drug delivery devices for its clients, some of which have new abilities that have not yet been seen on the market. The most interesting new capabilities are confidential, but Springboard can confirm that there are devices under development with:

- Remote control of the drug delivery (both a customisable delay before start of delivery, and dose rate profile during delivery)
- Complex dose regimes from more than one drug container, or even more than one delivery device
- Connection with diagnostics. A well-known example is the combination of an insulin pump with a continuous glucose monitor, but diagnostics can be useful for indications other than diabetes.

The biggest remaining risks and challenges around connected drug delivery devices are:[1]

- **Expecting connectivity itself to solve adherence:** Connectivity is unlikely to make all patients adherent, but has great potential in enabling support and training to be focused on those who need it most.
- **Usability:** Adding features and functions can be confusing and increase risks.
- **Affecting critical functions:** Where possible, devices should function safely and effectively, even if the connected features fail.
- **Cybersecurity:** We have seen exploits on insulin pumps and infusion systems. Devices and systems must have high security to maintain the confidence of users, regulators and clinicians.
- **Data silos:** Proprietary systems will tend to lock data into separate, incompatible silos, but there are various campaigns to increase interoperability.
- **Regulatory change:** The first connected drug delivery devices have been approved, but, as a new area, we can expect changes and evolution of requirements and interpretations.
- **Environmental impact:** Adding electronics to devices can increase environmental impact but this can be minimised by making them reusable, long-lasting and recyclable.
- **Business models:** Expecting the patient to pay directly for connectivity is unlikely to be successful for many therapies. However, innovative business models, which involve pay-per-results (for which connectivity provides the evidence of adherence), are being rolled-out.

NASAL INHALATION

Nasal inhalation remains an area of active research, particularly for delivery of:

1. Central nervous system (CNS) drugs to cross the blood-brain barrier
2. Biologics, particularly peptides.

The main attractions of the nasal inhalation option are the potential to cross the blood-brain barrier, faster absorption and greater molecule survivability than in the gastrointestinal tract, and the avoidance of needles.

Various projects are underway for the delivery of drugs to the CNS, including the treatment of epilepsy, schizophrenia and pain management. Recently, there has been an increase in interest in nasal delivery of established molecules, such as ketamine and cannabinoids, which potentially have a faster route to market than new chemical entities.

The nasal route for delivery of biologics has already been proven for peptides to treat numerous conditions, such as osteoporosis, haemophilia and vitamin B12 deficiency. Larger proteins remain a challenge due to the limited permeability of the nasal mucosa relative to the rate of mucociliary clearance.

Springboard has substantial experience in how to design drug containers and delivery devices to work without damaging sensitive biologics.

ULTRA-SMALL NEEDLES

Needles are generally disliked by patients, but the drug delivery industry has struggled to move to non-needle methods. Oral delivery of biologics, such as insulin, is making progress with various clinical trials underway, but many candidates have failed over the years. Needle-free injectors seem to have fallen out of favour, perhaps because they tend to involve high-pressure or high-velocity jets, which mean loud noises and risk of bruising and pain. Therefore, there is a great deal of focus on ultra-small needles.

Terumo (Tokyo, Japan) has its tapered needles, for which the tip goes down to 34G.[2] The Nanopass 34G pen needle is intended for use with a pen injector device for the subcutaneous injection of drugs, including insulin (Figure 2). Becton, Dickinson and Company (NJ, US) and

Figure 2: Terumo's Nanopass 34G pen needle for the subcutaneous injection of drugs. (Image courtesy Terumo Pharmaceutical Solutions. Reproduced with kind permission.)

other companies are making extra-thin wall and ultra-thin wall needles available in more formats, such as in staked needle syringes.

Figure 3: Midas Pharma's 3 mL NIS autoinjector. (Image courtesy Midas Pharma. Reproduced with kind permission.)

The length of ultra-small needles is limited, due to both manufacturing constraints and risk of bending in use, but this is being addressed by clinical investigations into the possibility of shallower injections, and in optimising the grip of the needle in the device or syringe. Thin needles also increase the pressure required to inject in a reasonable time – see this example of the design of a powerful autoinjector.[3]

2021 will see continued, and probably increased, effort into achieving injection with ultra-small needles without requiring very high injection pressure. The NIS 3 mL autoinjector from Midas Pharma (Ingelheim, Germany) is a cartridge-based autoinjector. The two-step device can be easily modified to become the first "one-step" autoinjector on the market (Figure 3).

SUMMARY

We have touched on five areas of drug delivery work that we believe will be important in 2021. There are, of course, many others that did not make the list.

In most years, the trends tend to be dominated by improving the experience and outcomes for individual patients, which is entirely appropriate and encouraging. On the other hand, we see one trend this year – reduced environmental impact – which is intended to improve outcomes for society and the wider environment, rather than the individual patient. One could argue that preparation for, and protection against, pandemics is similar, in that it may be driven more by the benefit for wider society (and the national economy) than for the individual patient. Perhaps we will see more focus on such trends in the future.

ABOUT THE COMPANY

Springboard specialises in developing devices from concept to manufacture for regulated markets. The company is expert at creating innovative yet robust designs and solving difficult technical problems quickly. Springboard does not have internal projects so it is as fast and cost effective as possible, and the intellectual property belongs to its clients.

REFERENCES

1. *Oakley T "Risks and Real-World Solutions for Connected Medical Devices". ONdrugDelivery Magazine, Issue 108 (June 2020), pp 16–20.*
2. *"Nanopass® 34G Needle for Pen Injectors". Terumo website.*
3. *Oakley T, "Development of a New High-Performance Autoinjector". Springboard.pro, April 3, 2020.*

ABOUT THE AUTHOR

Tom Oakley leads engineering and scientific teams developing new injection devices, pumps and inhalers. He has been the named inventor on dozens of patents throughout his 20 years' experience in industry. Mr Oakley is a regular speaker at various international conferences on innovation and medical device development, and mentors engineering and MBA students on innovation and device development at the Cambridge University Engineering Department and the Judge Business School. He read Engineering at Cambridge University before becoming the Choate Fellow in Human Physiology and Pathology at Harvard University.

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HOSTAFORM® POM ECO-B – PROVEN, VERSATILE, EASY AND ENVIRONMENTALLY SUSTAINABLE

In this article, Kevin Norfleet, Senior Program Manager, Sustainability & Emerging Markets, and Rob Haley, Global Marketing Director, Medical & Drug Delivery Devices, of Celanese discuss the need for environmentally sustainable materials in the medical device industry, and how Celanese's Hostaform® MT® POM ECO-B meets that need, being an exact equivalent to the company's existing material but produced using up to 97% bio-content using a potential greenhouse gas as feedstock, accounted for using the mass balance approach.

To support a more environmentally sustainable future, it is imperative to reduce the volume of greenhouse gases being released into the environment. As such, governments and industries worldwide are introducing targets and setting goals to become carbon neutral over the next few decades, reducing their net greenhouse gas emissions to zero. Taking measures to achieve this goal can contribute to keeping the global temperature rise below 2°C.

Naturally, the medical industry is no exception. However, when it comes to materials, the medical industry faces a specific challenge that many others do not; it is not a trivial matter to recycle medical-grade material. Drug-containing devices, such as prefilled syringes, must be made of virgin material to comply with regulatory standards. Simultaneously, there is a need to provide safe and convenient prefilled devices to enable at-home self-administration of medicines by patients, particularly within the injectables space, which necessitates a ready supply of difficult-to-recycle medical-grade materials.

> "There is a pressing need for innovation to find a way to meet the demand for more environmentally sustainable production of these materials. For the medical industry, Celanese has developed and launched Hostaform® MT® POM ECO-B: a sustainable, pharmaceutical-compliant grade of Hostaform® POM made by transforming potential pollution into polyacetal material."

Therefore, there is a pressing need for innovation to find a way to meet the demand for more environmentally sustainable production of these materials. For the medical industry, Celanese has developed and launched Hostaform® MT® POM ECO-B: a sustainable, pharmaceutical-compliant grade of Hostaform® POM

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made by transforming potential pollution into polyacetal material. Hostaform® MT® POM ECO-B is in every respect the same product as traditional Hostaform® MT® POM, and as such can be swapped into production pipelines without impacting the properties of the end product, increasing development risks or introducing the need for product requalification.

AN OVERVIEW OF POM AND CELANESE'S HOSTAFORM® POM ECO-B

Polyoxymethylene (POM), sometimes called acetal or polyacetal, is a highly crystalline, high-performance engineering polymer used across a variety of industries, including automotive and consumer products, as well as medical. POM is a highly versatile material that can be processed in a multitude of ways and has a low coefficient of friction, excellent wear resistance, high modulus and resistance to a wide range of solvents.

These properties make POM an attractive polymer for use in medical devices. Celanese has a long history of expertise working with POM, and today is a leading provider of POM worldwide, with the company's Hostaform® POM being a trusted brand on the market since the 1960s. Hostaform® POM is traditionally used in medical devices for moving parts, low-friction assemblies, release mechanisms and spring assemblies, in large part due to its durability and tuneable tribological properties.

It is with this expertise that Celanese developed Hostaform® POM ECO-B, a sustainable alternative to its standard Hostaform® POM for companies looking to reduce their carbon footprint. Hostaform® POM ECO-B contains up to 97% bio-content using an ISCC+ certified mass-balance approach. Hostaform® POM ECO-B's CO2 footprint per kilogram of polymer is less than half that of regular Hostaform® POM (Figure 1), and yet is considered an equivalent virgin material, a feat achieved by the conversion of bio-gas into plastic.

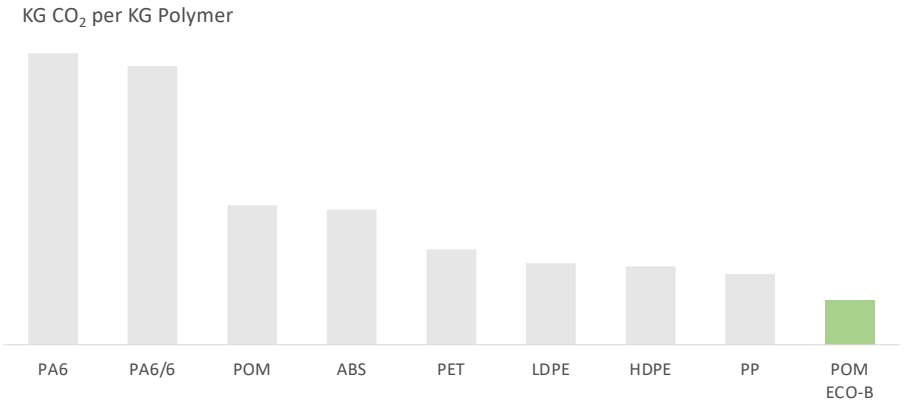

Figure 1: Looking at the library CO2 footprint per kilogram of polymer for a variety of polymers, Hostaform® POM ECO-B is the lowest, and is less than half that of regular Hostaform® POM.

Rob Haley, Global Marketing Director, Medical & Drug Delivery Devices, at Celanese, highlights that "Because Hostaform® MT® POM ECO-B is functionally the same material as Hostaform® MT® POM, Celanese can offer its partners exactly the same regulatory service support they have come to expect. Celanese's full MT® service package, including drug master files, letters of authorisation for regulatory filing support, and biocompatibility compliance, is available for Hostaform® MT® POM ECO-B."

THE MASS-BALANCE APPROACH

A variety of reaction steps go into making POM, but the starting molecule is methanol, which can be produced from several energy sources, including methane (commonly known as natural gas). Methane can be found in the ground as fossil fuel, but is also released when organic matter decays in an anaerobic environment. Kevin Norfleet, Senior Program Manager at Celanese, explains that "The mass-balance approach preserves Celanese's production scale and efficiency, while also linking end products to sustainable feedstocks. While green molecules are not tracked, the sustainable feedstocks are fed into the start of the process and then accounted for separately to allocate the benefits to specific products at the very end."

This is a similar principle to "green" electricity. When it's on the grid, all electricity is equal, so purchasing green electricity is a question of accounting; marking off electricity used by the buyer against electricity that was sustainably produced. It's the same for a chemical process like the production of POM; methanol is methanol and methane is methane. Once in the polymer production process, both fossil-based and bio-based feedstock can be mixed, but accounted for separately, with conventional Hostaform® POM produced by mass of conventional feedstock used, and Hostaform® POM ECO-B produced by mass of green feedstock used (Figure 2).

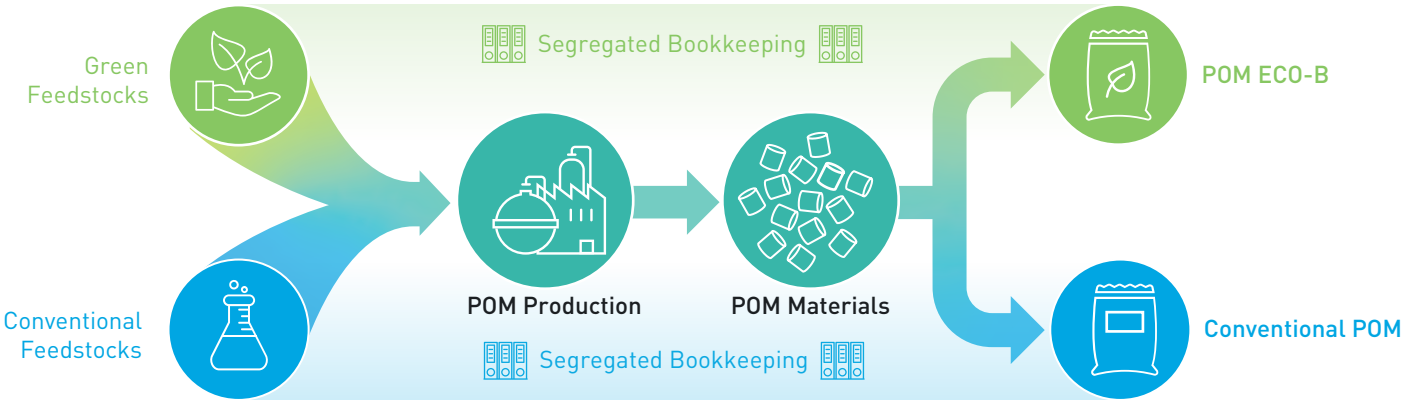

Figure 2: Using the mass-balance approach, green and conventional feedstock can be mixed during production but accounted for separately.

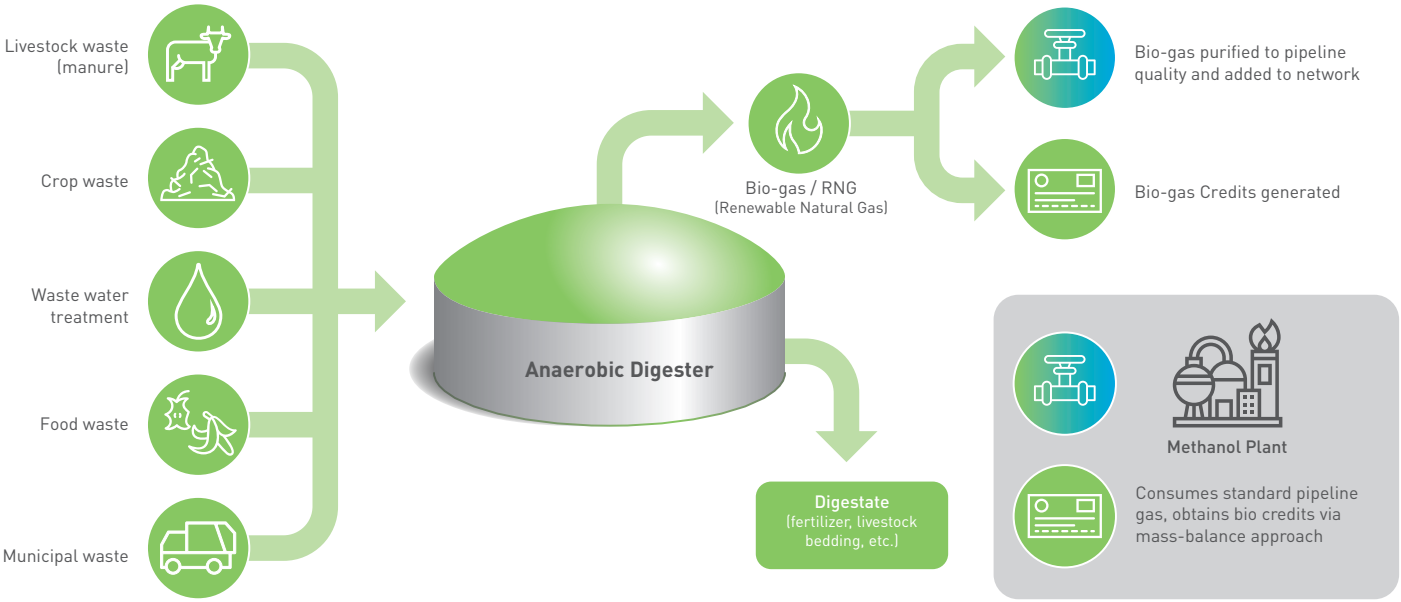

Figure 3: bio-gas is produced from the anaerobic decaying of organic waste material.

> "Bio-gas is a renewable resource, but also a potent greenhouse gas if not collected; by using it as feedstock it creates both a more sustainable material and a robust market for the collection of bio-gas."

The methanol used to produce Hostaform® POM ECO-B uses bio-gas as feedstock, a mixture of gases produced by the anaerobic respiration of bacteria during the decomposition of organic matter, such as agricultural waste and sewage (Figure 3). Bio-gas is a renewable resource, but also a potent greenhouse gas if not collected; by using it as feedstock it creates both a more sustainable material and a robust market for the collection of bio-gas. Furthermore, the process for producing Hostaform® POM ECO-B is ISCC+ certified, demonstrating compliance with the EU Renewable Energy Directive.

Because the mass-balance approach means that in all respects Hostaform® MT® POM ECO-B is functionally identical to regular Hostaform® MT® POM, Celanese can offer it as an option on any grade of Hostaform® POM in the company's portfolio and, as mentioned, switching to an equivalent grade of Hostaform® POM ECO-B involves no change in the downstream manufacturing processes and no need for product requalification.

HOSTAFORM® POM ECO-B IN ACTION – YPSOMATE ZERO

Hostaform® MT® POM ECO-B (specifically Hostaform® MT® POM ECO-B MT12R01) is a component in Ypsomed's YpsoMate Zero, the first autoinjector produced with a net-zero carbon footprint (Figure 4). In order to achieve such a significant milestone in sustainability for the medical device industry, it was necessary for YpsoMate Zero to make use of novel, more environmentally friendly materials, such as Hostaform® MT® POM ECO-B. YpsoMate Zero represents an answer to two major unmet needs in the medical device industry: the need for a more patient-centric approach to healthcare, focusing on easy-to-use devices that patients can self-administer at home, and the need for more environmentally sustainable practices and products.

ONdrugDelivery featured YpsoMate Zero in its inaugural Drug Delivery & Environmental Sustainability issue in 2020. In that article, Sebastian Gerner, Innovation

Figure 4: Hostaform® MT® POM ECO-B MT12R01 is a key material used in Ypsomed's YpsoMate Zero, the drug delivery device industry's first carbon neutral autoinjector.

BOX 1: YPSOMATE ZERO, HOSTAFORM® MT® POM ECO-B AND THE FUTURE

As part of its commitment to reach net zero carbon emissions by 2030, Ypsomed identified its state-of-the-art YpsoMate autoinjector as a prime candidate for optimisation to reduce its carbon footprint, in large part due to its nature as a single-use, prefilled product. In order to develop YpsoMate Zero, the world's first carbon neutral autoinjector, Ypsomed performed a lifecycle analysis of YpsoMate to identify its environmental impact hotspots. This analysis highlighted the use of alternative, more environmentally sustainable polymers as a high-priority focus point for the development of YpsoMate Zero. In pursuit of this goal, Celanese's Hostaform® MT® POM ECO-B MT12R01 emerged as a favourite candidate for several of the components of YpsoMate Zero.

Sebastian Gerner, Innovation & Business Development Manager at Ypsomed, explains how "A critical factor in this decision was the fact that Hostaform® MT® POM ECO-B is functionally identical to standard Hostaform® MT® POM and there is no need for additional product testing upon switching to Hostaform® MT® POM ECO-B. This fact means that Hostaform® MT® POM ECO-B is both convenient to switch to and reduces the risks involved in the development of YpsoMate Zero. As such, it was an easy, natural decision for Ypsomed to partner with Celanese and use Hostaform® MT® POM ECO-B."

Celanese and Ypsomed have an excellent and long-lasting working relationship, and both companies are pleased to be able to play their part in moving the drug delivery industry towards a sustainable, carbon neutral future. For Ypsomed, YpsoMate Zero is simply their first carbon neutral injection device, with more to follow on Ypsomed's journey to zero (for more details, see https://yds.ypsomed.com/zero). On Celanese's part, Hostaform® POM ECO-B represents a major step in support of its commitment to sustainable materials and technologies, with more products already in the development pipeline.

& Business Development Manager, and Andreas Schneider, Innovation & Business Development Director, of Ypsomed noted that the materials used for the device components of the standard YpsoMate autoinjector had the greatest impact on the device's total carbon emissions, with the polymer components, such as the device housing, syringe holding unit and components used to remove the needle guard, accounting for approximately 60% of the total carbon emissions associated with the device. As such, partnering with Celanese and using the carbon footprint reduction offered by Hostaform® MT® POM ECO-B was a significant part of making YpsoMate Zero a successful carbon neutral product (Box 1).

> "As shown by its use in Ypsomed's industry-leading YpsoMate Zero, Hostaform® MT® POM ECO-B is both simple to switch to and reduces the risk and difficulties involved in making products that are more environmentally sustainable."

CONCLUSION AND OUTLOOK

To meet the enormous challenges presented to create environmentally sustainable products, all industries are looking for ways to reduce their carbon footprint. A key element for success will be transitioning to more carbon neutral materials, especially in the medical industry where recycling medical-grade materials is a significant challenge.

Celanese has stepped up to the challenge with Hostaform® MT® POM ECO-B, which uses the mass-balance approach to provide a material that is functionally identical to the company's existing Hostaform® MT® POM but produced with up to 97% bio-content using a potential greenhouse gas as feedstock. As shown by its use in Ypsomed's industry-leading YpsoMate Zero, Hostaform® MT® POM ECO-B is both simple to switch to and reduces the risk and difficulties involved in making products that are more environmentally sustainable.

Jonas Koenecke, Celanese Global Marketing and Sales Director, Medical & Drug Delivery Devices for Engineered Materials, summarises that: "Hostaform® MT® POM ECO-B is a strong response to the need for more environmentally sustainable materials, helping Celanese customers improve their brand value and reach their sustainability goals with a certified virgin material. All those benefits are underpinned by the company's full-service regulatory support and dedicated team who can help support Hostaform® MT® POM in a wide range of products for the medical industry, including wearables, injection devices and inhalers. All these advantages make Hostaform® MT® POM ECO-B the ideal candidate polymer for the development of environmentally sustainable medical devices."

To find out more about Hostaform® MT® POM ECO-B and Celanese's wide-ranging expertise and experience partnering for the development of a broad range of medical devices, including inhalers, autoinjectors, wearable injectors and many others, please visit healthcare.celanese.com.

ABOUT THE COMPANY

Celanese Corporation is a global technology leader in the production of differentiated chemistry solutions and specialty materials used in most major industries and consumer applications. The company's businesses use the full breadth of Celanese's global chemistry, technology and commercial expertise to create value for its customers, employees, shareholders and the corporation. Celanese partners with its customers to address their most critical business needs, and strives to make a positive impact on communities and the world through The Celanese Foundation. Based in Dallas (TX, US), Celanese employs approximately 7,700 employees worldwide and had 2020 net sales of US$5.7 billion (£4.1 billion).

Celanese has supported key applications and the demanding requirements of the medical market for more than 40 years and has developed one of the broadest ranges of high-performance polymers

and thermoplastics in the world. The company is expanding design possibilities as its customers find new ways to improve patient care with cutting-edge medical and pharmaceutical material solutions. Celanese's continuously expanding medical technology portfolio includes solutions and technologies for multiple applications in the space of drug delivery, medical devices, orthopaedics, advanced surgical instruments and connected devices.

Celanese's innovation platforms and customised solutions provide high-quality, advanced and biocompatible polymers to help its customers innovate healthcare technologies, mitigate risk through regulatory compliance and create eco-responsible materials.

From feasibility to development to commercialisation, Celanese's scientists and engineers are there to provide development services, GMP material supply and regulatory support. The company's objective is to help its customers reduce time and risk in research and development, so their applications achieve a higher chance of success.

ABOUT THE AUTHORS

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BENJAMIN DIETIKER, WEIDMANN MEDICAL TECHNOLOGY

Benjamin Dietiker is Key Account Manager, Pharma Primary Packaging at Weidmann Medical Technology, a Weidmann Group company and a leading developer and producer of innovative high-quality injection-moulded plastic components. He is responsible for key accounts in the pharmaceutical market, for business development and strategic innovation projects. Mr Dietiker has a BSc in Engineering & Management from the FFHS University of Applied Science in Switzerland.

In this exclusive interview with ONdrugDelivery, Mr Dietiker discusses how the company has successfully implemented a growth strategy over the past six to seven years by focusing on key areas, plans for expansion, the effect covid-19 has had on the business, and how the company differentiates itself from larger competitors by focusing on quality and service.

Q What changes have occurred in the industry over the 25 years that Weidmann Medical Technology has been providing injection moulded plastic components, and modular assembly and packaging solutions, in particular with regard to prefillable syringes and other parenteral primary packaging such as wearable injectors?

A From our perspective as a producer, some of the most marked changes we've seen in terms of the requirements from our customers who are active in the field of combination products relate to increasingly stringent regulatory standards around the detection and monitoring of particles, microbiology, and in-line testing. We take such customers' demands very seriously and we can adapt rapidly. For instance, we are currently able to produce prefilled syringe closures in an ISO class 5 environment, whereas ISO class 7 or 8 requirements are the usual industry standard.

From a material perspective, the majority of the world's prefillable syringes are still produced with glass barrels, but in recent years we have seen a notable increase in the proportion with plastic barrels – such as prefilled syringe barrel with threaded closures (Figure 1). There is an industry trend towards plastic and also hybrid (glass/polymer) materials.

Over the past decades, there has also been a move away from parenteral medication always being administered in the clinical setting towards self-administration at home.

> "I am very proud to be part of an organisation that rises to the challenge and has the know-how and capabilities to co-develop and produce such high-quality devices, maintaining product quality without compromise."

Figure 1: Customised syringe barrel with threaded sealing closure, comprising tip cap, rigid cap and Luer lock adapter. Components are steam sterilisable, medical grade, and biocompatible per ISO 10993-1 and USP Class VI.

Q Please can you expand on the move towards self-administration?

A Moving from clinical point-of-care towards self-administration at home can ease the burden on hospitals and doctors, but it can also help to make treatments more convenient for patients, which ultimately helps to reduce the healthcare costs and improve outcomes. So pharmaceutical products and the devices used to deliver them have evolved and adapted to this trend, becoming safer, more intuitive and suitable for use by patients. Likewise, devices have evolved in response to the rise of biologic-based therapeutics. For example, more viscous formulations and higher dose volumes have become more common and so devices with larger capacities – including prefillable syringes with larger barrels, and wearable injectors – have emerged.

Q What changes have occurred in the industry in terms of technology?

A One very significant change has been the emergence of digital technologies, in particular the Internet of Things (IoT). On the patient side, we have seen the rise of connected devices. Today, diabetes patients can monitor their glucose level through a wearable continuous glucose monitoring (CGM) system and administer the requested insulin amount through a wearable insulin pump. This is a great example of how technology can increase patient quality of life significantly.

I am very proud to be part of an organisation that rises to the challenge and has the know-how and capabilities to co-develop and produce such high-quality devices, maintaining product quality without compromise. For example, we offer repeatable high precision production under the highest clean room environment standards. We worked hard to acquire the specific skills and knowledge required to achieve current quality levels and as industry and regulatory expectations grows, likewise we are always striving to improve still further with every day.

Q Can you talk about how the industry is seeking to improve product identification and traceability?

A That is indeed highly demanded, not only by our customers in the prefilled syringe field, but also by regulatory health authorities. The US FDA describes under 21 CFR section 610.14 the identity requirements for container products. There are increased requests not only to mark products, but to include information about the material and batch number directly on the container for biologics. Colour coded rings are the identification method of choice today, but there are some constraints regarding investments and requested floor space for labelling lines, limited flexibility and data readability in assemblies, to name a few.

Q What can Weidmann Medical Technology contribute to meet that demand?

A We started to look at the integration of the radio frequency identification (RFID) technology into plastic products through injection moulding techniques more than 10 years ago. I would say we were pioneers at that time, and probably even a bit early, but we gained knowledge and kept improving on our methods. Today, our previous investments seem to have paid off and we believe we bring important value to the table here. We can support our customers straight away with our knowledge and our RFID tagging and labelling as well as an RFID reader supplier base. And, most importantly, we are very lucky to have a team of dedicated and experienced development engineers, who are able to accommodate requested RFID tag or label designs, together with our suppliers, to fulfil our customers' needs.

> "Any customer can see at any given time where their production stands; if they're fully loaded, what their OEE would be, and many other valuable metrics."

Q Have you also implemented connectivity within your manufacturing facilities?

A Absolutely. On the industrial side, the way our factory and machines are connected has certainly completely changed. Today we run a state-of-the-art MES (manufacturing execution system) and CAQ (computer-aided quality). The cloud-based MES software supports all tasks connected with planning and controlling equipment and production processes. It allows real-time monitoring (Industry 4.0), meaning that any customer can see at any given time where their production stands; if they're fully loaded, what their OEE (overall equipment effectiveness) would be, and many other valuable metrics. We use it for preventive maintenance and continuous improvement processes (CIP) with a target to cut cost for our customers. Some customers just harvest that data and keep it as peace of mind, others really put this data to work for their own purposes. It's an area where we truly differentiate and add value. The offering around our MES is a prime example of one key way in which we're differentiated from our competitors. When it comes to transparency, we are ready and able to share this kind of real-time data with our customers.

Q Please could you describe some of the changes that Weidmann Medical Technology has undergone over the past few years, and the growth that the changes have prompted?

A We certainly noticed that the industry has become far more competitive and cost-conscious over time, and so has Weidmann Medical Technology. We only expect to receive projects if we offer both excellent quality and value. The Weidmann Group has been in existence for more than 140 years, it is family owned, with a reputation built on Swiss quality. In the past, Weidmann Medical Technology was very R&D driven, and a bit of a "jack of all trades" in that we catered to five markets, including labware and, most dominantly, microfluidic applications. We're still using the knowledge that we established during our stint in microfluidics for present production. But we found the R&D-driven strategy made it difficult to generate significant growth so, in 2014/2015, we refocused on production, and we streamlined our portfolio tremendously to cater to just two or three markets: pharma (predominantly primary packaging closures); IVD (*in vitro* diagnostics); and also medical devices.

> "The industry has become far more competitive and cost-conscious over time, and so has Weidmann Medical Technology."

Q What has changed since you streamlined your portfolio and refocused on production?

A Since refocusing, we've experienced steep growth in these key areas, and we remain aware that as a medium-sized company we always have to maintain that very tight balance between R&D and growth. When we do R&D, it has to be bespoke R&D directly related to a customer's demand or project. As mentioned, we have developed specific know-how in the field of RFID in the field of prefilled syringes, which can be seen as one of our USPs (unique selling propositions) and that helps us to secure our position in the market. In line with our strategy, this is not just a research concept. Rather it comes from collaborating (co-development) with our customers on a live project, on how to implement RFID technology into their existing products. We've helped them develop the right design and manufacturing approach, the geometry for the RFID tags and finding the right suppliers. We can confidently say that we have established deep experience in over-moulding of RFID tags or chips in existing products. But for us the most important thing is that we

focus on production, keep all our processes state-of-the-art, develop them and bring additional value our customer.

Q How has covid-19 affected the company?

A Having been focusing on the IVD market for several years, as the covid-19 pandemic emerged we were in the fortunate situation that we could provide the market, namely PCR and point-of-care testing consumables, with new and existing products, and two of the world's market leading companies in the IVD area were already longstanding customers. As a result, we have seen substantial growth in 2020 and this will continue in 2021.

We received significant orders not only for existing machines, but also for new production lines, which have been implemented in record time. It was an impressive experience working with such major companies at such lighting speed. This was done without cutting corners of course, but the pandemic made it necessary for projects to be accelerated. That was done on both sides very, very successfully. Everybody was pulling together in the same direction – our suppliers, sub-suppliers, customers and ourselves alike. It fills us with pride, to be honest, because our products go directly towards the covid-19 testing effort.

Q Is this success only related to your Swiss site in Europe?

A No, it's not. We were fortunate to be able to take the momentum and expand our Mexican site, which is very exciting for our organisation and our colleagues overseas. Our Mexican operators are already receiving comprehensive training at our site in Switzerland, and the tech-transfer of the entire injection moulding machinery, tools and assembly lines is expected to happen during the coming months. Our long-term trusted partnership with one of the world's major IVD players has made this possible. This move will certainly strengthen our position in the North American market.

Q How did the pandemic affect your organisation operationally?

A The pandemic did affect us operationally, as it did all organisations, and we took all the appropriate safety measures of course.

Figure 2: To keep its team safe during the pandemic, Weidmann Medical Technology divided operations by cleanroom rather than by shift.

At a very early stage, the Swiss government granted the Weidmann Group divisions the status of being system relevant to essential infrastructure. In order to achieve the rapid project turnarounds the pandemic demanded, whilst at the same time keeping our team safe, simply put we divided our operations by cleanroom and no longer by shift (Figure 2). We have more clean rooms than we have shifts, and so the advantage of this system is that if there had been somebody infected with covid-19 we would not have had to send the whole shift home as a consequence, but only the team of one cleanroom. So far, fingers-crossed, we have successfully isolated the few cases that we've had, and we have avoided any co-worker at our facility contracting the disease from somebody onsite, so I would call that a success.

Q Do you see the recent growth being sustained, and will it feed through to an uptick in demand on the delivery systems and parenteral packaging side of things as well as IVD?

A I would express our firm assumption that this is not a short-term trend. It's a long-term change that started before the pandemic and will persist after covid-19. The perceptions of people, the perceptions of companies and the perceptions of governments will have all changed. We will find it much more important to test more frequently and to test more widely even when we have beaten the pandemic. Obviously, it starts with IVD but demand for primary packaging will follow because treatments and vaccines against the disease need to be administered.

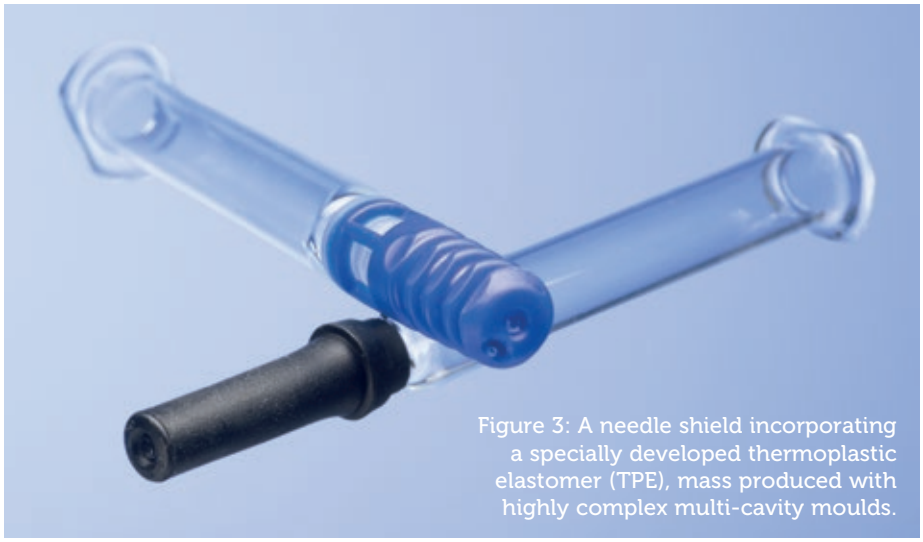

Figure 3: A needle shield incorporating a specially developed thermoplastic elastomer (TPE), mass produced with highly complex multi-cavity moulds.

Figure 4: Weidmann Medical Technology has a Swiss production site, another in Mexico and is establishing a third large production site at its Swiss headquarters.

Q What are the main insights you've picked up from trends in enquiries from customers?

A In one sense, because we are already producing, for example, needle shields (Figure 3) and prefilled syringe closures, enquiries come through because the industry community knows already that we are doing this. But then, as mentioned, during the pandemic, enquiries relating to covid-19 testing consumables have surged for obvious reasons and, with regards to prefilled syringes, we've been asked about prefilled syringe needle shields, soft and rigid closures, threaded closures as well. Enquiries have not been limited to closures but have also been about polymer syringes. Lately, potential customers have been asking about the capacity we have, what our capacities are in terms of cleanroom space (Figure 4). We have one Swiss production site and, as we have touched upon, one in Mexico, and we're underway establishing a third production site, also in Switzerland, at our headquarters.

Q Tell us more about your new site at your headquarters in Switzerland.

A This is most exciting news. Because of the solid growth of Weidmann Medical Technology over the past few years, we decided to expand our production capacity at our headquarters in Rapperswil, Switzerland. The beauty is that the expansion will take place in an existing Weidmann Group facility, previously used by Weidmann Electrical Technology, in the very centre of Rapperswil. This is a substantial milestone for the entire Weidmann Group and a clear commitment to the Swiss location. It is a site with substantial capacity because we have the demand for large machines and production lines. This expansion is not related to covid-19; the site was established more than a year ago and we have begun implementing the lines. The overall potential is huge here at our headquarters. By 2025 we expect our production site to be >6,000 m^2.

Q Weidmann Medical Technology prides itself on a truly differentiated service offering to its customers, unparalleled transparency and dedicated people for each customer. Could you go into a little bit more detail about this service offering?

A Weidmann Medical Technology has explicitly only ever grown organically and growing organically just takes a longer time. That's a rule of nature. Weidmann Group itself has been around for more than 140 years, employs almost 3,000 people, and generates a turnover of around CHF350 million (£270 million), so we benefit from being part of that large group. But still the medical division, in comparison with our competitors, is rather small and so we need to find out where it can make a difference. For us that is certainly customer centricity. It's part of our DNA, we are family owned. I would say that we can turn around projects much faster than our bigger competitors because we can make decisions and release budgets much faster. This has been of value for customers, we have that feedback. Additionally, although it's not necessarily a focus, we are willing to accept smaller orders, let's say, one line, a second-source project, or maybe an end-of-life project. The experience we have had is that being willing to help a customer out on these sorts of projects, which we are allowed to do by our management, builds up trust and loyalty which is not forgotten when something more attractive comes around the corner. The feedback we get from customers is that we are always available to them, at least for a call, if not a visit.

> "The feedback we get from customers is that we are always available to them."

ABOUT THE COMPANY

Weidmann Medical Technology is an independent Swiss injection moulding company serving the medical device and pharma industry, focusing on the development of innovative, technically advanced injection-moulded components. The company's core competence lies in the conversion of product ideas to industrialised products for international manufacture. Its capabilities include automation, assembly and packaging; industrialisation and scale-up; quality control via in-line camera systems; high-volume plastic consumables. It has production sites with clean-room ISO Classes 7/8 in Switzerland and Mexico.

Weidmann Medical Technology is part of the Weidmann Group, a major global supplier of technical products with a >140-year history, which employs almost 3,000 people in some 30 production sites and service centres worldwide.

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ON drugDELIVERY

2021/22 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
April	Ophthalmic Drug Delivery	Mar 25, 2021
April/May	Pulmonary & Nasal Drug Delivery	Apr 8, 2021
May	Delivering Injectables: Devices & Formulations	Apr 22, 2021
June	Connecting Drug Delivery	May 6, 2021
July	Novel Oral Delivery Systems	Jun 3, 2021
August	Industrialising Drug Delivery	Jul 1, 2021
September	Wearable Injectors	Aug 5, 2021
September/October	Drug Delivery & Environmental Sustainability	Aug 19, 2021
October	Prefilled Syringes & Injection Devices	Sep 9, 2021
November	Pulmonary & Nasal Drug Delivery	Oct 7, 2021
December	Connecting Drug Delivery	Nov 5, 2021
January 2022	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 2, 2021
February	Prefilled Syringes & Injection Devices	Jan 6, 2022

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ROOM FOR INNOVATION?

Darren Mansell, Regulatory Affairs Manager at Owen Mumford Pharmaceutical Services, examines US FDA guidance on biosimilar interchangeability and asks whether there is room for innovation.

As a growing number of biologics are seeing their patent-exclusivity period expire, the window of opportunity for biosimilars to enter the market continues to expand. The increased competition that will ensue typically entails a reduction in the cost of the affected therapies. This cost reduction can also be tied to the fact that biosimilar manufacturers may rely in part on the FDA's previous determination of safety and effectiveness of the reference product for approval, rather than carrying out additional clinical trials required for a standalone application.

Indeed, the purpose of a biosimilar development programme is to show interchangeability between the proposed biosimilar product and the reference product. While this may facilitate the approvals process, it has been suggested that FDA guidance on biosimilar interchangeability may also, in fact, be impeding innovation for the device element of the combination product. A closer examination of the document shows that new product developments are, in fact, welcome, but that the confusion around the FDA's 2019 interchangeability guidelines has meant that no biosimilars have yet been approved as interchangeable by the FDA to date.[1]

THE AGE OF BIOSIMILARS

Biosimilar development is currently at a decisive turning point. The window of opportunity for biosimilar manufacturers could be highly profitable, with Owen Mumford research estimating the biosimilar market opportunity to be US$3.12 billion (£2.24 billion) per year over a five-year period in Europe.[2] Furthermore, the "second wave" of biologicals, with patents expiring in the next 5–6 years, is expected to see peak sales of $100 billion (£72 billion) before patent expiry.[3] As manufacturers look to gain a slice of this market, they will need to find ways to stand out from their counterparts. Some will seize the opportunity to innovate in the area of drug delivery devices, knowing that device design can play a critical role in retaining patients if it improves the overall experience.

> "Room for innovation gives device designers the chance to rethink their devices from a patient's perspective, placing their comfort and ease of use at the centre. Without innovation, any opportunity for improvement is immediately squashed."

FDA GUIDANCE ON INTERCHANGEABILITY

At first glance, the FDA guidance document titled 'Considerations in Demonstrating Interchangeability with a Reference Product' may appear to hinder innovation for drug delivery devices, requesting that sponsors developing an interchangeable product "should not seek licensure for a presentation for which the reference product is not licensed".[4] This statement implies that sponsors could not apply for regulatory approval for a biosimilar presented in an autoinjector device if its reference product was marketed in a vial and prefilled syringe, for example.

Yet device design innovation and improvements are important as their impact on patient adherence and outcomes can be positive. Room for innovation gives device designers the chance to rethink their devices from a patient's perspective, placing their comfort and ease of use at the centre. Without innovation, any opportunity for improvement is immediately squashed.

Confusingly, the same FDA document later encourages manufacturers to seek delivery device enhancements, should they benefit the end user. In recent years, the FDA has recognised human factors as an important consideration to improve the

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"If, when adding new features, manufacturers can demonstrate improvements over the original reference product, then such modifications should be encouraged by the FDA."

overall patient experience and, subsequently, therapeutic outcomes. If, when adding new features, manufacturers can demonstrate improvements over the original reference product, then such modifications should be encouraged by the FDA. It is therefore hoped that any guidance issued by the FDA around interchangeability would promote innovation within the device-design field if it were to benefit the patient.

ASSESSING DRUGS AND DEVICES SEPARATELY

One way around this issue can be seen by looking to the EU, where regulatory pathways for biosimilars were already emerging in 2005, compared with only 2012 in the US.[5] The EU's equivalent guidance document from the EMA assesses interchangeability for the device and the drug element separately.[6] This separation is crucial for making space for device innovation, which is not only fundamental to the mission of improving patient outcomes and adherence but also a way for pharmaceutical companies to gain a competitive advantage over their counterparts.

Understanding where the line between "similar" and "not similar" lies will therefore be central to pharmaceutical companies when developing their sales strategy – be it biosimilar manufacturers looking to break into the market or the reference biologic producer trying to stand its ground in the face of increased competition.

MODE OF DELIVERY AND SELF-ADMINISTRATION

This also provides scope for offering patients a different mode of delivery – for instance, by developing a biosimilar suitable for subcutaneous delivery where the reference biologic was designed for intravenous administration. Given that subcutaneous injections are better adapted to the rising trend of self-administration for patients with chronic conditions, this change would allow patients greater involvement with their own medication regime and greater independence, while also freeing up time and resources for healthcare services.

FORGING A PATH TOWARDS INNOVATION

The purpose of the FDA's document is to offer guidance to sponsors hoping to demonstrate that their biosimilar product can be substituted for a reference product, without the patient having to go past a prescribing healthcare provider. However, the guidance can be ambiguous and, consequently, may dissuade manufacturers from innovating and improving the patient experience.

A likely outcome of the non-specific FDA guidance on interchangeability is that one portion of pioneering pharmaceutical companies will lead the way in terms of device innovation and the rest will trail behind in their footsteps. The pioneering companies will have to engage directly with the FDA in the early developmental stages and carve a path forward together. These initial attempts will most likely provide greater clarity on the issue of interchangeability and pave the way for change for the remaining pharmaceutical companies.

"A likely outcome of the non-specific FDA guidance on interchangeability is that one portion of pioneering pharmaceutical companies will lead the way in terms of device innovation and the rest will trail behind in their footsteps."

It is also hoped that articles such as this, which foster developmental debates on the issue, may also push matters in the right direction – towards greater clarification and in favour of innovation. In fact, the FDA has, since publishing the guidance, issued a draft Q&A guidance which provides new insights, notably on applications to support biosimilarity of a biologic but not of the device.[7]

ABOUT THE COMPANY

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

REFERENCES

1. *"Interchangeability, naming and pharmacovigilance of biosimilars". GaBI, Feb 12, 2021.*
2. *"Competitive Entry". Owen Mumford Pharmaceutical Services Report, Nov 2019.*
3. *"The Second Wave Of Biosimilars: New Scenarios, New Rules". Biosimilar Development, Dec 15, 2020.*
4. *"Guidance for Industry: Considerations in Demonstrating Interchangeability With a Reference Product". US FDA, May 2019.*
5. *"Biosimilar Products: Regulatory complexities and challenges of biosimilars". TOPRA, Feb 2019.*
6. *"Guidance for Industry: Biosimilars in the EU". EMA, 2019.*
7. *"FDA offers new Q&A on biosimilars and interchangeable products". RAPS, Nov 20, 2020.*

ABOUT THE AUTHOR

Darren Mansell has worked with Owen Mumford Pharmaceutical Services for over 14 years and is integral to ensuring products meet regulatory requirements, to facilitate compliance and sales in worldwide markets. He works in a cross-functional team, with colleagues from operations, R&D and sales, to deliver new and existing drug delivery and diagnostic products to customers. As well as securing regulatory approval for OMPS products, Mr Mansell also provides expert compliance advice and support to customers.

HOW TO KEEP THE GRANDFATHER DILEMMA FROM INTERRUPTING DRUG REDEVELOPMENT

In this article, Pfizer CentreOne's Associate Director, Regulatory Affairs, Chris Rojewski, provides programme insights into approval pathways for the redevelopment of pharmaceutical compounds.

Clearer approval pathways and new administration technologies are driving interest in redeveloping a range of legacy over-the-counter and generic compounds. Destined for new indications and better patient performance, rehabilitating old formulations is a growing part of pharma's business models and product strategies.

Many of these compounds have been on the market and used safely for a long time, in certain cases, even predating the requirement for a compliant regulatory application being approved by US FDA in order to market the product; these products are termed as "marketed unapproved drugs", sometimes referred to as "grandfathered". In the context of new development paths, these legacy products may not be compliant with current regulatory standards, and thus can't be referenced – requiring specific remediation before an old drug can win new approval.

"In the context of new development paths, these legacy products may not be compliant with current regulatory standards, and thus can't be referenced – requiring specific remediation before an old drug can win new approval."

ROBUST REMEDIATION RESPONSE REQUIRED

The majority of Pfizer CentreOne customers (i.e. drug innovators) seek approval for their US product(s) along the 505(b)(2) regulatory pathway. Although every aspect of the drug product and its manufacture may have been previously approved, a robust programme to remediate critical filings is needed – even for seemingly straightforward, highly prescribed drug products.

Two key pieces of FDA guidance in 2011 and 2013 set the stage for the necessity to contemporise the regulatory filings of drug products being redeveloped and approved for renewed manufacture. This guidance helped set regulatory filing expectations for new drugs intended for new markets, as per the FDA's stance on marketed unapproved drugs and combination products.

Two recent sterile injectable programmes delivered by Pfizer CentreOne, came up against complexities related to a grandfathered product and a combination product. Challenges included the "compliance-readiness" of the application reference, design history file and similar regulatory filings.

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Case #1: Revitalising A Vintage Combination Product For Modern Medicine

A long-term customer engaged Pfizer CentreOne to revitalise one of its mature finished drug products. Marketed commercially for more than a decade, the formulation was packaged as a combination product in a prefilled syringe (PFS). This combination product was originally approved through the FDA Center for Drug Evaluation and Research as a new drug.

The device component of the product is owned by Pfizer and was referenced through a Type III drug master file (DMF) that was managed by Pfizer. FDA combination product regulations have evolved over the years, which added the risk of having to apply new compliance standards for this product with post-approval modifications. Thankfully, in 2013, the FDA offered guidance to clarify how to handle some of the uncertainties related to this situation.[1]

As the programme ramped up, it soon became clear that key reference files could not meet today's combination product regulatory requirements. This roadblock introduced additional complexity into an already complex sterile parenteral programme. To keep project timelines on track, the company's regulatory team quickly pivoted, implementing a robust remediation programme for how the product referenced the device DMF and how it tied into the device design history file (DHF).

Like many relationships with contract development and manufacturing organisations (CDMOs), manufacturing a finished drug form may involve the legacy intellectual property of several parties. One of the complexities involved in this sterile injectable fill/finish project was the fact that the DHF for the PFS was owned by a third party. Fortunately, that third party was Pfizer Global Supply (PGS), which pushed through remediation of the package's DHF in parallel with the drug innovator's combination product remediation programme.

The complexities of this programme and the demands of the product required a phased approach to regulatory filings. This enabled the team to complete the product-specific validation studies necessary to include the product within the scope of the device DHF.

Once DHF remediation was complete, the product application was able to reference the DMF for the PFS, which made the drug innovator's application compliant with current regulatory expectations. Ultimately, the process took nearly 12 months, but all filings across the finished drug product were compliant with current combination product regulations, and ready for post-approval changes when submitted by the drug innovator.

Case #2: The Absent Regulatory Application

Another customer engaged Pfizer CentreOne to help renew manufacturing an extremely mature sterile injectable diluent, which was being repurposed for use with a commercial biologic product as part of a convenience pack. This product predated current regulatory approval practices, and was considered a marketed unapproved drug that was grandfathered. The FDA encourages the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug and Cosmetic Act, or run the risk of removal of the products from the market.[2]

As this product was the asset of a third party (in this case PGS), providing the product intellectual property to the customer for submission as part of their application was not preferred. A programme was needed to formalise this grandfathered product into a compliant regulatory application for approval, which could then be referenced by the drug innovator.

This was more than a regulatory exercise, however, as some revalidation effort was necessary to bring the product up to current standards. The customer's remediation programme required a focus on framing the design correctly for the intended use with the biologic product, then building a new regulatory application from scratch.

A ROBUST PROGRAMMATIC APPROACH TO REMEDIATION IS REQUIRED

These cases are not unique and drug innovators are encountering these hurdles more frequently as they pursue drug strategies leveraging the 505(b)(2) approval pathway. According to the FDA, 64 products were developed under this guidance in 2019, and tremendous growth is expected for the category.[3]

"Drug innovators are encountering these hurdles more frequently as they pursue drug strategies leveraging the 505(b)(2) approval pathway. According to the FDA, 64 products were developed under this guidance in 2019, and tremendous growth is expected for the category."

Both examples demonstrate how regulatory complexities can crop up unexpectedly, even with previously approved or grandfathered compounds, and during long-term commercial manufacturing relationships. Fortunately, a robust approach provided the necessary remediation responses to achieve product compliance and win subsequent product approvals from regulators.

DRESS PRODUCT FILES FOR SUCCESS

To align documentation for compliance and regulatory filing success, Pfizer CentreOne follows a methodology adopted by Pfizer for its own internal documentation remediation. Offering a structured approach to the process, the company can ensure compliance with current standards, which should lessen the risk of regulatory scrutiny with customers' applications.

With more of these kinds of products being renewed commercially, the issues related to grandfathered product data will need a focused programmatic approach. Regulatory application remediation can help keep 505(b)(2) programme timelines on track, while assuring compliance and market approval.

ABOUT THE COMPANY

Pfizer CentreOne is a global CDMO embedded within Pfizer and a leading supplier of specialty APIs. Pfizer CentreOne's global manufacturing network includes more than 35 sites across six continents. Backed by Pfizer resources, the company delivers technical expertise, global regulatory support and long-term supply. Working together with its customers, Pfizer CentreOne combines its knowledge with open dialogue to solve challenges as part of an intelligent collaboration.

REFERENCES

1. *"Guidance for Industry and FDA Staff: Submissions for Post approval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA". US FDA, Jan 2013.*
2. *"Guidance for Industry: CPG Sec. 440.100 Marketed New Drugs Without Approved NDAs and ANDAs". US FDA, Sept 2011.*
3. *"2019 505(b)(2) NDA Approvals in Review". Camargo, Mar 2020.*

ABOUT THE AUTHOR

Chris Rojewski has over 10 years of experience in regulatory affairs and more than 25 years in the pharmaceutical industry. After obtaining his Bachelor of Science in Chemistry from the University of Iowa, US, Mr Rojewski began his career as an Analytical Chemist at Abbott Laboratories, later joining Pfizer in 2016. With extensive experience in chemistry, manufacturing and controls, Mr Rojewski now expertly manages Pfizer CentreOne's Regulatory team as Associate Director of Regulatory Affairs.

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IMAGE

Two polymorphs of cholesteryl acetate recrystallised from the melt Gary Nichols, Materials Characterisation, Sandwich, UK.

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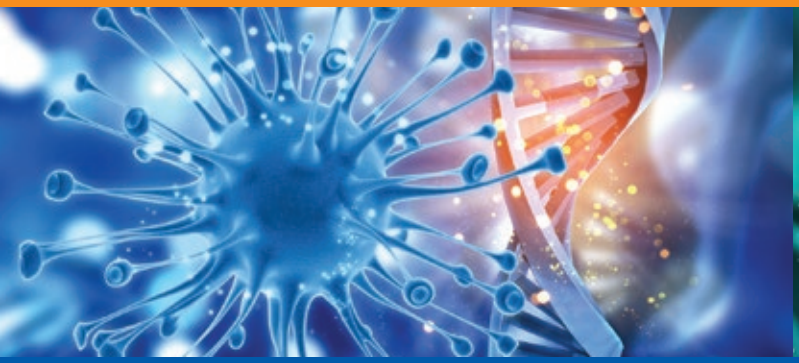

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STEVANATO GROUP AND EITAN MEDICAL BRING NEXT-GENERATION WEARABLE DRUG DELIVERY SOLUTIONS TO MARKET

In this article, Chiara Mussoi, Product Manager for the Cartridge Platform, and Riccardo Prete, Product Manager for the Vial Platform, both of Stevanato Group; and Mindy Katz, Vice-President, Marketing and Alliance Management – Pharmaceutical Solutions at Eitan Medical, outline the benefits of collaboration when it comes to bringing wearable drug delivery solutions to market.

The collaboration between Stevanato Group and Eitan Medical (developer of the Sorrel wearable injection device platform) is founded on the principal aim of bringing to market wearable injection solutions for the simple and efficient subcutaneous administration of large-volume and high-viscosity medications that serve the interests of both patients and pharmaceutical companies. As a leading producer of primary packaging and integrated capabilities for drug delivery systems, Stevanato Group plays a key role in the optimisation of primary containers – both cartridges and vials – for integration into large-volume wearable injectors.

The collaboration began with the development of cartridges to serve as primary drug reservoirs for Eitan Medical's Sorrel wearable device line, later expanding to include the supply of glass containers for vial-based configurations of the device. Sorrel devices are, by design, primary-container agnostic, being able to accommodate a variety of different container types in a range of volumes and dimensions. Although not tied to a specific primary container manufacturer or proprietary design, the unique collaboration leverages the core strengths of both companies: Stevanato Group's extensive experience in the design and testing of glass primary containers and its position as a leading provider of containment solutions combined with Eitan Medical's development expertise in the area of smart, electromechanical drug delivery and infusion devices.

Both companies are united in their commitment to improve the self-administration experience and outcomes for patients, while helping pharmaceutical partners mitigate risks and minimise time to market with proven technical, regulatory and manufacturing expertise.

> "The Sorrel wearable drug delivery device platform is designed to provide both a patient-centric and partner-focused solution for the self-administration of large-volume and high-viscosity medications."

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Figure 1: The Sorrel platform is primary container agnostic.

"The Sorrel platform's proprietary technology provides a distinctive solution for drawing medication directly from a vial, while still enabling a prefilled and preloaded configuration."

THE SORREL WEARABLE DRUG DELIVERY DEVICE PLATFORM

The Sorrel wearable drug delivery device platform is designed to provide both a patient-centric and partner-focused solution for the self-administration of large-volume and high-viscosity medications. The prefilled and preloaded configuration encourages adherence to treatment therapies while reducing the risk of medication errors. The incorporation of multiple smart sensors and indicators further guarantees patients a successful self-administration experience.

Because the platform is primary-container agnostic (Figure 1), pharmaceutical companies working with the Sorrel platform enjoy the flexibility to use the primary container of their choice, thus enabling Eitan Medical to collaborate with multiple pharmaceutical partners across a wide range of molecules, volumes and indications. Additionally, the Sorrel platform's proprietary technology provides a distinctive solution for drawing medication directly from a vial, while still enabling a prefilled and preloaded configuration, presenting several advantages to customers. Pharmaceutical partners can thereby save considerable time and risk by commercialising a combination product with the device constituent being a Sorrel vial-based wearable injector.

Eitan Medical's decision to introduce a vial-based configuration for its Sorrel wearable platform provides a number of key benefits for pharmaceutical partners. Glass vials constitute the most versatile primary packaging containment solution, as almost all pharmaceutical companies already possess internal vial filling capabilities. This can help to ensure compatibility with a wearable drug delivery platform from the initial development stages of new drug formulations, while also enhancing the lifecycle management of those products already on the market with established supply chains.

OPTIMISING GLASS CONTAINMENT SOLUTIONS

Stevanato Group's contribution to the development of the Sorrel wearable devices surpasses the mere provision of glass primary packaging to include technical, analytical and project management competencies that provide fully integrated containment solutions for wearable drug delivery devices. The customised package comprises several key components, primarily high-quality primary packaging in the form of Stevanato Group's SG EZ-fill format. Also included is the identification of the most suitable add-on components according to the final application and the filling process, leveraging Stevanato Group's proficiency and long history of collaboration with leading closure manufacturers of rubber plunger stoppers, lined caps, front caps and aluminium crimps for cartridges, as well as front caps and aluminium crimps for vials.

Stevanato Group can additionally provide standard and ad-hoc testing of drug-container and container-device interaction within the company's ISO/IEC 17025 certified internal laboratory. Additionally, project management support enables partners to focus their energies on core activities while Stevanato Group co-ordinates parties to provide container closure systems that are ideally suited for the device platform. Internally developed glass converting technologies, scalable and flexible assembly solutions and sterilisation processes allow the company to strictly control all manufacturing parameters relating to drug product quality and safety.

SG EZ-FILL FOR ASEPTIC MANUFACTURING

Stevanato Group's EZ-fill platform provides a fully integrated pre-sterilised solution for aseptic manufacturing, developed in close collaboration with equipment manufacturers in response to the growing demand for increased operational flexibility. Available in a double secondary packaging

"Pharmaceutical companies can easily address specific concerns – such as breakages, cosmetic issues and particle generation – enabling them to devote greater energy to core activities such as new drug development."

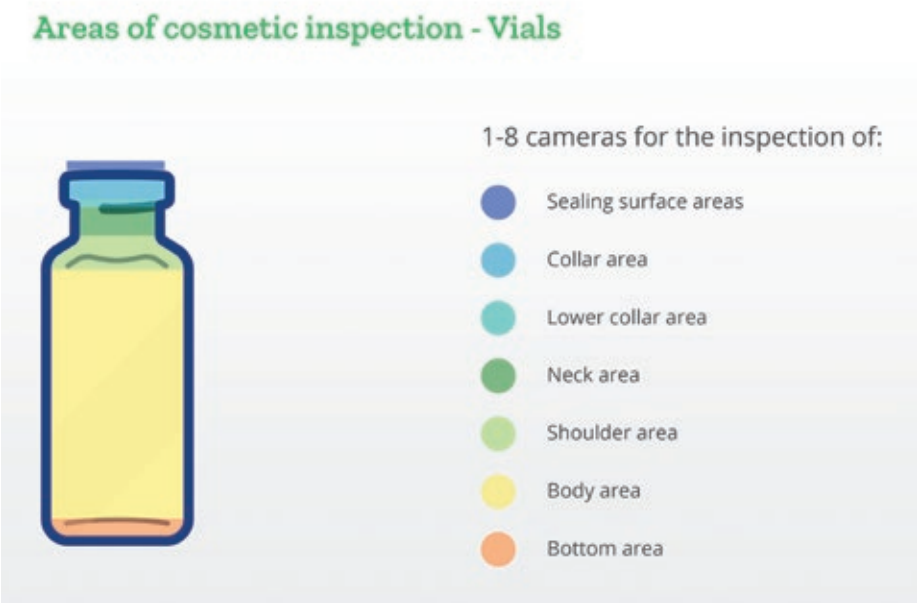

Figure 2: Cosmetic controls on Stevanato Group vials.

configuration (nest-and-tub and tray), SG EZ-fill provides an optimal solution for both small-batch and industrial-scale production.

Close collaboration with key providers of ready-to-use closures and add-on components has enabled Stevanato Group to offer systems fully compliant with international regulations. Pharmaceutical companies can therefore easily address specific concerns – such as breakages, cosmetic issues and particle generation – enabling them to devote greater energy to core activities, such as new drug development. Additionally, by using proven packaging, SG EZ-fill is able to maximise filling efficiency by allowing for different filling nozzle combinations. Every aspect of the filling process can therefore be streamlined, from incoming material to final product shipment.

The use of a nest-and-tub configuration confers further key benefits to the SG EZ-fill platform, minimising glass-to-glass contact, increasing cosmetic quality and reducing particles, which results in a lower risk of rejection and waste of drug products, along with higher mechanical resistance, thus reducing the risk of container breakage and further drug loss.

PRIMARY CONTAINER CONSIDERATIONS FOR OPTIMISATION INTO LARGE-VOLUME WEARABLE DEVICES

Using the SG EZ-fill format enables Stevanato Group to provide large-volume primary cartridges ranging from 5 mL to 20 mL that can be integrated into wearable delivery systems suitable for treatment of chronic illnesses. With complete control of the forming conditions, and through continuous product improvement, Stevanato Group can optimise the internal shape of the primary container, thus maximising dosing accuracy. Furthermore, every aspect of the drug reservoir – length, diameter, volume, neck size, flange design and closure – can be customised according to a specific device's technical needs.

With the aim of obtaining a homogenous silicone layer in terms of thickness and distribution, the proper and optimised silicone recipe for each format is defined by a tailored design of experiment study. Using proprietary siliconisation technology and automatic camera controls guarantees optimal results for gliding profile and good cosmetic appearance.

As a full solution provider, Stevanato Group is further able to support plunger development to reduce the dead volume and optimise "glideability" by using the partner's preferred rubber manufacturer, formulation and coating. Moreover, Stevanato Group can pre-assemble cartridges with the customer's closure of choice (for example, a front stopper with or without flip-off) from all major closure manufacturers. Specific in-line cameras are dedicated to control the quality of the crimping to improve container closure integrity.

EVOLUTION OF A PROVEN VIAL SOLUTION FOR INTEGRATION IN WEARABLE DEVICES

Stevanato Group has developed rigorous inspection protocols to ensure compliance with the strictest partner requirements in terms of both dimensional and cosmetic parameters. Dimensional conformance is integral to ensuring compatibility between primary containers and drug delivery devices, while maintaining cosmetic standards reduces the risk of non-quality rejection in fill-and-finish lines, avoiding wastage of valuable drugs (Figure 2).

Dimensional and cosmetic quality of the vials is maintained through automated inspection systems installed in production lines. Cameras positioned before the packing station detect scratches, deformations, bubbles, pressure marks, airlines,

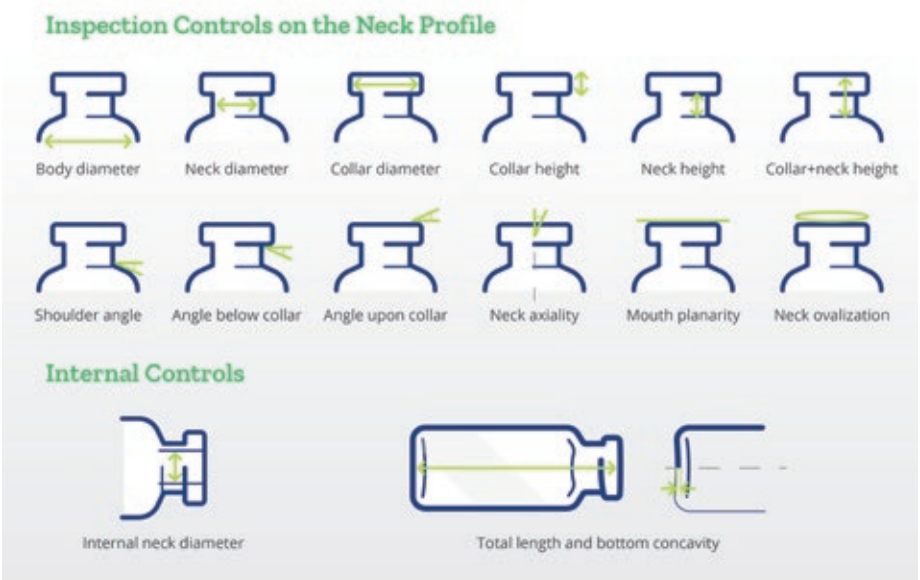

Figure 3: Dimensional controls on Stevanato Group vials.

Figure 4: Sorrel testing of new primary containers in process.

chips and cracks. Manual controls are performed before, during and after both the production process and the SG EZ-fill process. Using specially designed techniques and instruments, quality control teams ensure that all products fully meet both customers' and regulators' quality and dimensional requirements (Figure 3).

SORREL DEVICE ASSESSMENT PROTOCOLS

In addition to the inspection protocols performed by Stevanato Group, once received by Eitan Medical a thorough testing regime is conducted by the verification and validation teams, ensuring that the Sorrel device and the relevant primary container and closure components work together seamlessly.

General dose accuracy testing is performed with any new primary container and components to determine overall device performance and functionality. Needle penetration force and depth measurements are taken for each new device/container/component configuration, optimising the depth to which the needle penetrates the septum to ensure it always clears the rubber partition to enter and draw medication from the primary container.

To ensure proper mechanical fit of the primary container within the Sorrel device, Eitan Medical can easily customise the device's plastic casing to adapt to different dimensions of a primary container. Certain device configurations include an internal adapter that can be employed to allow smaller primary containers to use the same device for testing purposes. For example, the Sorrel fully functional 20R vial-based wearable injector can easily be configured to accommodate 10R vials, allowing pharmaceutical companies to test different vial sizes with just a quick insertion of an adapter in the device assembly line. This is yet another example of how pharmaceutical companies can test products more quickly, and kick off development projects faster, with the platform approach of a medical device manufacturer (Figure 4).

Hold-up volumes of both vial and cartridge primary containers are measured alongside the dead volume within needles to provide an overall understanding of the hold-up volume of the entire wearable system. This allows for primary container fill volumes to be further adjusted as needed to guarantee optimal performance.

To overcome the inherent challenge of maintaining sterility in preloaded devices, the Sorrel devices use UV-C LED technology for disinfection at the point of care, disinfecting the point of engagement between the primary container and the device's fluid path. Intensive UV disinfection validations are therefore performed on every rubber septum to conform to the six-log bacteria reduction as stipulated by the US FDA for low-level disinfection.

THREE-WAY COLLABORATION FROM THE OUTSET

The collaboration between Eitan Medical and Stevanato Group has resulted in the ability to offer a full portfolio of subcutaneous wearable drug delivery solutions, in both vial and cartridge configurations and across a range of different sizes, that are able to meet any drug development phase, from preclinical studies to lifecycle management, and can be easily adapted to the maturity of a project.

However, when looking to introduce drug delivery combination products to market, it is imperative that all participants – the device manufacturer, primary container manufacturer and drug developer – are brought into play and that collaboration is established as early in the process as possible. As activities are often intertwined, early engagement will ensure

"Early co-operation can expedite the introduction of new drug delivery systems for the benefit of all parties – the device manufacturer, container provider, pharmaceutical developer and, ultimately and most importantly, the patient."

that interdependencies are considered, and timelines aligned to streamline the entire process. This early co-operation can thus expedite the introduction of new drug delivery systems for the benefit of all parties – the device manufacturer, container provider, pharmaceutical developer and, ultimately and most importantly, the patient.

ABOUT THE COMPANIES

Established in 1949, **Stevanato Group** is the world's largest privately-owned designer and producer of glass primary packaging for the pharmaceutical industry. From its outset, the group has developed its own glass converting technology to ensure the highest standards of quality. The group comprises a wide set of capabilities dedicated to serving the biopharmaceutical and diagnostic industries: from glass containers with its historical brand Ompi, to high-precision plastic diagnostic and medical components, to contract manufacturing for drug delivery devices, to vision inspection systems, assembly and packaging equipment. Stevanato Group also provides analytical and testing services to study container closure integrity and integration into drug delivery devices, streamlining the drug development process.

Eitan Medical is reimagining drug delivery, with reliable innovations that put patients at the centre of care, making drug delivery easier and safer than ever before. Patient safety and care are only the starting point, as Eitan Medical goes beyond – delivering connected, intuitive drug delivery and infusion solutions that are designed to improve patient and clinician quality of life across the continuum of care, including hospital, ambulatory and home-care environments. For over a decade, Eitan Medical has provided safe, intuitive and flexible solutions that meet evolving drug delivery needs.

Eitan Medical's product lines include the Sapphire infusion platform*, providing connected infusion therapy systems in hospital and ambulatory settings; the Sorrel wearable drug delivery platform**, the patient-centric on-body injector for delivery of biologic treatments; and Avoset***, connected infusion systems for the home-care market.

** Q Core Medical Ltd is the legal manufacturer of the Sapphire infusion pump.*
***Sorrel Medical Ltd is the legal manufacturer of the Sorrel wearable drug delivery platform (FDA investigational device).*
****Avoset devices are currently under development.*

ABOUT THE AUTHORS

Chiara Mussoi is the Product Manager for the Cartridge Platform at Stevanato Group. She is responsible for the development and definition of the go-to-market strategy of glass cartridges (ready-to-use and bulk). After studying Economics and Business Administration at Udine University (Italy) and Copenhagen Business School (Frederiksberg, Denmark), she accumulated extensive knowledge working as a Product Manager for medical devices for injectable products. Since joining Stevanato Group in 2016, Ms Mussoi has been in charge of evaluating and promoting new products that meet customers' needs and expectations

Riccardo Prete is currently part of the Product Management team of Stevanato Group, overseeing the sterile and bulk glass vials business. With a background in Economics and a Master's degree in Business Administration from Ca' Foscari University of Venice (Italy), he joined Stevanato Group in 2017 as a Product Specialist for glass bulk products.

Mindy Katz is Vice-President, Marketing and Alliance Management at Eitan Medical where she heads the company's alliance management, marketing and product management activities for the Pharmaceutical Solutions business unit. Ms Katz's involvement in the company's early days influenced Eitan Medical's decision to pursue the wearable drug delivery market, resulting in the development of the Sorrel wearable drug delivery platform. To date, Ms Katz has held a number of positions within the group, including serving as Vice-President of Marketing and Director of Product at Sorrel Medical, and prior to that as Program Manager at Q Core Medical, where she worked across multidisciplinary teams to build structured and collaborative partnerships between companies in the world of drug delivery. She holds a BSc in Biomedical Engineering from the Technion – Israel Institute of Technology.

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Dr. Andrei Yosef, General Manager, Pharmaceutical Solutions at Eitan Medical

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INNOVATING IN THE VISCOSITY DESIGN SPACE FOR HANDHELD COMBINATION PRODUCTS: A NEW 2.25 ML AUTOINJECTOR PLATFORM

In this article, Karima Yadi, Global Marketing Lead for the Autoinjector Platform, and Lionel Maritan, Senior Program Manager, Autoinjectors Platform, both at BD Medical – Pharmaceutical Systems, discuss BD's response to the need for an autoinjector platform that reconciles the demands of biologics with safety, reliability and ease of use during self-injection: the Intevia™ 2.25 mL disposable autoinjector.

Multi-disciplinary teams at BD set out to develop an autoinjector platform that builds on past successes, while meeting the requirements of the highly viscous, high volume[1] biologics that are upcoming in the chronic disease space. The result is an autoinjector platform that delivers an enhanced experience for patients,[2] extends the design space beyond traditional subcutaneous (SC) delivery for biologics and can lower development risks for biopharmaceutical partners.

Chronic diseases represent a major burden to the healthcare system, accounting for approximately 77% of the total disease burden and 86% of all deaths in Europe.[3] Today, innovative drug therapies, such as biologics, are contributing towards an improvement in the quality of life for chronic disease sufferers. Simultaneously, innovations in the drug delivery device space are making it possible for chronic disease sufferers to manage their drug therapies from home.[4] Subsequently, many innovations in this area seek to improve the patient self-injection experience by addressing issues, such as injection frequency, pain perception, needle phobia, needlestick injuries, accidental intramuscular (IM) injection risk and dose accuracy and consistency. Beyond greater comfort and convenience for patients, moving the centre of care from the clinic to the home, when possible, contributes to better management of healthcare costs.[1]

THE NEXT STEP IN BIOLOGICS

A high success rate has contributed to making biologics one of the fastest growing segments within the pharmaceutical

> "Biological drugs are often characterised by large molecules requiring administration in large injection volumes and/or high concentrations. These proteins require parenteral administration via IV or SC injection, due to their low bioavailability via other routes. This can present a challenge for existing SC autoinjector technologies that have been limited to lower viscosities and volumes."

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industry.[5] In 2018, the biologics market was valued at US$251.5 billion (£183.8 billion) and in 2019 was predicted to grow at a compound annual growth rate of 11.9%, reaching $625.6 billion (£457.1 billion) by 2026.[6] Within the biotherapeutic space, the market for monoclonal antibody-based drugs (mAbs) has undergone significant growth of its own, thanks to mAbs' high target specificity, good therapeutic outcomes and limited side effects.[7] As of December 2019, 79 therapeutic mAbs had been approved by the US FDA.[7]

Biological drugs are often characterised by large molecules requiring administration in large injection volumes and/or high concentrations.* These proteins require parenteral administration via intravenous (IV) or SC injection, due to their low bioavailability via other routes.[8] This can present a challenge for existing SC autoinjector technologies that have been limited to lower viscosities and volumes.

There is a need for a delivery solution in the SC self-injection space capable of reconciling the demands of biologics with safety, reliability and ease of use during self-injection. There are many important incentives for meeting this need, including providing patients with longer intervals between injections, reducing injection-associated pain and discomfort,[1] increasing therapeutic adherence, limiting overall costs and creating greater freedom from IV parenteral injections.[9]

ENLARGING THE AUTOINJECTOR DESIGN SPACE

With the launch of the BD Intevia™ disposable autoinjector platform, BD offers a range of devices combining an autoinjector and a prefillable syringe in one integrated system, specifically designed for high-viscosity, high-volume biologics. The BD Intevia™ 2.25 mL disposable autoinjector** expands the Intevia™ range beyond the already-launched BD Intevia™ 1 mL disposable autoinjector (Figure 1). Created using BD's quality-by-design approach, the BD Intevia™ 2.25 mL disposable autoinjector is a robust and integrated two-step, push-on-skin device that serves a broad design space, providing pharmaceutical companies with additional degrees of freedom and flexibility in drug formulation. The BD Intevia™ 2.25 mL disposable autoinjector delivers drugs with viscosities up to 40 cP safely and effectively.[10,11] Pharmaceutical companies can adapt the BD Intevia™ 2.25 mL disposable autoinjector to deliver a range of drug volumes and viscosities without any need for customisation of the system or of its components.[10]

Figure 1: Intevia™ 2.25 mL disposable autoinjector.

Figure 2. BD Neopak™ glass PFS.

INTEGRATING BD NEOPAK™ XTRAFLOW™ 2.25 ML GLASS PREFILLABLE SYRINGES

The BD Intevia™ 2.25 mL disposable autoinjector integrates the BD Neopak™ XtraFlow™ 2.25 mL glass prefillable syringe, featuring innovative 8 mm needles with Thin Wall (TW) cannula technology (Figure 2). BD Neopak™ prefillable syringes are characterised by breakage resistance, design quality, autoinjector compatibility and dimensional precision for dose accuracy.[10] By directly addressing many of the risk factors that can cause development delays,[12,13] BD Neopak™ glass prefillable syringes contribute to reduced time to market and optimised commercialisation of biopharmaceuticals.[13]

The integration of the BD Neopak™ XtraFlow™ glass prefillable syringe simultaneously supports crucial objectives of the BD Intevia™ disposable autoinjector platform – simpler adaptation to drug volumes and viscosities and reliable combination product performance. This may contribute to cost savings for biopharmaceutical partners,[13] while also contributing to comfort, safety and convenience for patients.[1,11]

"Created using BD's quality by design approach, the BD Intevia™ 2.25 mL disposable autoinjector is a robust and integrated two-step, push-on-skin device that serves a broad design space, providing pharmaceutical companies with additional degrees of freedom and flexibility in drug formulation."

EXTENSIVE PIPELINE SUPPORT WITHOUT CUSTOMISATION

The Neopak™ XtraFlow™ glass prefillable syringe simplifies the burden of device integration faced by pharmaceutical companies. With its robust integration into the BD Intevia™ disposable autoinjector platform, the BD Neopak™ XtraFlow™ glass prefillable syringe helps eliminate the

risks associated with the integration of components from diverse manufacturers,[11] as well as the risks associated with the customisation of the secondary device. With BD Intevia™ disposable autoinjectors, one device configuration addresses a broad range of viscosities and volumes without the need to customise system and subsystem components.

This high degree of flexibility is made possible by accommodating the demands of different viscosities and volumes solely through the parameters of the needle integrated into the Neopak™ XtraFlow™ glass prefillable syringe. By using a shorter needle and increasing its inner diameter without increasing the external diameter (by reducing the thickness of the needle wall), injection force is reduced by up to 46% compared with a commonly used 12.73 mm needle.[14] This is achieved without compromising needle robustness[15] or increasing pain perception.[16]

To manage a range of viscosities and injection volumes, Neopak™ XtraFlow™ 2.25 mL glass prefillable syringes are available with 27G UTW, 27G Special-Thin Wall and 29G Thin Wall 8 mm needles.

Thanks to BD Intevia™ 2.25 mL disposable autoinjector and BD Neopak™ XtraFlow™ 2 mL glass prefillable syringe system, a single autoinjector is equipped to handle biologic formulations with viscosities ranging from aqueous to 40 cP and fill volumes up to 2.25 mL.

PUTTING PATIENTS FIRST

The BD Intevia™ disposable autoinjector platform supports pharmaceutical companies that wish to take the lead in patient comfort[1] in the injection of biologics at dose volumes of up to 2 mL via SC delivery. The platform is the direct of result BD's patient-centric design approach and commitment to developing drug delivery solutions tailored to home care, with the aim to improve patient adherence to chronic disease treatments. This patient-centric approach is reflected throughout BD Intevia™ disposable autoinjector design factors. The BD Neopak™ XtraFlow™ 2 mL glass prefillable syringe 8 mm needle technology usability was supported by two human factors studies. They address several unmet needs including a reduction in injection or needle-related anxiety, pain perception and reduced risk of accidental IM injection. It was also calculated that the reduction in the needle length increases the chances of targeting the subcutaneous space by two to six times, thus ensuring an optimal efficacy of injectable therapies while avoiding potential adverse effects for the patients.[11]

> "Both the BD Physioject™ disposable autoinjector and the Intevia™ disposable autoinjector platform are the result of a system-integration approach that aligns BD teams technically, bringing together both system-level data and the whole cascade of requirements and specifications to the component level."

The BD Intevia™ 2.25 mL disposable autoinjector's patient-friendly design makes it easy to hold and manipulate,[11] enabling a simple, two-step, push-on-skin injection by the patient (Figure 3).[10] The device promotes patient confidence through feedback indicators that visually show patients when the correct dose has been delivered, both and with an audible click.[11] Robust system design improves patient safety by protecting the needle at all times, from the start to the end of the injection process (when the needle is removed from the skin).

CONTINUITY AND INNOVATION – FROM PHYSIOJECT™ TO INTEVIA™

BD Medical – Pharmaceutical Systems manufactures more than 2.5 billion drug delivery systems each year, mainly in the glass prefillable syringe segment.[17] The sheer number of systems produced provides BD with a vast knowledge base and data repository that enables extensive system analysis and ongoing improvement. In creating the Intevia™ disposable autoinjector platform, BD has leveraged this data and all the lessons learned during 13 years of experience developing, launching and commercialising the BD Physioject™ disposable autoinjector. Both the BD Physioject™ disposable autoinjector and the Intevia™ disposable autoinjector platform are the result of a system-integration approach that aligns BD teams technically, bringing together both system-level data and the whole cascade of requirements and specifications to the component level. A truly interdisciplinary approach analyses integration goals from the areas of chemistry, mechanics, fluid dynamics and manufacturing engineering. Cross-functional teams of scientists and engineers at BD contribute to product development technical excellence, including requirements and specifications management. Thanks to this unique organisation and expertise,

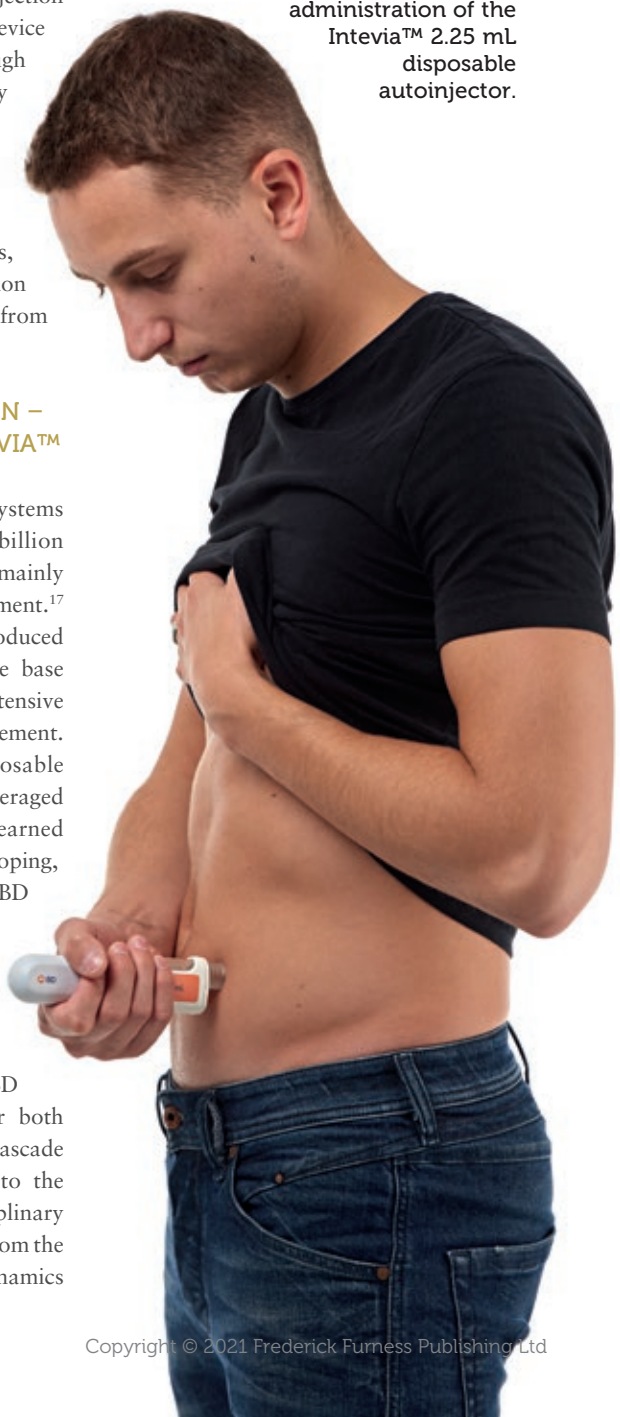

Figure 3. BD Patient administration of the Intevia™ 2.25 mL disposable autoinjector.

nine years after its launch, and with 90 million autoinjectors on the market, the BD Physioject™ disposable autoinjector has an extremely low level of reported complaints (3 ppm) linked to system integration.

TIMING IS A CRITICAL FACTOR IN THE LAUNCH OF A NEW DRUG

Painful manufacturing or supply issues linked to component control plan issues and complex incoming inspection activities can delay product launch timelines. Avoiding these errors and issues can result in potentially significant time and cost savings. BD's integrated approach is focused on ensuring that all components function cohesively, including the barrel, stopper, needle, needle shield, primary container and secondary delivery system. Change control management during the lifecycle of the combination product is eased and secured due to robust management of all of the components' critical parameters.

Beyond traditional functional testing, BD performs statistical tolerance analysis, including manufacturing variations. This tolerance analysis serves to verify system performance at extremes, with the aim of minimising combination product failure occurrences. BD also performs simulations and modelling, such as injection time prediction correlated with functional testing, in air and *in vivo*, to de-risk pharmaceutical companies' development processes.

BD's approaches are intended to develop and manufacture a robust and sustainable delivery system ensuring outstanding performance at high production volumes.

SERVICES AND DATA THAT REDUCE RISK FOR COMPLEX BIOLOGICS

BD offers a range of services and data to support its customers' combination product development programmes. These services may include assembly guidance, combination product testing, design validation using thorough and rigorous human factors testing, supportive human factors data and validated platform instructions for use. BD also performs extensive preclinical and clinical studies to help de-risk combination product development processes and enable a reduced time to market.

These services are designed to help customers limit development complexities related to primary containers and secondary delivery systems, and to reduce risks to timelines and costs. In addition, BD provides robust data as part of standard documentation packages for the BD Intevia™ disposable autoinjector and BD Neopak™ XtraFlow™ glass prefillable syringe, as well as R&D summary reports, according to the customers' requirements.

GLOBAL RECOGNITION OF EXCELLENCE

The BD Intevia™ autoinjector platform has earned BD the Frost & Sullivan Global 2020 Technology Innovation Award in the autoinjector drug delivery device market. This prestigious award recognises innovations or disruptive breakthroughs within the context of strict adherence to best practices. The Frost & Sullivan team identifies these best practices based on achievement in two sets of key criteria: Technology Attributes and Future Business Value. Of particular note are the Technology Attributes of: Industry Impact, Product Impact, Scalability, Visionary Innovation and Application Diversity. As Frost & Sullivan stated when granting the award, "BD Intevia™ disposable autoinjectors enable smooth drug administration without raising the injection force within the traditional injection time constraint. BD's technology manages the variance and variability of all component interfaces for robust subsystem integration and compatibility, enabling high performance and scalability."

In December 2020, BD Intevia™ 2.25 mL disposable autoinjector was recognised with a Good Design Award, which is the world's most prestigious, well-recognised and oldest design awards programme, organised annually by The Chicago Athenaeum Museum of Architecture and Design in cooperation with the European Centre for Architecture, Art, Design and Urban Studies and Metropolitan Arts Press, Ltd. The Good Design Award covers new consumer products, graphics and packaging designed and manufactured in Europe, Asia, Africa and North and South America.

SUMMARY

The growth of biologics has been driven in part by their high efficacy in treating leading chronic diseases. For many compelling reasons, it is desirable to make these innovative drug formulations available to patients for safe and convenient self-injection at home. To help achieve this, the BD Intevia™ 2.25 mL disposable autoinjector extends the design space available to pharmaceutical companies to include high-viscosity, high-volume formulations in an end-to-end integrated combination device.

BD recognises the growing challenge that the integration of combination products poses to pharmaceutical partners as injection devices increase in sophistication and capabilities. With the BD Intevia™ disposable autoinjector platform, BD aims to help customers achieve a higher level of patient care and comfort, greater control of development and manufacturing risk, and lower treatment costs as the industry positions itself to usher in new and demanding biologic therapies.

ABOUT THE COMPANY

BD is a large, diverse, global medical technology company. Its Medical Pharmaceutical Systems division is the world's largest syringe manufacturer. It offers prefillable syringes, self-injection systems, safety and shielding solutions, and needle technologies and associated pharma services.

**High viscosity: Viscosities >20 cP; High volume: Volume ≥2 mL*
***BD Intevia™ 2.25 mL is under development; some statements are projections and are subject to a variety of risks and uncertainties.*

REFERENCES

1. *Li Z, Easton R, "Practical Considerations in Clinical Strategy to Support the Development of*

Injectable Drug-Device Combination Products for Biologics", MAbs, 2018, Vol 10(1), pp 18–33.
2. *"Validation Study of BD Intevia™ 1 mL Two-Step Disposable Autoinjector". Internal Study, 2019, Becton Dickinson and Company.*
3. *"Chronic Disease Policy". European Chronic Disease Alliance website.*
4. *Bart J, et al, "A Portfolio of Biologic Self-Injection Devices in Rheumatology: How Patient Involvement in Device Design Can Improve Treatment Experience" Drug Deliv, 2019, Vol 26(1), pp 384–392.*
5. *Smietana, K, Siatkowski, R and Møller, M, "Trends in Clinical Success Rates". Nat Rev Drug Discov, 2016, Vol 15, pp 379–380.*
6. *Biologics Market by Product (Monoclonal Antibodies, Vaccines, Recombinant Hormones/Proteins), By Application (Cancer, Infectious Diseases, Autoimmune diseases), By End Use (Hospitals, Clinics, Diagnostic Centres), and Region, Forecasts to 2027". Research Report, Reports and Data, July 2020.*
7. *Lu, RM, et al, "Development of Therapeutic Antibodies for the Treatment of Diseases". J Biomed Sci, 2020, Vol 27(1), p1.*
8. *Patel, A, Cholkar, K, Mitra, AK, "Recent Developments in Protein and Peptide Parenteral Delivery Approaches". Ther Deliv, 2014, 5(3), pp337–365.*
9. *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.*
10. *"Design Input Specification for BD Intevia™ 2,25mL". Internal Report, 2017, Becton, Dickinson and Company.*
11. *"PHS-20-LVA06 HF Late Formative Study for BD Intevia™ 2.25 mL Two-Step Disposable Autoinjector formative study". Internal Study, 2020, Becton Dickinson and Company.*
12. *Rathore, N, et al, "Variability in Syringe Components and its Impact on Functionality of Delivery Systems". PDA J Pharm Sci Technol, 2011, Vol 65(5), pp 468–480.*
13. *"System Integration Challenges in Combination Products for Injectable Drugs". Internal Study, 2019, Becton, Dickinson and Company.*
14. *"Injection Time and Ejection Force Calculation". Internal Study, 2020, Becton, Dickinson and Company.*
15. *"BD Neopak™ XtraFlow™ Needle Resistance Simulation". Internal Study, 2020, Becton, Dickinson and Company.*
16. *Pager, A, et al, "User Experience for Manual Injection of 2 mL Viscous Solutions is Enhanced by a New Prefillable Syringe with a Stacked 8 mm Ultra-Thin Wall Needle". Expert Opin Drug Deliv, 2020, Vol 17(10), pp 1485–1498.*
17. *"Global syringes and needle market report 2020 by key players, types, end users, countries, market size, forecast to 2026." Research Report, NxtGen Reports, September 29, 2020.*

ABOUT THE AUTHORS

Karima Yadi is the Global Marketing Lead for the Autoinjector Platform at BD Medical – Pharmaceutical Systems. She provides commercial leadership to BD delivery system platforms and defines, develops and launches patient-centred injection solutions in collaboration with cross-functional, commercial and regional teams. Prior to joining BD, Ms Yadi held various roles of increasing responsibility within Pfizer in Marketing and Business Development, and at Zoetis in Regional Marketing in their Companion Animal Business Unit. She has extensive experience in product launches and product lifecycle management, from the development phase to the commercialisation phase. Ms Yadi has a BSc (Hons) in Management Science from the University of Warwick Business School (Coventry, UK) and an MSc in International Business Management from London South Bank University (UK).

Lionel Maritan, Senior Program Manager, Autoinjectors Platform, joined BD in 2005 and has held roles of increasing responsibility within R&D. Mr Maritan has extensive experience in drug delivery systems design and development from the innovation stage through to commercialisation. He developed the BD Physioject™ autoinjector and is listed on many patents. Prior to joining BD, he worked in the automotive industry. Mr Maritan has an MSc in Engineering, with a specialisation in plastic parts design and manufacturing.

THE DIFFERENCE OF ONE DRUG DELIVERED

WITH A RELIABLE, INTEGRATED SYSTEM THAT HELPS PUSH THE BOUNDARIES OF VISCOSITY. At BD, we understand that for some patients self-injecting medication can be intimidating—enough that they may forego treatment altogether. That's why we designed the **BD Intevia™ 1 mL** handheld autoinjector, a two-step disposable autoinjector, to encourage patients with chronic disease who self-inject to have more confidence, comfort and compliance with every 1 mL treatment. Because it is made entirely by BD, the components of our autoinjector work together seamlessly for reliable, robust performance with high-viscosity medications.[1,2] Our discreet, ergonomic new design has two-step activation and audible, visual and tactile indicators,[1] and smart technology available for added insight with every dose. Discover how smarter design can enhance the self-injection experience. **Discover the new BD.**

BD INTEVIA™ 1 ML, TWO-STEP DISPOSABLE AUTOINJECTOR

A reliable, integrated system that helps push the boundaries of viscosity[1,2]

1 Design input specification for BD Intevia™ 1mL [internal report]. Pont-de-Claix, FR: Becton Dickinson and Company; 2017
2 Activation gliding force and injection time on syringe filled with viscous solutions assembled in Intevia™ [internal report]. Pont-de-Claix, FR: Becton Dickinson and Company; 2017

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SURFACE-MEDIATED AGGREGATION – CONTROL OF THE LIQUID-SOLID INTERFACIAL STRESS

In this article, Shane Smith, PhD, Chief Business Officer, Eoin Scanlan, PhD, Chief Scientific Officer and Co-founder, and Paula Colavita, PhD, Executive Officer and Co-founder, all at Glycome BioPharma, discuss how the company's technology has evolved to create a stable and biocompatible coating that maintains device performance and safety.

Developability of biologics is often associated with a number of major stumbling blocks – mostly related to potency, safety and manufacturability – that can significantly hinder their commercial viability. Protein stability is one developability obstacle that needs to be resolved during clinical development to avoid costly late-stage safety issues. Proteins are innately susceptible to instability due to their complex molecular architecture and their intrinsic sensitivity to interfacial stresses (air-liquid, liquid-solid and liquid liquid) encountered during manufacturing, storage and administration only exacerbates the problem.

INTERFACE STRESS AND CLINICAL EVIDENCE

The problem with interfacial stresses is that they induce instability and, consequently, can lead to the formation of aggregated proteins. Simplistically, aggregation involves some measure of protein conformational change away from the native folded structure that permits a protein-protein interaction chain reaction, leading to the growth of protein aggregates with size in the subvisible and even visible ranges (Figure 1).

Formation of aggregates may elicit an immune response; therefore, systematic evaluations of aggregate formation are routinely performed during product development. For example, during formulation development, the primary packaging container and protein of interest are incubated together for various periods of time. The protein and particle concentration is calculated before and after the incubation to determine the container/drug stability profile. Another undesirable consequence of liquid-solid interfacial interaction (adsorption and aggregate formation) phenomena is the reduction in formulation potency and, ultimately, therapeutic efficacy.

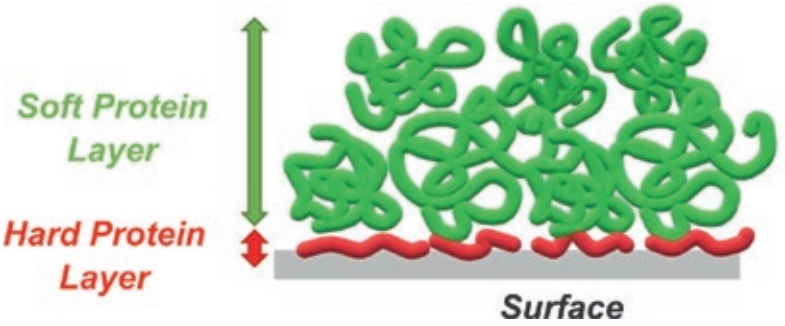

Figure 1: Schematic of typical protein adsorbate structures formed at a generic solid surface.

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"Surface-mediated unfolding (liquid-solid interface) is a significant challenge for drug delivery device manufacturers considering the intrinsic propensity of some materials to adsorb/desorb proteins."

Both the US FDA and the EMA are becoming increasingly vigilant towards protein immunogenicity and have published guidelines for industry.[1] Within these guidelines, the FDA has detailed clinical consequences in efficacy and safety that can result from reduced stability and pose a major risk for product failure and recalls.

The development of anti-drug antibodies as an immune response following the administration of protein therapeutics is a very serious and growing concern among manufacturers, physicians, informed patients and regulatory bodies alike. For example, insulin is administered frequently by diabetic patients and continues to elicit an antibody response regardless of purity and origin.[2] Similarly, beta interferon, administered regularly for the treatment of multiple sclerosis, triggers neutralising antibodies associated with a loss of bioactivity and decreased clinical efficacy of the drug.[3] At the extreme end of the spectrum, the production of antibodies against erythropoietin can result in very serious adverse side effects, including an almost total cessation of the production of red blood cells.[4]

LIQUID-SOLID INTERFACIAL STRESS IN STORAGE CONTAINERS

For more than two decades, prefillable syringes (PFSs) have been increasingly adopted by pharmaceutical companies for their increased safety, improved dosing accuracy and convenience for patient and medical workers. However, surface-mediated unfolding (liquid-solid interface) is a significant challenge for drug delivery device manufacturers considering the intrinsic propensity of some materials to adsorb/desorb proteins. The current understanding is that aggregation from the surface may occur as a result of (i) misfolding on the surface then desorption as aggregates and/or (ii) misfolding rapidly upon desorption in solution. Regardless of the mechanism, absorption of proteins at interfaces has been empirically implicated in aggregate formation.[5-7]

Cyclic olefin polymer (COP) PFSs are well-known for their advantages over glass, including the flexible moulding design for various drug delivery devices and reduced risk of breakage. In fact, the number of biopharmaceuticals supplied in COP PFSs is increasing dramatically. Although COP has, on occasions, displayed a reduced propensity to adsorb and aggregate protein compared with glass, it has been shown that it is not always the case.

For example, a study comparing the stability of various proteins demonstrated that COP and glass induced comparable percentages of cytokine adsorption formation at chilled temperatures, but at accelerated temperatures slightly more protein adsorbed to COP.[8] However, in the same study, a monoclonal antibody (mAb) tested had negligible adsorption with COP, unlike the glass after prolonged storage.[8] Therefore, the magnitude of the adsorption/aggregation is protein unique and requires product specific stability profiling with the intended primary packaging material. Characterised desorbed proteins from COP and glass have been reported to be a mixture of monomers, dimers and even small amounts of high molecular weight aggregates.[8-10]

Protein aggregation can also be mediated by normal syringe operation stresses.[10] For example, it was revealed that during ejection, sweeping of the inner barrel surface by the plunger head resulted in displacement of adsorbed proteins and particle generation. It was concluded that micron aggregate concentration in ejected solutions generally increased with increasing density of adsorbed proteins. Although the COP syringes tested exhibited lower aggregate concentrations compared with glass, it was attributed to lower adsorption densities, which we know is not a general trend for proteins.

A major concern is that biologics require higher therapeutic doses – on average 0.1 mg to 3 mg per kg of patient body weight – and therefore require substantially more concentrated formulations (which can exacerbate adsorption/aggregation). This is intensified further by the push for intravenous administration of volumes that are small enough for patient convenience and comfort. To ameliorate these problems and offer an improved safety profile for patients, clearly there is a need for a new suite of technologies to minimise and control protein adsorption and aggregation.

SURFACTANTS – THE DANGERS OF POLYSORBATES

As their name implies, surfactants have been adopted as a strategy to alleviate unwanted protein therapeutic adsorption, however, they possess some significant caveats. Surfactants mitigate aggregation mediated by liquid-solid interactions and are believed to function through competing access to surfaces.[11] Unlike ionic surfactants, non-ionic surfactants usually do not denature proteins and therefore remain the premier choice for biologic formulations. Yet, adequate stabilisation is reliant on the selection of surfactant and its formulation concentration, as well as on a variety of factors, including a biologic's concentration, other excipients, container type, and headspace and test methodology.

In biotherapeutics, polysorbates are among the most commonly used functional excipients. Surprisingly, these polyoxyethylene-based surfactants (polysorbate 20 and polysorbate 80) spontaneously autoxidise, yielding reactive peroxides, which, in turn, produce oxidative changes in the protein that consequently induces immunogenicity.[12] Furthermore, the rate of oxidative damage is not limited

"Surfactants mitigate aggregation mediated by liquid-solid interactions and are believed to function through competing access to surfaces. Unlike ionic surfactants, non-ionic surfactants usually do not denature proteins and therefore remain the premier choice for biologic formulations."

to the concentration of reactive oxidative species, the concentration of the therapeutic protein itself contributes also. As discussed prior, the problem is exacerbated further by the trend towards more concentrated formulations.

More concerningly, polysorbates are attracting attention as an inducer of anaphylaxis. Anaphylaxis is a serious allergic reaction that is connected with the administration of some therapeutic proteins, and as proteins themselves are often inducers of anaphylaxis, naively few, if any, attempts are made to differentiate them from excipients.[13] However, clinical evidence is mounting that supports excipient-related anaphylaxis. For example, two patients receiving mAb omalizumab had significant anaphylaxis reactions and subsequent intradermal testing linked it to polysorbate[14] and skin prick examinations of erythropoietin-reported hypersensitivity with polysorbate formulations only.[15]

With polysorbates being formulated with more than 70% of mAbs and other biologics, it is not surprising that rituximab, ofatumumab, obinutuzumab, trastuzumab, tocilizumab, infliximab, adalimumab and omalizumab, which all contain polysorbate surfactant, have reported drug hypersensitivity in patients (Table 1).[16] Polysorbates' application in preventing unwanted immunogenicity can certainly be contradictory, given that immunogenic aggregates are prevented by the addition of surfactants and surfactant-generated peroxides cause an increase in unwanted protein immunogenicity.

IMMOBILISED SUGAR STABILISERS – A BETTER SOLUTION

Sugar-based excipients have been used for decades to stabilise proteins and consequently have received a reliable reputation. Although, sugars function as excellent stabilisers for therapeutic proteins, it is acknowledged that because each biotherapeutic presents unique formulation challenges, no one stabiliser works best for all molecules. For example, sugars can spontaneously covalently attach to the biologics (glycation), affecting the protein's structure and function. For instance, it has been reported that glycation of immunoglobulin G2 (IgG2) mAb can occur with sucrose formulations. Analysis mapped the glycation sites to 10 lysine residues throughout the mAb.[17] Furthermore, a consideration for formulators is that sugars can detach during freeze-thawing resulting in poor stabilisation efficiency. Freezing and drying are routinely practised for long-term stabilisation and storage of therapeutic proteins. Sucrose is the only recognised sugar to maintain the critical amorphous stabilising state during freezing and thawing.

> "Using the success of sugars as a foundation to build upon, Glycome BioPharma has created the next generation of carbohydrate-mediated protein stabilisation technology by covalently immobilising sugars onto protein-container interfaces."

Using the success of sugars as a foundation to build upon, Glycome BioPharma has created the next generation of carbohydrate-mediated protein stabilisation technology by covalently immobilising sugars onto protein-container interfaces. This commercially validated platform uses only native human sugars (non-derivatised or non-synthetic), similar to those found in the extracellular region of the cell membrane, known as the glycocalyx, and contributes to the steric repulsion that prevents undesirable non-specific adhesion of other molecules and cells.

Researchers have alluded to the opportunities of using glycan-modified surfaces in biomedicine, yet commercialisation proves challenging due to use complex or unsafe functionalisation methodologies. For instance, dextran physisorption has been shown to reduce albumin and plasma adsorption by 90% and 70% at polyethylene surfaces. However, mere physisorption can result in potential leachates, while the dextran modifications required to enhance surface immobilisation involved potentially harmful reactants.[18] Additional examples of these commercialisation barriers can be found in studies by Frazie *et al*, 2000, and Angione *et al*, 2015.[19,20]

Given the willingness of biotech and drug delivery device manufacturers to work together to advance safety for patients, Glycome BioPharma has evolved its technology for commercialisation with olefin devices (PFSs, autoinjectors and patch pumps). The one-step covalent surface modification methodology to functionalise olefin polymer surfaces using native human glycans, creates a safe, stable and biocompatible coating that is resistant to leaching/peeling. Critically, this proprietary steric barrier coating has been designed not to compromise device performance or safety.

Comprehensive studies have demonstrated the protein-stabilising properties of this technology and how it can be used to reduce unspecific protein aggregation at the solid-liquid interface. Using quantitative and qualitative fluorescent measurements of treated versus untreated, Glycome BioPharma demonstrated up to 83% and

Product	API Concentration (mg/mL)	Polysorbate Conc. (mg/mL)	Hypersensitivity Reactions
Rituximab (Rituxan®)	10.000–500.000	0.700	5–10%
Ofatumumab (Arzerra®)	20.000	0.200	2%
Trastuzumab (Herceptin®)	22.000	0.090	0.6–5%
Tocilizumab (Actemra®)	80.000–400.000	0.500	0.1–0.7%
Infliximab (Remicade®)	100.000	0.500	1%
Adalimumab (Humira®)	40.000	0.800	1%
Omalizumab (Xolair®)	202.500	0.500	0.9–0.2%

Table 1: Examples of case reports of hypersensitivity in biologics formulated with polysorbates.[16]

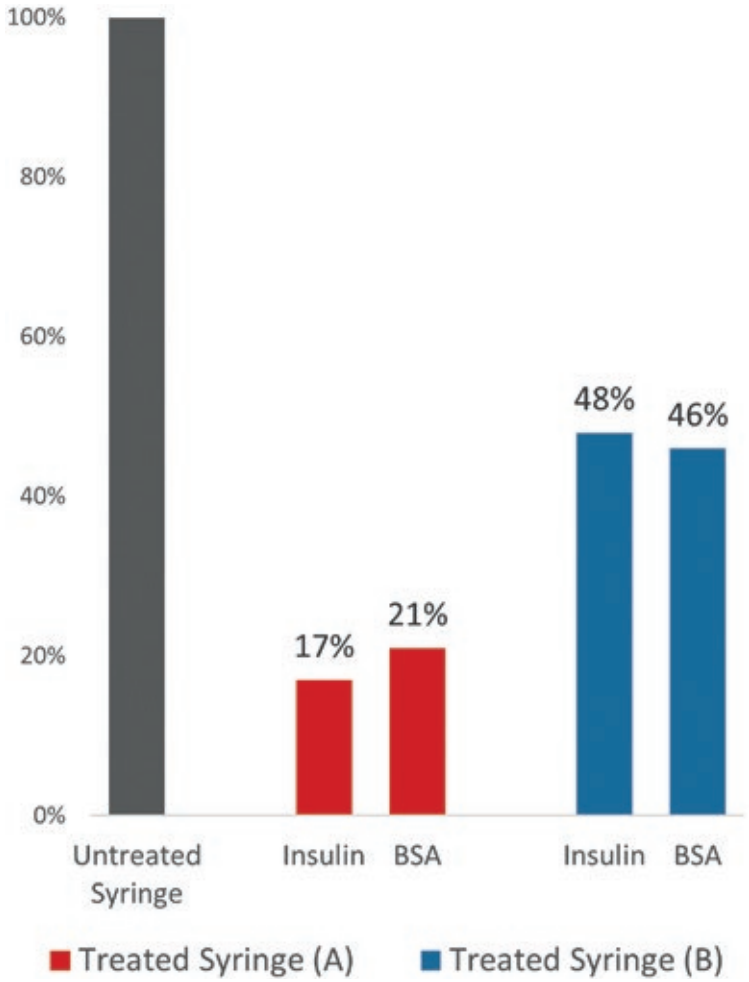

Figure 2: Reduction in adsorbed protein on commercially available olefin PFSs.

79% reduction in bound insulin and bovine serum albumin respectively on commercially available olefin syringe barrels, a general protein repulsion and functionalisation trend with varying olefin polymer blends (Figure 2). This novel technology commercialisation is timely, given the pressing efforts to the deliver therapeutics to global destinations in the context of our present public health emergency.

ABOUT THE COMPANY

Glycome BioPharma is a leader in glycoscience, serving the global pharma and biopharma industry. The company has significant development capabilities in the field of organic chemistry for the development of novel methodologies, functional materials and their optimisation, tailored to partners' applications/products and manufacturing requirements. Glycome BioPharma's approach to methodologies design and product development is through concurrent engineering partnerships in which the different stages run simultaneously, rather than consecutively. It decreases product development time and also the time to market, leading to improved productivity and reduced costs. The overarching goal is to maximise realised benefits in partner projects.

REFERENCES

1. *"FDA Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products". US FDA, Aug 2014.*
2. *Fineberg SE et al, "Immunological responses to exogenous insulin". Endocr Rev, 2007 Vol 28(6), pp 625–652.*
3. *Creeke PI, Farrell R, "Clinical testing for neutralizing antibodies to interferon-β in multiple sclerosis". Ther Adv Neurol Disord, 2013, Vol 6(1), pp 3–17.*
4. *Rossert J, Pure Red Cell Aplasia Global Scientific Advisory Board (GSAB), "Erythropoietin-induced, antibody-mediated pure red cell aplasia". Eur J Clin Invest, 2005, 35 (Suppl 3), pp 95–99.*
5. *Norde W, Lyklema J, "Interfacial behaviour of proteins, with special reference to immunoglobulins. A physicochemical study". Adv Colloid Interface Sci, 2012, Vol 179–182, pp 5–13.*
6. *Biddlecombe JG et al "Determining antibody stability: creation of solid-liquid interfacial effects within a high shear environment". Biotechnol Prog, 2007, Vol 23(5), pp 1218–1222.*
7. *Biddlecombe JG et al, "Factors influencing antibody stability at solid-liquid interfaces in a high shear environment". Biotechnol Prog, 2009, Vol 25 (5), pp1499–1507.*
8. *Waxman L, Vilivalam VD, "A Comparison of Protein Stability in Prefillable Syringes Made of Glass and Plastic". PDA J Pharm Sci Technol, 2017, Vol 71(6), pp 462–477.*
9. *Perevozchikova T et al, "Protein adsorption, desorption, and aggregation mediated by solid-liquid interfaces". J Pharm Sci, 2015, Vol 104(6), pp 1946–1959.*
10. *Maruno T et al, "Sweeping of Adsorbed Therapeutic Protein on Prefillable Syringes Promotes Micron Aggregate Generation". J Pharm Sci, 2018, Vol 107(6), pp 1521–1529.*
11. *Kapp SJ et al, "Competitive adsorption of monoclonal antibodies and nonionic surfactants at solid hydrophobic surfaces". J Pharm Sci, 2015, Vol 104(2), pp 593–601.*
12. *Maggio ET, "Alkylsaccharides: circumventing oxidative damage to biotherapeutics caused by polyoxyethylene-based surfactants". Ther Deliv, 2013, Vol 4(5), pp 567–572.*
13. *Huby RD, Dearman RJ, Kimber I, "Why are some proteins allergens?". Toxicol Sci, 2000, Vol 55(2), pp 235–246.*
14. *Price KS, Hamilton RG, "Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy". Allergy Asthma Proc, 2007, Vol 28(3), pp313–319.*
15. *Limaye S et al, "An allergic reaction to erythropoietin secondary to polysorbate hypersensitivity." J Allergy Clin Immunol, 200, Vol 110(3), p 530.*
16. *Bonamichi-Santos R, Castells M, "Diagnoses and Management of Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: Reactions to Taxanes and Monoclonal Antibodies". Clin Rev Allergy Immunol, 2018, Vol 54(3), pp 375–385.*
17. *Gadgil HS et al, "The LC/MS analysis of glycation of IgG molecules in sucrose containing formulations". J Pharm Sci, 2007, Vol 96(10), pp 2607–2621.*
18. *Marchant RE, Yuan S, Szakalas-Gratzl G, "Interactions of plasma proteins with a novel polysaccharide surfactant physisorbed to polyethylene". J Biomater Sci Polym Ed, 1994, Vol 6(6), pp 549–564.*
19. *Frazie RA et al, "Characterization of protein-resistant dextran monolayers". Biomaterials, 2000, Vol 21(9), pp 957–966.*
20. *Angione MD et al, "Enhanced Antifouling Properties of Carbohydrate Coated Poly(ether sulfone) Membranes". ACS Appl Mater Interfaces, 2015, Vol 7(31), pp 17238–17246.*

ABOUT THE AUTHORS

Shane Smith, PhD, Chief Business Officer at Glycome BioPharma, specialised in biotechnology and bio-business out of the University of Aberdeen (Scotland, UK) and National University of Ireland, Galway, and brings a wealth of operational management experience across multiple sectors in the biotechnology industry. Dr Smith's background is in improving efficiency, controlling costs, strategic planning, and he is well versed in overseeing lean operations across international facilities. Dr Smith has held pivotal positions in a number of small to large sized biotech companies. Currently Shane holds the position of Chief Operations Officer at BioCyto Ltd (Co Cork, Ireland), and is a Life Science Investment Adviser for PanEuro Technology Ventures (Co Cork, Ireland). He joined Glycome BioPharma in 2019.

Professor Eoin Scanlan, PhD, Chief Scientific Officer & Co-founder at Glycome BioPharma, completed his PhD at the University of St Andrews (Scotland) in 2004. Following postdoctoral work at the University of Bern, Switzerland, and at the University of Oxford (UK), he joined the School of Chemistry in Trinity College Dublin (Ireland) in 2008 where he is Associate Professor of Organic and Medicinal Chemistry and a Principal Investigator in the Trinity Biomedical Sciences Institute. He leads an international research team in Trinity College with a focus on new synthetic methods and the discovery of novel therapeutics, diagnostics and biomaterials.

Professor Paula E Colavita, PhD, is Executive Officer & Co-founder of Glycome BioPharma. Dr Colavita completed her PhD in physical chemistry in the University of South Carolina (US) and carried out postdoctoral research work at the University of Wisconsin-Madison (US). In 2008, she joined the School of Chemistry at Trinity College Dublin where she is currently an Associate Professor and a College Fellow. She is the author of more than 70 publications, co-inventor of two patents and leads a research team at Trinity College Dublin, whose activities focus on understanding and achieving control of interfacial processes and reactions.

Glycome BioPharma

Leaders in Glycoscience

Glycome Biopharma *Pro-Tects*
(Protein Protection Technology)

Formulation integrity

Reduced Risk of Immunogenicity

Stability & Shelf Life

Inert Contact Surface

Flexibility

Durability & Dimensional Consistency

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PERFORMANCE BENEFITS

Flexibility
Pro-Tects' drug contact surfaces can be customized to reduce burden of formulation development.

Inert Contact Surface
Pro-Tects offers the stabilising properties of natural glycans and does not involve use of leachable coatings or inorganic modifiers.

Stability & Shelf Life
Patented Pro-Tects barrier coating system enhances stability of biotherapeutics across a range of storage conditions (pH, temperature) thus assuring biotherapeutics efficacy and shelf-life.

Durability & Dimensional Consistency
Protects and preserves high value contents; offers higher dosing accuracy and better consistency with auto-injectors.

Formulation integrity
Pro-Tects reduces protein losses at the container wall hence maintaining biotherapeutic concentration and pre-filled formulation performance descriptors.

Reduced Risk of Immunogenicity
Protein aggregation triggered by interfacial stresses is a leading cause of adverse immune effects. Pro-Tects reduces protein aggregation, leading to reduced risk of adverse immune response.

BUILDING A BETTER PREFILLED SYRINGE FOR COVID-19 VACCINE PACKAGING

In this article, Carina Van Eester, Global Platform Leader, Prefilled Syringes and Cartridges, at Datwyler, shares key learnings since the launch of the company's NeoFlex plungers at the start of the covid-19 pandemic.

At the onset of the covid-19 pandemic, Datwyler launched its NeoFlex plungers onto the market. A year later, more is known about the virus, the vaccines being developed to fight it and how NeoFlex plungers can be an effective tool in distributing the vaccines to the global population.

> "With more filling lines being developed to process ready-to-fill vials, cartridges and PFSs, the demand for ready-to-use stoppers and plungers is growing every year."

As is standard for most new drugs entering the market, vials are the preferred option for packaging the drug product. For covid-19 vaccines, this is especially true since vials hold more doses of the vaccine, allowing for more vaccinations, and vial components and filling lines are more widely available to drug developers. Even though vials are the preferred initial packaging for covid-19 vaccines, syringes are the ideal packaging application due to ease of administration, reduced risk of contamination, minimised risk of injuries during use and improved accuracy. With these clear benefits to packaging the covid-19 vaccine in a syringe application, Datwyler's NeoFlex plungers are well-equipped for packaging this life-saving drug product.

NEOFLEX PLUNGERS FOR SENSITIVE DRUG PRODUCTS

NeoFlex plungers for prefilled syringe (PFS) and cartridge applications are part of Datwyler's platform of coated products, which also includes OmniFlex stoppers for vial applications. Both OmniFlex stoppers and NeoFlex plungers are made with the same high-quality compound formulation, FM457, and proprietary fluoropolymer spray-coating technology. By using the same compound and technology for the various components, customers can easily transition from an OmniFlex stopper for a vial to a NeoFlex plunger for a syringe or cartridge, with minimal risk to compatibility.

COMPATIBILITY WITH VARIOUS STERILISATION METHODS

One of the biggest differences between OmniFlex stoppers and NeoFlex plungers is the preferred method of sterilisation. In general, stoppers are typically steam sterilised by the manufacturer, whereas plungers are supplied to the customer ready to use (in combination with ready-to-fill syringes packaged in tubs). With more filling lines being developed to process ready-to-fill vials, cartridges and PFSs, the demand for ready-to-use stoppers and plungers is growing every year, and with more demand comes more variety in how these components are processed and sterilised by pharmaceutical companies. To meet the various requirements from customers all over the world, NeoFlex plungers were designed to be compatible with a variety of sterilisation methods. Studies have been conducted to assess the influence of different sterilisation methods on the chemical and functional properties of Datwyler's fully coated components and the results were positive.

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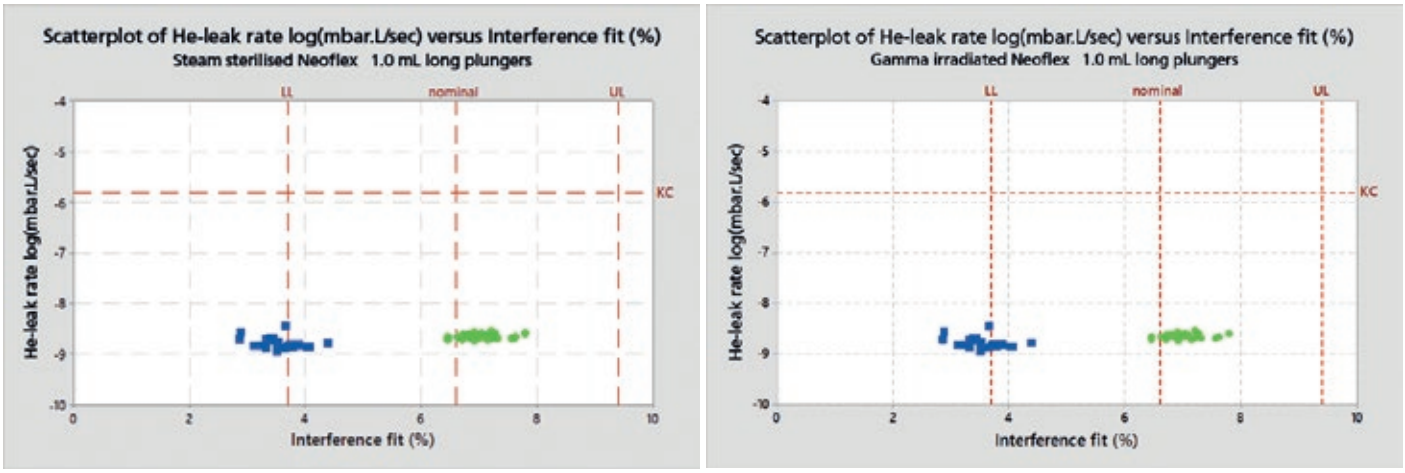

Figure 1: He-leak rates of gamma irradiated 1 mL long NeoFlex plungers with different interference fits. All cases easily meet the Kirsch Criterion (1.6x10−6 mbar.L/sec). Even with the worst-case scenario of a low interference fit, the seal integrity is still maintained.

Chemical Properties

To determine the chemical properties of FM457 and NeoFlex, the components were tested according to ISO 8871-1, which encompasses the most stringent requirements of the applicable compendial chapters on rubber closures – namely US Pharmacopeia (USP) General Chapter <381>, and European Pharmacopoeia (EP) Chapter 3.2.9. After irradiation up to 40 kGy and storage times of two years, FM457 and NeoFlex continue to adhere to ISO 8871-1 and thus, also adhere to USP <381> and EP 3.2.9. No significant difference is observed between steam sterilisation and gamma irradiation in the standard chemical testing of NeoFlex, and the same is true for extractables.

Functional Properties

The functional properties of NeoFlex plungers, specifically container closure integrity, gliding properties and plunger movement, have been investigated in worst-case conditions.

Container Closure Integrity

Helium (He) leak testing of the plungers treated with steam sterilisation, as well as plungers irradiated with 25 kGy gamma irradiation, show safe He-leak rates for all NeoFlex designs. This test is conducted with nominal plungers and with plungers that are 0.2 mm smaller than the nominal in order to simulate the worst-case conditions for container closure integrity (simulating the plunger at minimum specification and the barrel at maximum specification). Also, as a result of this study, it can be concluded that even the plunger/barrel with the lowest interference shows excellent He-leak rates regardless of whether they were gamma irradiated or steam sterilised (Figure 1).

Gliding Properties

The break-loose force of NeoFlex plungers slightly increases over time and is higher at room temperature and 40°C, but the impact of gamma irradiation versus steam sterilisation is minimal and still within an acceptable range with regard to usability and end-user acceptance criteria. The data that were created with plungers 0.2 mm larger than the nominal (which should represent the worst-case conditions when the barrel is small and plunger is big), show that no significant difference is detected between steam sterilisation and gamma irradiation for break loose and gliding forces. The same is true for the gliding force. As a result, no difference is detected between steam sterilisation and gamma irradiation (Figure 2).

Plunger Movement

This test simulates the conditions of an aeroplane using a pressurised cabin corresponding to an altitude of 8,000 ft, non-pressurised. The test is also performed in worst-case conditions where the plunger is 0.2 mm smaller than nominal to simulate the scenario in which the smallest plunger is positioned in the largest barrel. The plunger impact is the same for both steam-sterilised and gamma-irradiated plungers. In both cases, it can be concluded that syringes filled with a head space below 7 mm will show plunger movement that is lower than the distance between the third and the second rib, and likely can count on two ribs to secure the container closure integrity (Figure 3).

A ROBUST DESIGN FOR COLD STORAGE CONDITIONS

During the functionality testing of NeoFlex plungers, testing was done at 5°C, room temperature and 40°C. In the context of covid-19 vaccines, extremely low temperature storage is required, e.g. -20°C and -80°C. From a theoretical perspective, it can be concluded that storage at -80°C may pose a challenge but storage at -20°C is possible.

When temperatures drop, elastomers harden and become less flexible, and when the temperature reaches the glass transition temperature, elastomers lose their rubber-like properties entirely. At extremely low temperatures, i.e. the brittle point, elastomers may crack. Changes in elastomer properties due to low temperatures are typically physical and fully reversible. For halobutyl rubber – the most common type of rubber used for plungers – the glass transition temperature is around -60°C. For styrene-butadiene rubber – the rubber used for needle shields and tip caps, such as Datwyler's FM30 – the glass transition temperature is only around -40°C. Thus, the best-case scenario

"One of the main advantages of NeoFlex plungers is that the compression in the barrel is rather high compared with other coated plungers on the market."

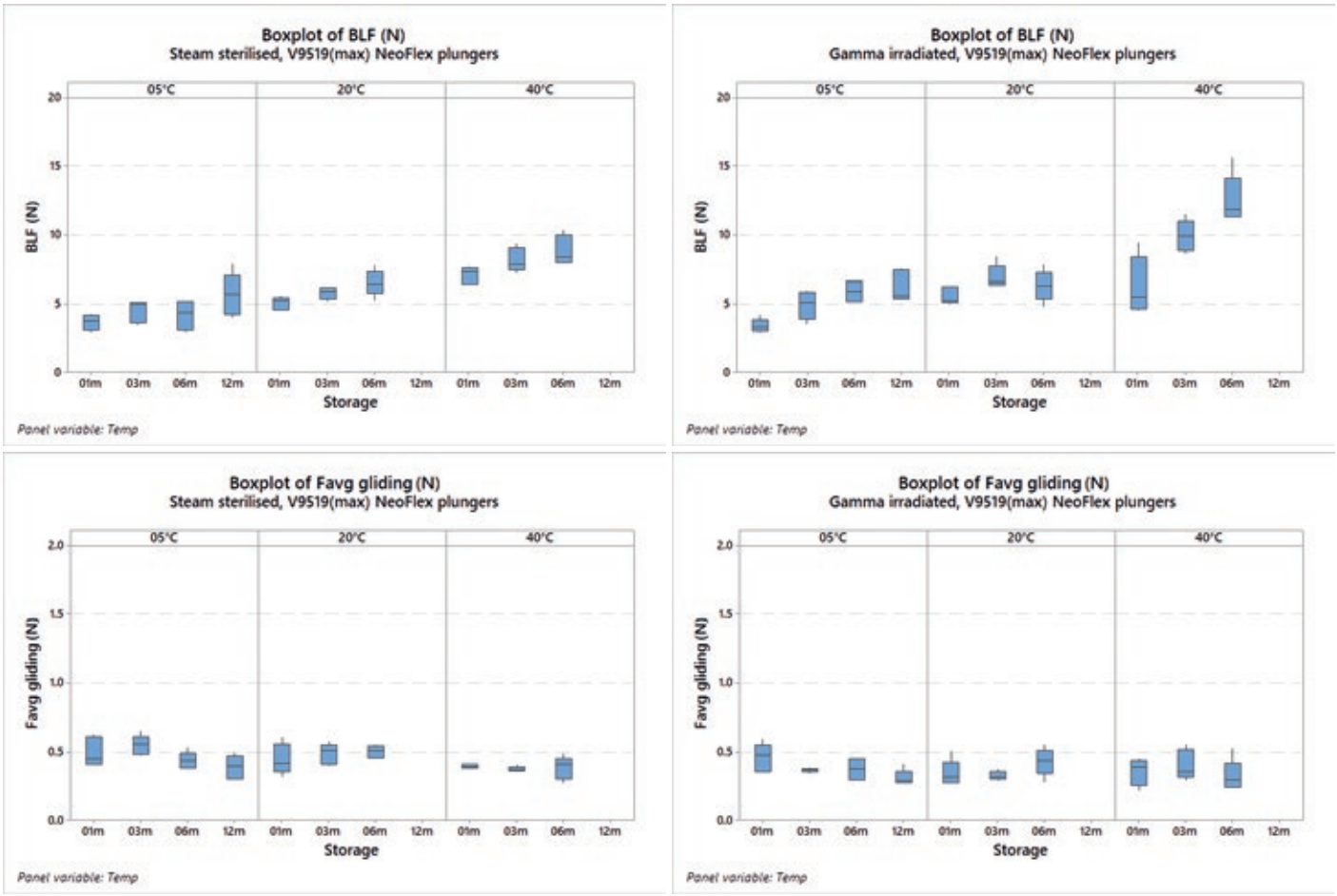

Figure 2: The above graphs show the consistency in break-loose force and gliding forces for both steam and gamma irradiated NeoFlex 1 mL long plungers.

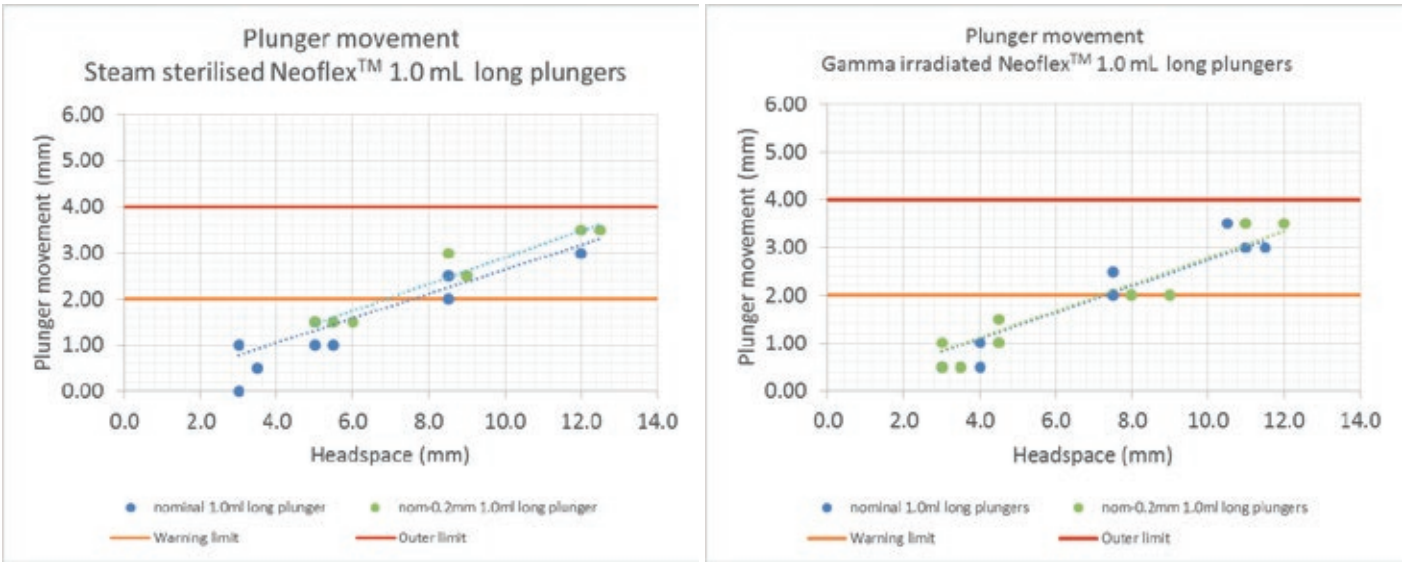

Figure 3: The above graphs show that, for plungers in a highly pressurised setting, plunger movement is minimal and well below the outer limit, regardless of whether the plungers were steam sterilised or gamma irradiated.

for sealing at low temperatures can only be guaranteed at a minimum temperature of -40°C for syringe applications.

One of the main advantages of NeoFlex plungers is that the compression in the barrel is rather high compared with other coated plungers on the market. NeoFlex has a nominal compression between 6% and 6.6% while other coated plungers have a nominal compression between 2.8% and 3.8%. In addition, the fluoropolymer coating is thin and flexible, which prevents it affecting the sealing properties (Table 1).

In addition to container closure integrity of the plunger and barrel, other functional aspects of the syringe need to be investigated in these extreme cold conditions before a system can be provided and deemed successful at these low temperatures.

	1 mL			1–3 mL		
Input Voltage (VDC)	min	nominal	max	min	nominal	max
NeoFlex™	3.73	6.62	9.42	3.85	5.98	8.06
Partially coated plunger 1	0.77	3.79	6.72	0.57	2.81	5.00
Partially coated plunger 2	2.27	5.22	8.09	2.23	4.42	6.56

Table 1: Comparison of compression percentages between different coated plungers on the market. NeoFlex has a higher compression than other coated plungers on the market, which should have a positive effect on container closure integrity during storage in extreme cold conditions.

"The processability of a coated plunger helps to determine the success of a packaged drug."

NEOFLEX PLUNGERS COMPATIBLE WITH MULTIPLE PLUNGER POSITIONING TECHNOLOGIES

The processability of a coated plunger helps to determine the success of a packaged drug. In general, it is known that most existing syringe fill-finish lines are equipped with vent tube stoppering for stopper positioning. It is also known that this technology poses challenges for coated plungers. During vent tube placement, the plunger is compressed to a high extent in the vent tube, then a plunger rod pushes it through the vent tube and finally into the syringe where the plunger is deflated and seals the syringe. When the plunger passes through the vent tube, high forces are required and temperature increases. The high forces can be improved by applying a bit of silicone (10–25 µg silicone/cm²) on top of the coating. Figure 4 shows that, during plunger positioning, the temperature increase goes down from 57°C to 38°C and the force required for stoppering goes down from 40 N to 25 N. Of course, this is only a viable solution if the drug is not sensitive to silicone.

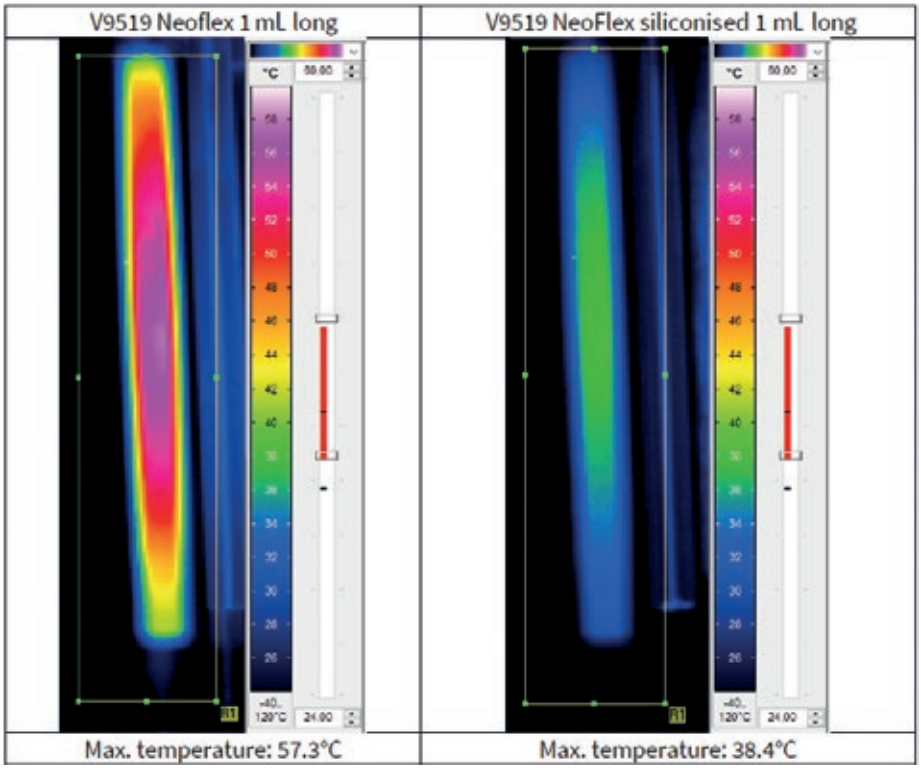

Figure 4: Temperature of vent tube in combination with NeoFlex 1 mL long and NeoFlex siliconised 1 mL long. Data provided by Bausch & Stroebel pharma services.

Another option for plunger positioning is to use a short insertion tube with vacuum assistance. In this scenario, the vent tube can have a larger diameter, which means less compression of the plunger and less friction. Ultimately, the ideal positioning option for coated plungers is using vacuum placement. With the understanding that each technology has specific requirements that impact the final syringe product, NeoFlex plungers were designed to work with each positioning technology and the successful placement of the plungers has been proven with testing at different machine manufacturers.

COMPATIBILITY WITH A VARIETY OF SILICONISED BARREL MATERIALS

While glass is still the most widely used material for syringes, plastic barrels in cyclic olefin copolymer (COC) and cyclo olefin polymer (COP) are also emerging as viable options for syringe manufacturing. With regard to the covid-19 vaccines, glass, COC and COP barrels are all being considered to package certain vaccine products due to worldwide shortages of raw materials.

Guaranteeing proper gliding in a syringe with a traditional halobutyl rubber plunger requires that the barrel, regardless of composition, is uniformly siliconised. Depending on the sensitivity of the drug product to silicone, standard siliconised

"With an accelerated timeline for manufacturing and distributing the various covid-19 vaccines, it is important that pharmaceutical companies have the necessary packaging available to them as the vaccine transitions from vial applications to PFSs."

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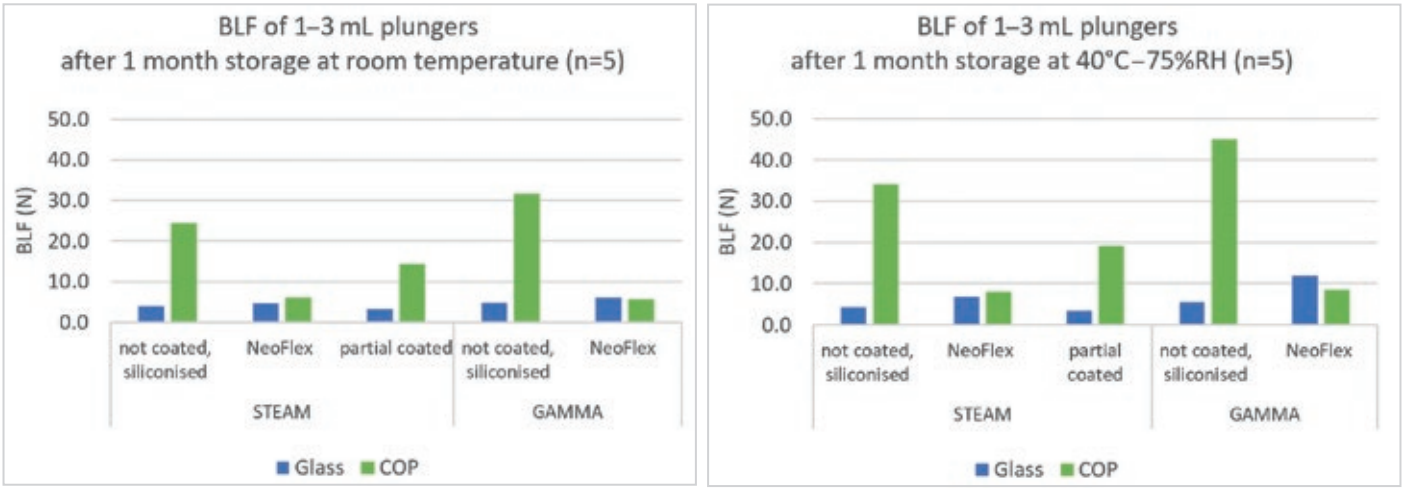

Figure 5: The above graphs show that, for plungers in a highly pressurised setting, plunger movement is minimal and well below the outer limit, regardless of whether the plungers were steam sterilised or gamma irradiated.

barrels, low siliconised barrels and baked-on or plasma-treated siliconised barrels can be used.

For each of these iterations, NeoFlex plungers perform without concern. Due to the 100% coating of the NeoFlex plunger, the halobutyl rubber never comes into contact with COC or COP barrels, causing the break-loose and gliding forces to be identical to the results obtained in glass barrels. This is not the case with partially coated plungers (Figure 5). NeoFlex plungers were also tested in combination with barrels from different suppliers and only small differences were detected.

CONCLUSION

With an accelerated timeline for manufacturing and distributing the various covid-19 vaccines, it is important that pharmaceutical companies have the necessary packaging available to them as the vaccine transitions from vial applications to PFSs. Datwyler's NeoFlex plungers are not only ready to be used for these vaccine products but represent an important piece of the puzzle in building a better vaccine packaging solution for drug manufacturers combatting a global pandemic.

ABOUT THE COMPANY

Datwyler focuses on high-quality, system-critical elastomer components and has leading positions in attractive global markets such as healthcare, mobility, oil and gas, and food and beverage. With its recognised core competencies and technological leadership, the company delivers added value to customers in the markets served. With more than 20 operating companies, sales in over 100 countries and more than 7,000 employees, Datwyler generates annual sales of more than CHF 1,000 million (£809 million). Within the healthcare solutions business area, Datwyler develops, designs and manufactures solutions for injectable packaging and drug delivery systems to help customers create a safer medical environment for the future.

ABOUT THE AUTHOR

Carina Van Eester graduated as an industrial engineer in chemistry and started her career in pharma, where she gained 15 years of experience as a packaging development engineer and project manager. She has been with Datwyler for 12 years, spending seven years as a Technical Key Account Manager, providing technical support to customers, and four years as a Global Qualification and Validation Manager. She moved into the role of Global Platform Leader for Prefilled Syringes and Cartridges in 2018, making sure that the standard portfolio of rubber components used for these applications secures Datwyler's position as a market leader.

BD HYLOK™ – GLASS PREFILLABLE SYRINGE FOR IV APPLICATIONS

In this article, Sophie Trémeau, Regulatory Affairs Specialist, Maxime Nicolas, R&D Engineer, and Myriam Leszczynski, R&D Project Manager, all of BD Medical – Pharmaceutical Systems, discuss BD Hylok™, a prefillable glass syringe for intravenous applications, including the rigorous testing BD Hylok™ has undergone and the regulatory support BD is able to provide to its pharmaceutical partners.

Several factors motivate pharmaceutical companies and hospitals to use glass prefilled syringes for intravenous (IV) applications. By switching from vials and ampules to a glass prefillable syringe, hospitals have the potential to reduce medical errors,[1,2] improve workflow efficiency[3] and positively impact return on investment for hospital stakeholders.[4] Moreover, data from a study conducted by BD suggests that approximately 92% of hospital stakeholders are willing to use prefillable syringe for multiple drugs.[5]

For pharmaceutical companies, transitioning a fixed-dose drug from a vial or ampule format to a prefillable syringe can serve as a differentiation strategy in a market dominated by vials and ampules.[6,7] The benefits of glass as a prefillable syringe material include the inertness of the material and, in some cases, steam sterilisation resistance in the fill/finish process.[8] However, glass prefillable syringe formats for IV applications have historically experienced some challenges that needed to be addressed in order for pharmaceutical companies and hospitals to be able to access these benefits without reservation.

OVERCOMING THE LIMITS OF GLASS PREFILLABLE SYRINGE FOR IV APPLICATIONS

Health authorities have indicated cases in which glass prefillable syringe have become clogged and malfunctioned when connecting to pin-activated IV needleless access devices (NLADs),[9] including in emergency situations. Indeed, incompatibility between the syringe and the connector can result in the NLAD becoming clogged or the syringe tip being broken.[9]

To better understand these issues, BD conducted research in the US, UK, France and Germany.[10] The results showed that 27% of the clinicians surveyed have experienced the prefillable syringes and intravenous line becoming disconnected, and 71% of clinicians who experienced these disconnections consequently experienced drug leakage.[10]

> "The aim was to allow hospitals to take advantage of glass prefillable syringe formats for IV applications while mitigating the risks previously associated with glass syringes in relation to connector incompatibility. The BD Hylok™ glass prefillable syringes for IV precisely addresses the need for compatibility with commonly used NLADs."

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To address these issues, BD designed a glass prefillable syringe with connection performance specifically verified for IV applications.[11] The aim was to allow hospitals to take advantage of glass prefillable syringe formats for IV applications while mitigating the risks previously associated with glass syringes in relation to connector incompatibility. The BD Hylok™ glass prefillable syringe for IV (Figure 1) precisely addresses the need for compatibility with commonly used NLADs (Figure 2).[12]

BD HYLOK™

The BD Hylok™ glass prefillable Luer syringe is designed for the administration of IV drugs. Indeed, the BD Hylok™ Luer lock adapter (LLA) resists an average pull-out force three times higher and a rotational torque five times higher than those of comparable products (Figures 3 and 4).[13]

BD Hylok™ design features include:

- A new LLA thread design
- LLA bonding technology
- A Luer lock enlarged channel (LLEC).

RIGOROUS TESTING

Verification of BD Hylok™ took place in accordance with ISO standards, including ISO 11040-4 and ISO 80369-7, covering the product connectivity. The tests cover all BD Hylok™ syringe sizes as the tip and LLA designs are the same.[14,15] For design verification, the tests were performed on samples at 25°C, with and without ship tests (ISTA 3E), and filled with water for injection (after ethylene oxide and before steam sterilisation).

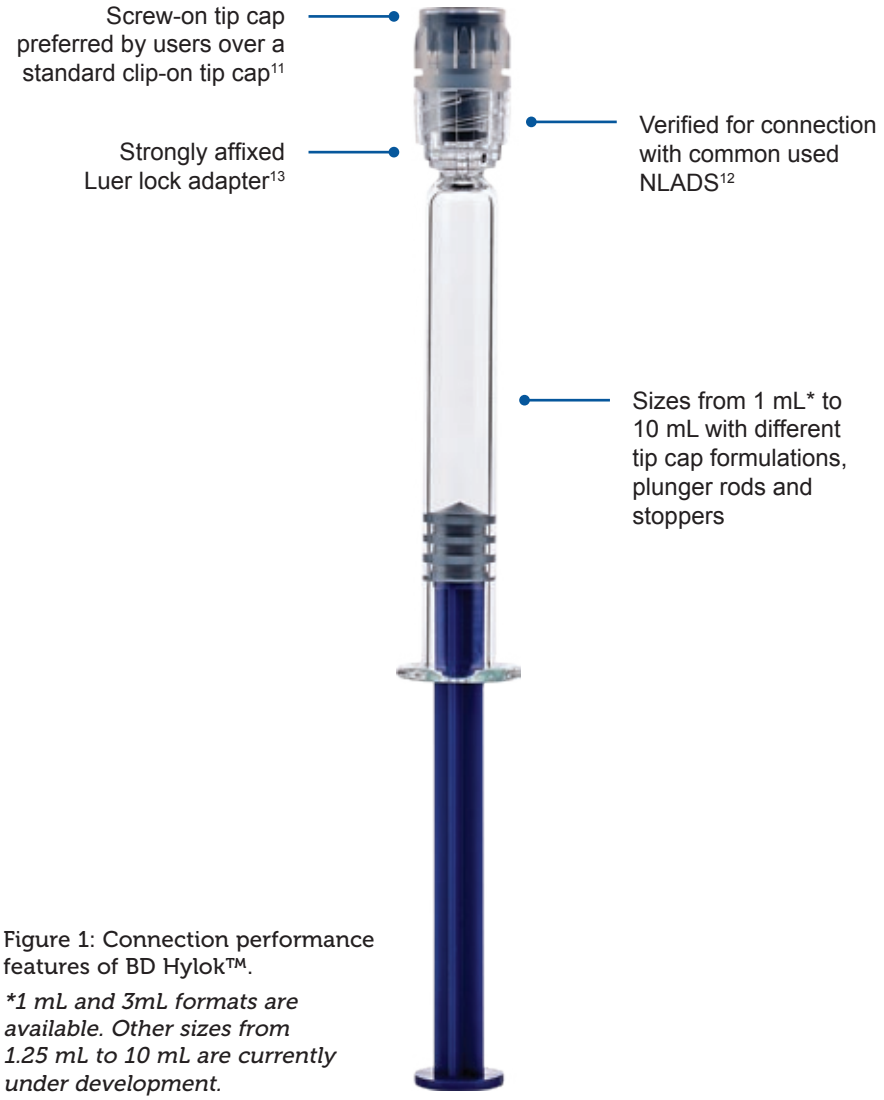

Figure 1: Connection performance features of BD Hylok™.

**1 mL and 3mL formats are available. Other sizes from 1.25 mL to 10 mL are currently under development.*

Verified for Steam Sterilisation

BD Hylok™ is suitable for both ethylene oxide (EtO) and steam sterilisation.[16] Typically, EtO sterilisation is conducted by BD and steam sterilisation is conducted by the pharmaceutical company filling the syringe. In one study, pull-out force and rotational torque performance were tested on BD Hylok™ after two EtO and two steam sterilisation cycles at 121°C, for 20 minutes.[13]

In another study, market comparables were subjected to a typical process of one EtO and two steam sterilisation cycles at 121°C for 20 minutes.[13] After EtO sterilisation, conditions were simulated in an environment where the glass syringe was prefilled and the LLA was subjected to pull-out force/rotational torque. After steam sterilisation, the resistance of the prefillable syringe to pull-out force and rotational torque was verified by subjecting the adapter to forces exerted in the act of screwing on the needle.

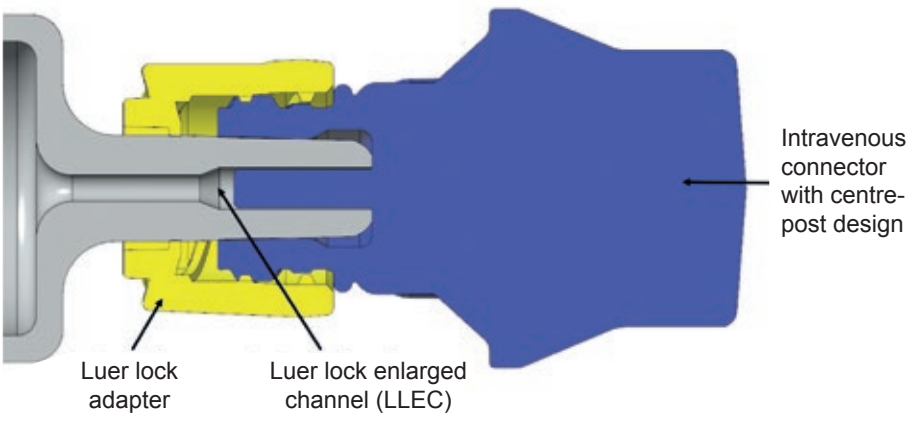

Figure 2: The LLEC of BD Hylok™ facilitates connection with commonly used NLADs.[12]

Compatibility with Commonly Used ISO Connectors

Compatibility with commonly used NLADs was verified through a series of tests evaluating the fluid path (absence of clogging) and connection tightness. BD

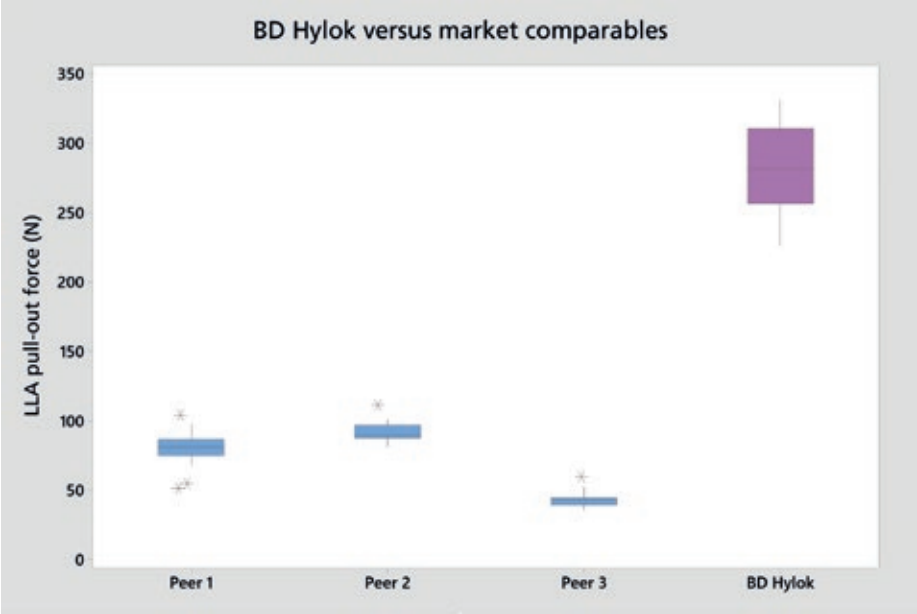

Figure 3: BD Hylok™ LLA resists a pull-out force three times higher than that of market comparables.[13]

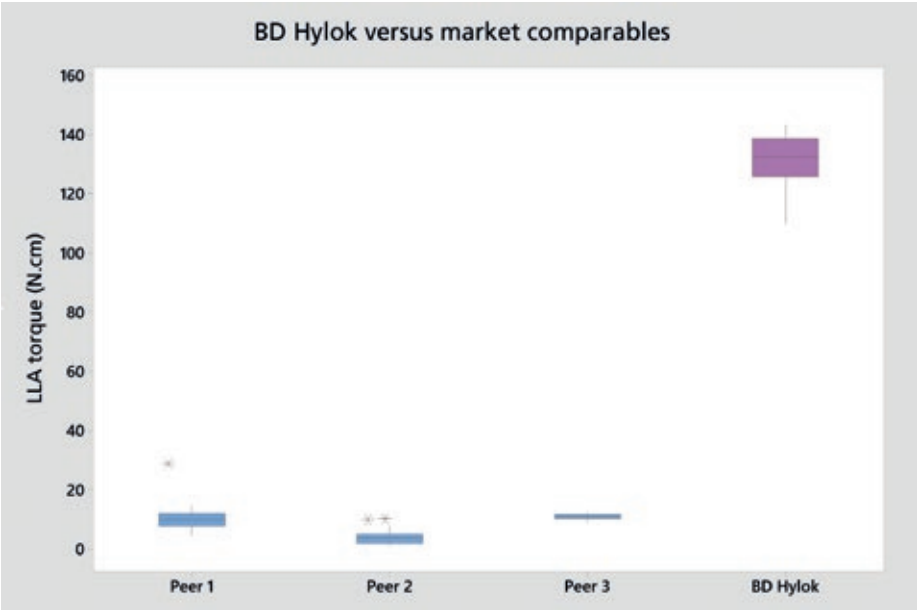

Figure 4: BD Hylok™ LLA resists rotational torque five times higher than that of market comparables.[13]

Connecta™ and BD Microlance™ were tested relative to ISO 80369-7 whereas other connectors were tested relative to ISO594-2.[12]

Three tests referencing ISO80369-7 May 2013 draft 6.1.2. and ISO594-2: 1998 were used to verify the tightness of the connector to the BD Hylok™:[17]

- **A pressure decay test** verified the tightness of the connection between the syringe LLA/tip and the connector.[17] An ISO connector or an NLAD was assembled on the syringe with a defined axial force and torque.
- **A sub-atmospheric test** verified the integrity of the connection between the syringe and the connector.[17] An ISO connector or NLAD was fitted on the syringe with a defined axial force and torque. The connection was then exposed to sub-atmospheric pressure and evaluated for leakage.
- **A stress cracking test** verified that the connection between the syringe and the connector could withstand stress at room temperature.[17] At the end of the time period, the connection was exposed to sub-atmospheric pressure and evaluated for leaks.

BD Hylok™ passed all three of the tests cited.[17]

Robust Connection Between Syringe and Connector

Three tests were used to verify the ability of BD Hylok™ to maintain the connection between the connector and the syringe tip, referencing ISO 80369-7 May 2013 draft 6.1.2. and ISO 594-2:1998:

- **A connector unscrewing torque test** verified that the connector did not disconnect from the syringe tip during injection.[17]
- **The connector separation force test** ensured that the connection with the Luer lock could withstand an axial load of 35 N.
- **An overriding torque test** confirmed the Luer lock's capacity to resist override of the threads or lugs of the connector when subjected to over-torque.[17]

Luer Lock Robustness

The robustness of the BD Hylok™ Luer lock was verified through tests evaluating the LLA's resistance to pull-off forces, and its resistance to rotation.[13] The tests referenced ISO 11040-4:2015 §6.5.3.5 and ISO 11040-4:2015 §6.5.3.6., respectively:

- **An LLA pull-off force test** verified that the LLA will not disconnect from the tip under an axial load of 22 N.
- **An LLA dismantling torque test** verified that the LLA will not disconnect from the tip under torque.[13]

REGULATORY FRAMEWORK FOR EUROPEAN MARKETS

BD Hylok™ prefillable syringes filled with drugs or biologics are considered an integral drug-device combination (DDC) in Europe. According to Article 117 of the European Medical Device Regulation (MDR) 2017/745, an integral DDC has to be assessed by an MDR-accredited notified body (NB), which should focus on the safety and performance of the device part of the DDC. The official date for implementation of European Medical Device Regulation, article 117, has been postponed by one year to May 26th, 2021, due to the covid-19 sanitary context.[18]

The applicable General Safety and Performance Requirements (GSPR) Annex I of the EU MDR are part of the design input specifications of BD Hylok™, which

means that BD will be able to provide evidence of safety and performance quality to its partners to help them build their own GSPR-compliant packages for the DDC.

In cases where BD Hylok™ would be introduced as a post-approval change, an NB's opinion should be submitted as part of the variation/extension application, as per section 2.6 of the Q&A document from the EMA (EMA/37991/2019 Rev.1 from October 21st, 2019).[19]

REGULATORY CONSIDERATIONS WHEN CONVERTING FROM VIAL TO PREFILLABLE SYRINGE

Converting from vials to prefillable syringes is considered to be a significant change that requires a variation and/or extension of the marketing authorisation in Europe and a prior approval supplement for the US market. From a regulatory perspective, the impact of the container closure system (CCS) change needs to be assessed and shown to not affect the quality, safety or efficacy of the DDC.[20,21] The following items must be considered:

- Biocompatibility testing
- Impact on product quality due to container interaction or new manufacturing process
- Comprehensive stability testing
- Extractables and leachables
- Shipping studies
- Preclinical or clinical studies
- Human factors studies
- Labelling.

COMPREHENSIVE DEVELOPMENT AND REGISTRATION SUPPORT

BD provides a robust and extensive data package to support development and registration of any combination products using BD Hylok™. The package includes, but is not limited to, quality statements, summaries of human factors user studies, product usage instructions, performance assessments and regulatory support. This package provides comprehensive support to enable a smooth transition to BD Hylok™, either from an existing prefillable syringe or adoption in the case of a new product launch.

"Switching to a prefillable syringe can create clinical and economic value for healthcare providers, while differentiating the drug-device combination in a space dominated by vials and ampules."

"BD provides a robust and extensive data package to support development and registration of any combination products using BD Hylok™. The package includes, but is not limited to, quality statements, summaries of human factors user studies, product usage instructions, performance assessments and regulatory support."

CONCLUSION

Switching to a prefillable syringe can create clinical[1–3] and economic[4] value for healthcare providers, while differentiating the DDC in a space dominated by vials and ampules. To meet this market need, the design and rigorous validation of BD Hylok™ enables hospitals to adopt glass prefillable syringes for their IV delivery needs with confidence.

ABOUT THE COMPANY

BD is a large, diverse, global medical technology company. Its Medical Pharmaceutical Systems division is the world's largest syringe manufacturer. It offers prefillable syringes, self-injection systems, safety and shielding solutions, and needle technologies and associated pharma services.

REFERENCES

1. *Vogl TJ, Wessling J, Buerke B, "An observational study to evaluate the efficiency and safety of ioversol pre-filled syringes compared with ioversol bottles in contrast-enhanced examinations". Acta Radiol, 2012, Vol 53(8), pp 914–920.*
2. *Adapa RM et al, "Errors during the preparation of drug infusions: a randomized controlled trial". Br J Anaesth, 2012, Vol 109(5), pp 729–734.*
3. *Subhi Y, Kjer B, Munch IC, "Prefilled syringes for intravitreal injection reduce preparation time". Dan Med J, 2016, Vol 63(4), A5214.*
4. *Benhamou D et al, "Ready-to-use pre-filled syringes of atropine for anaesthesia care in French hospitals – a budget impact analysis". Anaesth Crit Care Pain Med, 2017, Vol 36(2), pp 115–121.*
5. *"Drivers of use of prefilled syringes". Internal study, 2018, Becton, Dickinson and Company.*
6. *"Considerations and Options for Prefilled Syringes". White Paper, 2019, Baxter Healthcare Corporation.*
7. *Data taken from IQVIA dataset, extracted Dec 2019.*
8. *"Hylok value proposition confirmation". Internal study, 2017, Becton, Dickinson and Company.*
9. *"Connection problems involving certain needleless pre-filled glass syringes containing adenosine and amiodarone". US FDA Safety Announcement, 2011.*
10. *"Understanding needs of ICU Nurses, anaesthesiologists, risk/quality managers and infections control nurses in IV drug delivery in Acute care in relation to Prefilled Syringes (PFS) and the value associated with PFS". Internal study, 2017, Becton, Dickinson and Company.*
11. *"Simulated Human Factors Validation study of BD Hylok™ connectivity". Internal Report, 2017, Becton, Dickinson and Company.*
12. *"BD Hylok™ IV connectors and needles compatibility". Internal Report, 2018, Becton, Dickinson and Company.*
13. *"BD Hylok™ and BD Hylok™ competitor syringes performance evaluation". Internal Report, 2018, Becton, Dickinson and Company.*
14. *"ISO 80369-7:2016 Small-bore connectors for liquids and gases in healthcare applications – Part 7: Connectors for intravascular or hypodermic applications". ISO, published 2016.*

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1. IMS Health. IMS Health Global Midas Edition. Danbury, CT: IMS Health Inc.; 2015.

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15. *"ISO 11040-4:2015 Prefilled syringes — Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling". ISO, published 2015.*
16. *"BD Hylok™ Design verification results". Internal Report, 2019, Becton, Dickinson and Company.*
17. *"BD Hylok™ functional performances study". Internal Report, 2018, Becton, Dickinson and Company.*
18. *"Regulation (EU) 2020/561". Official Journal of the European Union, published 2020.*
19. *"Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)". European Medicines Agency Document, 2019.*
20. *Soikes R, "Moving from Vial to Prefilled Syringe". PharmTech, 2009, Vol 2009 Supplement, Issue 5.*
21. *Soikes R, "Shoot for Share! From Vial to Pre-filled Syringe". Webinar, Jun 2009, Baxter BioPharma Solutions.*

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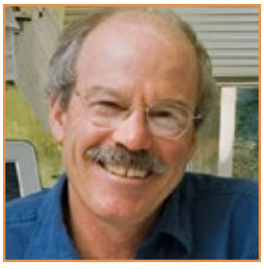

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CONSIDERATIONS FOR DEVICE SELECTION IN PARENTERAL APPLICATIONS

In this article, Mark Tunkel, Global Category Director, Services at Nemera, looks at the challenges involved in the selection of drug devices for combination products and the optimisation of the development process.

HOLISTIC DEVICE SELECTION AND USER-EXPERIENCE INNOVATION TO DRIVE DIFFERENTIATION

The complexities involved in selecting the correct device for a combination product have never been more challenging. A convergence of trends, including significant growth in the global drug-development pipeline, the need for more complex delivery devices to address targeted applications and drug attributes, and increased migration of care from clinical to self-administration in home settings have driven demand for a wide range of solutions. This is coupled with a crowded competitive landscape in the biologics, biosimilars and generics segments, in which multiple competitors may be pursuing the same applications. This drives the need for differentiation wherever possible, across the entirety of the care continuum, well beyond solely the drug administration event, to supporting the broader patient and clinical journey. All these factors lead to a need for developers to adopt a holistic approach to device selection, which is focused on the entire combination product that spans development stages and requires specialised expertise at every step, and recognition of a variety of factors and influences that need to be considered to better serve patients, whose expectations are increasing. Nemera believes embracing this approach will lead to better near- and long-term decision making across the life cycle of drug products.

"While patient centricity is the foundation for developing a robust device selection plan and completion of a successful combination product development initiative, developers need to remember there is a larger ecosystem that must be considered to ensure success."

COMBINATION PRODUCT ECOSYSTEM

While patient centricity is the foundation for developing a robust device selection plan and completion of a successful combination product development initiative, developers need to remember there is a larger ecosystem that must be considered to ensure success. This ecosystem includes **providers**, namely healthcare professionals, but also health systems; **payers**, in order to consider factors such as value-based care; and **regulators**, as the market for product introduction and the intended filing approach can significantly impact device selection approaches and development strategies. These factors then need to be considered within the available or emerging **technology** landscape. This broader understanding is critical in meeting the needs of patients and can impact how technology is selected, as well as early considerations around the impact of the other aspects of the ecosystem in development initiatives. Nemera believes that success will come from addressing these factors both strategically and tactically (Figure 1).

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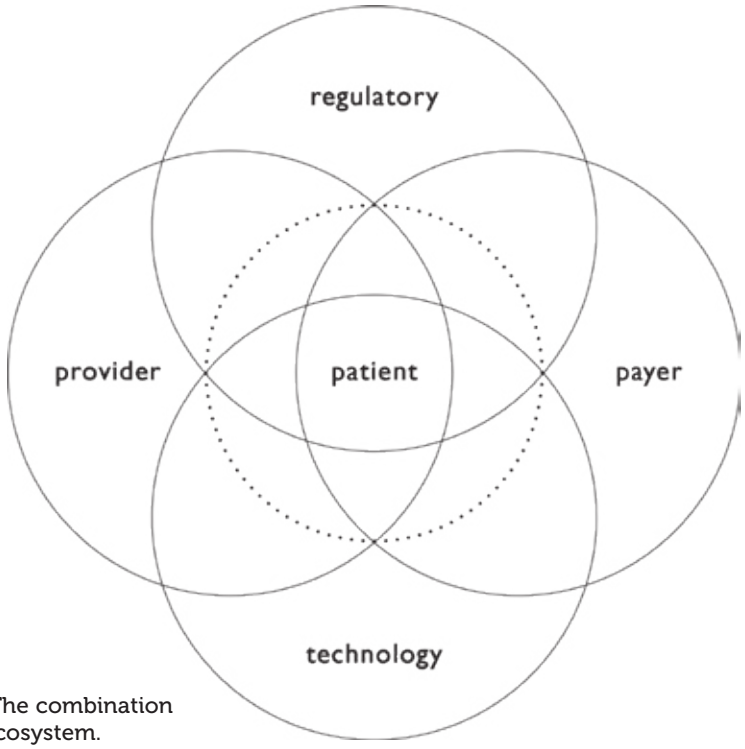

Figure 1. The combination product ecosystem.

THE PATIENT AND CLINICAL STAKEHOLDER JOURNEY

With respect to patient centricity, at the earliest stages of establishing the functional requirements and user needs for a device, it is critical to fully understand the patient journey, as well as any related clinical processes, to ensure every decision considers their needs first. Understanding both this journey and interactions with the healthcare system and healthcare provider experience enables the capture of the complete process patients go through in managing their disease – both from a self-administration standpoint and from a longitudinal perspective – as they progress with their condition and treatment through the healthcare system and life stages.

Nemera's design research experts do this by primarily using a technique called "applied ethnography". This method relies on a combination of interviews and in-context observations of practices, processes and experiences within the patient's home or actual use environment (Figure 2). At this stage, potential applications are looked at broadly, that is beyond the administration event or solely complying with instructions for use as you might see in a human factors study. This can potentially start from when a patient is first diagnosed, to receiving their device, through the entire process of preparing, administering and disposal, and the times in between treatment so it can be understood how that process changes over time and how the frequency of administration may impact the patient experience. This gives the most natural view of the patient experience in relation to their environment, social/emotional contexts and all the other factors that influence use. As mentioned, it is equally important to gain an understanding of the experience of healthcare professionals, as well as considering this in relevant settings in clinical environments. This is of particular importance in applications where care is provided in both home and clinical environments, as well as a migration of care – such as an oncology ward, which has built-in support systems – to an environment of self-administration where clinical personnel are not present, and the burden of support falls to a family member or caregiver. These cases are also driven by migration in drug-delivery modality such as from intravenous to self-administered subcutaneous injection.

The outputs from these approaches include patient journey and clinical process maps, a robust understanding of prioritised user needs and values, and identification of pain points, which can be leveraged by cross functional development and commercial teams to consider possibilities for improving the patient and provider experience across all aspects of the journey to fully engage with patients beyond medication delivery (Figure 3, next page).

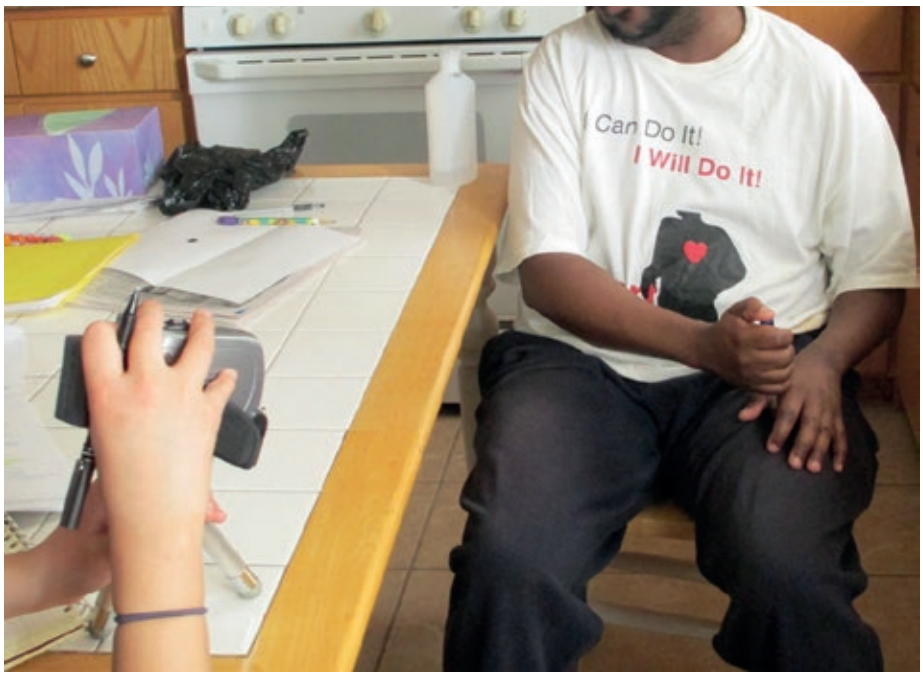

Figure 2. Contextual research provides a global understanding of the patient and clinical stakeholder experience in self-administration.

"With respect to the device, decisions can be taken around assessing the technology landscape to identify existing IP or platforms that may be fit for the intended purposes related to function and drug product attributes."

Figure 3: Key milestones along the patient journey and implications for delivery device design.

SYNTHESISING THE PATIENT JOURNEY AND ECOSYSTEM TO DRIVE DEVICE SELECTION

Having gained visibility of what the patient and stakeholder needs are, developers should consider how best to satisfy those needs as holistically as possible, while continuing to work with patients and clinical stakeholders prior to new product development processes. This requires synthesising the patient and stakeholder information with other ecosystem inputs into a device strategy roadmap, which can be used in several ways to make device selection decisions.

With respect to the device, decisions can be taken around assessing the technology landscape to identify existing intellectual property (IP) or platforms that may be fit for the intended purposes related to function and drug product attributes. This includes decisions around modality, such as autoinjector versus wearable injector, as well as variations within, if considering existing IP platforms. Early-stage lab and analytical activities may be used to assess any of this existing IP to ensure operational limits are sufficient for known user and functional requirements, as well as to assess compatibility with primary container solutions. This can help determine the need for customisation of existing IP. An example of this might be a modified form factor or affordance for user feedback on a pen or autoinjector, as well as refinement of operational aspects such as injection force to address targeted user groups.

If an existing technology or IP is not readily available, developers may choose to conduct early-stage technical concept generation and feasibility of new-to-the-world concepts/IP platforms while considering the ability of a concept to be scaled into commercial manufacturing.

In both instances, it is increasingly common to seek solutions that may be suitable across multiple drug products as part of a longer-term strategy to leverage a single device platform to drive efficiency in this manner. However, this brings the potential for a wide range of user and functional performance requirements, such as dose duration, frequency or patient population defining characteristics that need to be considered to ensure that targeted devices or concepts can be made to address specific requirements of each asset.

Regarding patient experience, it is useful to project future state-care models where devices are supported by digital health assets, training and other forms of engagement to address pain points and enhance the experience overall. This can help outline areas where partnerships with complementary providers may be necessary to address aspects of the model. Throughout this process, it is important to continue to work with patients and stakeholders to assess these options to ensure all needs are met. This provides confidence that the best decisions are being made at the earliest stages before resource intensive development activities.

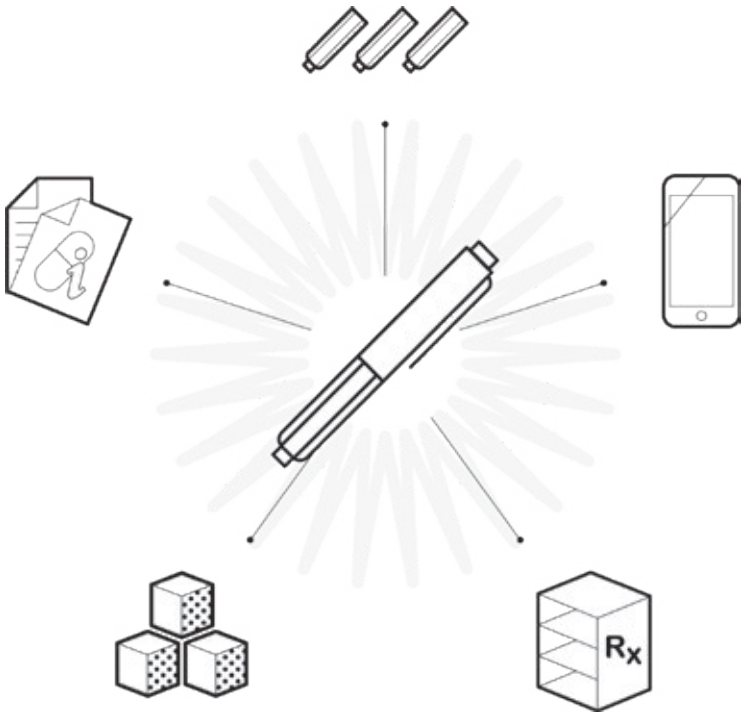

Figure 4. Optimising the development process and "surrounding the device" for differentiation is critical.

OPTIMISING THE DEVELOPMENT PROCESS AND "SURROUNDING THE DEVICE" FOR DIFFERENTIATION

Beyond making device selection decisions, it is important to use this foundation to consider the product development process including differentiation of the user experience, support of clinical trials from both a usability and device supply perspective that the broader capabilities at Nemera can support, and life-cycle management to extend the value of devices through enhancements based on market surveillance or other inputs, as competition may emerge. Ideally, this will all feed back into the definition and development process for next-generation devices (Figure 4).

It is key to drive user experience differentiation and to optimise the selected device for the target drug product. To achieve this, human factors and patient experience activities must be integrated for a successful drug-device combination product development process. It is incumbent on developers to ensure that the selected device, in combination with the drug, is appropriate, safe and effective for the target population. This also extends to executing the earlier-stage inputs to optimise the patient experience to create competitive differentiation and to ensure adherence and engagement with patients and clinical stakeholders. Using the foundation that established them defines the right blend of complementary user-experience elements to achieve these goals.

Good examples of this approach are Nemera's recently acquired pen injector portfolio and large-volume wearable concept under development. These devices are of interest to customers in the biologic, biosimilar or generic markets, where, in many cases, competitors are targeting the same reference drug or devices, and differentiation wherever possible is critical. Using the foundation discussed earlier, Nemera can support the entire combination product development process and help its customers in "surrounding the device" in every way possible including:

- Addressing the defined user groups/populations and early-use related risk analysis activities to define the human factors and usability programme necessary for the intended regulatory/filing strategy and identified clinical risks, through conducting formative and summative usability testing globally for all aspects of the device and supporting assets in alignment with the human factors programme definition, through human factors engineering report documentation for use in regulatory submissions.
- Developing instructions for use, value-added packaging specific to the application, which may include leveraging digital health related add-ons to support patient engagement/adherence, as well as extend the value of a device platform.
- Development of a formal training programme, including device training devices into the patient services model to create commercial differentiation. Nemera's partnership with Noble (Orlando, FL, US) Safe'n'Sound® sound device is an example of this approach.
- Leveraging Nemera's clinical and commercial manufacturing regardless of device modality.
- Programme management excellence to ensure all elements of the programme are integrated to drive efficiency and mitigate any programme risks proactively as a single partner for development of the combination product.

In summary, the combination of Nemera's strong IP platforms, development services and manufacturing services allows customers to achieve the outcome of a successful regulatory submission and commercial launch of safe, effective and differentiated combination products with a single partner who can manage all of the aspects critical for success.

ABOUT THE COMPANY

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

ABOUT THE AUTHOR

Mark Tunkel is Global Category Director for Insight Innovation at Nemera. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharmaceutical industry, Mr Tunkel has advised many of the world's leading companies on their product development and innovation strategies, with an emphasis on driving realisation and the most favourable business outcomes.

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PLATFORM TRAINING SOLUTIONS ADD VALUE FOR PHARMACEUTICAL COMPANIES

In this article, Alex Catino, Product Commercialisation Associate at Noble, an Aptar Pharma company, discusses the unmet need in healthcare for proper patient onboarding and training in the field of prefilled syringes and injection devices. Ms Catino uses Noble's training device for Ypsomed's YpsoMate® autoinjector as a case study for how bespoke training devices can be used to help improve the patient experience and adherence rates.

"Don't practise until you get it right. Practise until you can't get it wrong" is a saying often associated with athletes and entertainers, but one that can also apply to the healthcare industry, especially to patients who use prefilled syringes and injection devices to self-administer their prescribed medications.

BREAKING DOWN BARRIERS TO PATIENT ADHERENCE

With an increasing number of biologic medicines and drug delivery device options entering the market in recent years, pharmaceutical companies are making it possible – and more easily accessible – for patients to self-administer their drug therapies at home.

> "One issue that often arises is the fear of needles, known as trypanophobia. The *Diagnostic and Statistical Manual of Mental Disorders* recognises it as a phobia that affect approximately 50 million Americans, making it a top-10 fear."

While self-injecting prescribed biologics at home is more convenient for both patients and their healthcare providers (HCPs) than having to do so in a hospital environment, it also comes with its own unique set of challenges. Overall, when patients are put in charge of administering their own medication, there is a tendency for patients' adherence to their therapies to suffer. One issue that often arises is the fear of needles, known as trypanophobia. The Diagnostic and Statistical Manual of Mental Disorders recognises it as a phobia that affect approximately 50 million Americans, making it a top-10 fear.[1] Anxiety when it comes to needles is also attributed to causing nearly half (45%) of patients who rely on self-injection therapies to either skip or cease their injections.[2]

Another phenomenon working against patient adherence to self-injection is the "forgetting curve", which suggests that retention and recall worsen over time without practice and repetition. This theory postulates that 50% of the information patients receive from their HCP is forgotten within an hour. After that, patient memory declines rapidly by 80% in two days, with 90% of the information forgotten in a week.[3]

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As biopharmaceutical companies develop therapies that permit longer intervals between injections – and therefore an improved patient experience, with patients injecting fewer times throughout the overall course of their therapy – the risk becomes greater that patients will forget critical steps for proper injection, and thus administer their therapies incorrectly, potentially resulting in a lack of treatment efficacy, and lose the confidence they need to self-inject.

Finally, telemedicine is poised to transform the healthcare landscape as a mainstream alternative to traditional in-person methods of care delivery. The use of this remote healthcare technology grew from less than 1% of primary care visits before the covid-19 pandemic to nearly 43.5% by April 2020.

Based on this current trajectory and rapid adoption rate, the continued, sustained growth of telemedicine is predicted for years to come.[4] Of concern, however, is a report that found over 40% of people worry about their ability to obtain a proper diagnosis or treatment in a virtual setting.[5] This apprehension is well placed, especially for patients with chronic conditions who must self-administer their medication at home. This is compounded by a study conducted by Noble that revealed that nearly half of patients who self-inject receive no training on how to do so properly.

TRAINING DEVICES DELIVER LASTING BENEFITS FOR PATIENTS AND HCPS

When it comes to HCPs prescribing self-injected medications to treat chronic illnesses such as ulcerative colitis or rheumatoid arthritis, training devices need to be part of the protocol. Evidence has shown that issues arise for patients who do not receive proper training:

- 84% make errors when using their autoinjector devices
- 74% discontinue their biologic medication regime at least once
- 45% skip or avoid their injections due to fear or anxiety.

A Noble-conducted survey of HCPs who work with patient groups most often prescribed self-injectable biologics found that, while HCPs value training for their patients, they are still not providing it. Why? The primary reason is that HCPs themselves are not being trained on the proper use of the drug delivery device. However, 71% of HCPs said they would be "very likely" to prescribe their patients a self-injected medication that came with a robust training solution.

Drug delivery training devices – including prefilled syringe and autoinjector training devices – provide the practice necessary for patients to overcome their anxieties about the self-injection process, and thus administer their medications confidently and consistently. Coupled with a robust onboarding programme, these training devices can help patients adhere to their therapies longer, resulting in improved health outcomes (Figure 1).

PARTNERING WITH BIOTECH COMPANIES TO DELIVER PLATFORM DEVICE TRAINING SOLUTIONS

Given that 49% of patients who are prescribed injection-based therapies do not receive training in an HCP's office, and 90% of treatment information is forgotten within a week, it's imperative that pharmaceutical companies take a holistic approach to ensuring that patients are familiar and confident with the use of their devices, understand their condition and treatment plan, and become and remain adherent to their therapy.

YpsoMate® Autoinjector Platform

An example of this principle in practice is the fruit of Noble's partnership with Ypsomed, a diabetes specialist and a developer and manufacturer of injection and infusion systems for self-medication. Noble's injection training platform is based on Ypsomed's YpsoMate® autoinjector – an automated, disposable injection device for 1 mL and large-volume 2.25 mL prefilled glass or polymer syringes, suitable for all patient groups – and designed to Ypsomed's device specifications.

Figure 1: Noble's YpsoMate® training device.

Noble's YpsoMate® training platform replicates the real autoinjector device and incorporates proprietary features that are intended to give patients a realistic and repeatable simulated injection experience, including:

- Low reset forces
- A variable plunger speed system
- Device replication designed to demonstrate an actual drug delivery experience for patients.

There is also an option to incorporate a patented agitator tip designed for those 45% of patients who have a fear of needles. This feature slightly pricks – but does not at all puncture – the skin at the start of the injection to create the sensation at the injection site. The training device also allows for varying needle forces and ranges, depending on what the pharma company needs to best replicate its drug delivery device injection experience (Figure 2).

"A Noble-conducted survey of HCPs who work with patient groups most often prescribed self-injectable biologics found that, while HCPs value training for their patients, they are still not providing it. Why?"

In addition to the patient benefits and training device design technologies, Noble's YpsoMate® platform programmes also provide several benefits for individual brands, including:

- High speed-to-market
- Lower cost of entry
- The ability of brands to customise training devices to meet their unique specifications.

CONCLUSION

When it comes to using prefilled syringes and injection devices to self-administer prescribed medications, half of all patients are non-adherent due to gaps in their treatment experiences. The cost of this non-adherence and non-optimised therapy is steep – estimated at US$528 billion (£385 billion) annually – and everyone pays the price, from biopharmaceutical brands and payers to HCPs and their patients.[6]

It has been shown that injection device training can result in a decrease of up to 85% in patients who abandon their treatment regimen, making training devices critically important for the millions of patients across the globe who live with chronic illnesses.[7]

Finally, Noble also offers clients a full lifecycle of supporting solutions – from development to commercialisation – including market research, logistics management, training and product launch strategy services to further support pharma brands.

In much the same way that telemedicine is transforming healthcare delivery, training platforms and services are poised to change the future of adherence and onboarding through research-driven insights, innovative technologies and patient-focused solutions, helping patients practise until they can't get it wrong.

ABOUT THE COMPANY

Noble develops robust training devices and onboarding solutions for the world's top pharma and biotech companies and is focused on fostering healthy patient outcomes for those who self-administer drug therapies.

Figure 2: Noble's YpsoMate® training solutions, which include training devices and instructions for use in high-quality packaging.

Noble manufactures and commercialises training devices that mimic the exact feel, force and function of drug delivery devices, including autoinjectors, prefilled syringes, on-body injectors, nasal sprays and pulmonary inhalers, in order to increase patient adherence and confidence and decrease usage errors. Noble was founded in 1994 and is based in Orlando, Florida.

Noble is an Aptar Pharma Company, which is part of AptarGroup, Inc, a global leader in the design and manufacturing of a broad range of innovative drug delivery, consumer product dispensing and active material solutions that serve a variety of end markets, including pharmaceutical, beauty, personal care, home, food and beverage.

REFERENCES

1. *"Fear of Needles: The Fatal Phobia". PharmaJet blog, Nov 2013.*
2. *Guilliouma W, "Sensor Advancements in Drug Delivery Improve Compliance". ONdrugDelivery Magazine, Issue 107 (May 2020), pp 25–28.*
3. *Kohn A, "Brain Science: The Forgetting Curve–the Dirty Secret of Corporate Training". Learning Solutions, Mar 2014.*
4. *"Predicting the Future Role of Telemedicine". Modern Healthcare, Oct 2020.*
5. *"Survey Report: Americans' Perceptions of 5G Technology". Skyes, 2020.*
6. *Watanabe JH, McInnis T, Hirsch JD, "Cost of Prescription Drug–Related Morbidity and Mortality". Ann Pharmacother, 2018, Vol 52(9), pp 829–837.*
7. *Mease P et al, "Impact of a Patient Support Program on Abandonment of Adalimumab Treatment Initiation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis". Arthritis Rheumatol, 2016, 68 (suppl 10).*

ABOUT THE AUTHOR

Alex Catino, Product Commercialisation Associate at Noble, an Aptar Pharma company, is responsible for supporting development, launch and commercialisation of Noble's platform products. Alex holds BSc degrees in Business Administration and Psychology.

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I-PLATFORM DEVICE: THE SMART DEVICE WITH APTITUDE

In this article, Jimmy Fan, Marketing Vice-President at CCBio, outlines the capabilities and benefits of the I-Platform smart drug delivery device.

The dream of many pharma and biotech companies is to have a device that is capable of integrating with as many drug containers as possible – and functions as an Apple-like device that is easy to use, friendly, yet powerful and economic.

It can seem like too much to ask – yet CCBio treats this unmet need as a goal. It has become part of the company's everyday work, with the eventual aim of introducing the I-Platform device (Figure 1) to industries and users. The concept is simple – with one delivery unit, the I-Platform can adapt to cartridges or prefilled syringes and combine with either safety mechanisms or conventional needle shields. With the versatility of the Ascpo safety needle (Figure 2) and Beta safety pen needle (Figure 3) from CCBio, the I-Platform makes drug delivery safer and easier (Figure 4), whilst ensuring the necessary precision.

Versatility is one key benefit of the adaptable I-Platform. From many years' experience, CCBio understands the differences in dimensions and geometry between drug containers, depending on the manufacturers. These differences, although usually minor, can cause problems when it comes to functionality. For example, a difference of a few millimetres in the length of a cartridge may affect dose accuracy.

The I-Platform device (Figure 5) is very easy to fabricate and design changes can be implemented rapidly and economically because it is just one component and injection mould. During the preliminary study of a drug container, CCBio is able to detect and

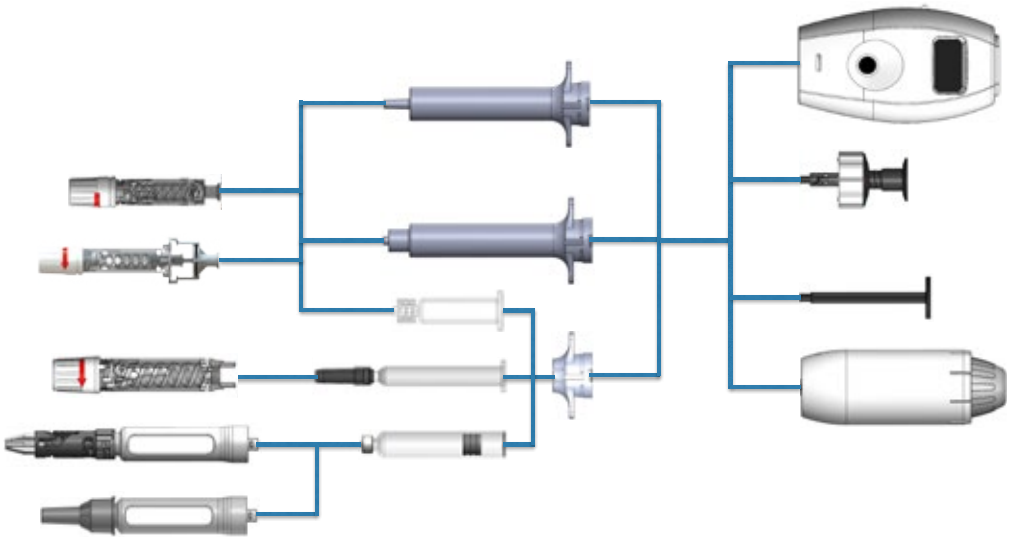

Figure 1: The I-Platform drug delivery device – showing the safety needles on the left, the containers and their adapters in the middle and the delivery units on the right.

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Figure 2: Prefilled syringe with Ascpo safety needle.

Figure 3: The Beta safety pen needle.

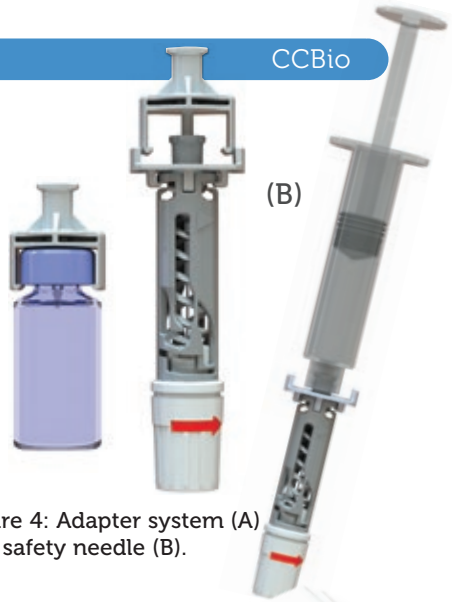

Figure 4: Adapter system (A) and safety needle (B).

Figure 5: The I-Platform drug delivery device.

correct any dimension issues and secure the final product functionality and performance from the very early stage of a project, which helps lead to successful design validation testing and outcomes. Such an approach also saves money.

The delivery unit at the heart of the I-Platform is state-of-the-art technology, incorporating Wi-Fi, Bluetooth and a microprocessing data system with a multifunctional LED display. Many other connectivity and smart capabilities can also be included and tailor-made for each specific requirement. The driving and power unit is extremely robust yet precise. And the device can handle viscosity up to 70 cP and dosage down to 0.1 mL, as well as allowing the injection speed and injection time to be programmed.

The result is that patient pain is reduced to a minimum to give a pleasant drug administration experience. Also, healthcare providers can reduce the risk of occupational injury from handling the injection of high-viscosity drugs. Making patients and healthcare providers love this device is the ultimate goal of CCBio. The company does not compromise the quality of the device – sourcing all the parts and important modules like the motor, battery, PCB and driving parts from local or Japanese suppliers. In addition to the electronic power unit station, CCBio can also offer manual and traditional spring-driven power unit sets – giving customers the flexibility and diversity they need.

CCbio is a 100% Taiwanese biotech and medical device company, which is a one-stop-solution company. It aims to satisfy customers' every need and resolve difficulties during product development, creating innovative products and devices and differentiating customers' products in the marketplace.

ABOUT THE COMPANY

CCBio is a medical device designer and manufacturer with core competencies including tooling, moulding, assembly, validation, R&D, RA and pharmaceutical testing, all in-house. It offers combination products, medical devices and medical containers to pharma partners and, ultimately, patients.

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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AN INCLUSIVE APPROACH TO THE DEVELOPMENT OF PLATFORM MEDICAL DEVICES

In this article, Finola Austin, Human Factors Engineering Manager at Owen Mumford, discusses the difficulties presented by designing a user testing programme for platform devices when the target patient population is as yet unknown, and presents the testing framework based on seven user groups that Owen Mumford uses to meet this challenge.

User-centred design can present a challenge to platform drug delivery device manufacturers in circumstances where the intended therapy area – and therefore intended patient characteristics – are not yet known. Applying an inclusive strategy to user evaluation studies helps to ensure device safety and effectiveness for a broad range of potential end-users. It is essential to comprehensively assess whether a device encourages adherence across various user groups and whether the needs of different patient groups have been addressed. Manufacturers therefore face the challenge of ensuring that study samples are sufficiently representative of the full range of potential end-users. Achieving this aspiration of representative sampling requires a realistic, carefully designed programme that makes the best use of company resources.

COMPREHENSIVE TESTING

Regulatory human factors guidance and international best practices advise that a medical device must be tested by the intended users to ensure that it is both safe and effective. User testing provides results that can be confidently considered representative of the wider user population. It is therefore important that the test participants correspond to the actual end users of the device.

However, this requires accurate identification of the intended user populations, which is not possible for platform devices where the intended therapy area has not yet been specified. For such devices, human factors sampling strategies for user testing must aim to encompass as wide a range of user capabilities as is practicably possible. This enables product designers to make informed decisions about design, whilst providing confidence to future business partners that all usability problems associated with the device's user interface have been discovered during early-stage development, and won't arise as an unwelcome surprise further down the line.

RECOMMENDED SAMPLE SIZE

Manufacturers must first determine an appropriate sample size to demonstrate a sound analysis of their device. Early in device development, it is generally accepted that usability tests require only five to

> "After five subjects have been tested, major usability problems will be observed repeatedly with successive subjects, and little additional usability information will be gained."

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Number of Users Tested	Minimum Percentage of Usability Problems Found	Mean Percentage of Usability Problems Found	Standard Deviation	Standard Error
5	55	85.6	9.3	0.9
10	82	94.7	3.2	0.3
15	90	97.1	2.1	0.2
20	95	98.4	1.6	0.2
30	97	99.0	1.1	0.1

Table 1: Percentage of total known usability problems found in 100 analysis samples (rounded to one decimal place).

Group	Description	Minimum Sample Size	
		Small Study (e.g. Early-Stage Evaluation)	Large Study (e.g. Late-Stage Evaluation)
1. Adults	Adult aged 18 years or more; no upper age limit.	3	7
2. Juveniles	Persons aged between 8 and 17 years.	2	7
3. Caregivers	Lay caregivers who help another person to administer their injected medication.	2	7
4. Healthcare Professionals	Healthcare professionals who administer injected medication to patients (e.g. nurse, pharmacist, general practitioner).	2	7
5. Perceptual Ability	Persons with visual impairment, plus at least one with auditory impairment.	2	7
6. Cognitive Ability	Persons with a range of moderate cognitive impairments (e.g. ADHD, autism, dyslexia, learning disability).	2	7
7. Action Ability	Persons with a range of physical (upper limb) impairments (e.g. rheumatoid arthritis, Parkinson's, multiple sclerosis).	2	7
	TOTAL	15	49

Table 2: Human factors sampling strategy.

"The US FDA states that caregivers, healthcare professionals, younger users and adults should be considered as distinct user types; these categories have been included as four groups in the sampling plan. The remaining three groups cover aspects of user/device interaction: perception, cognition and action."

eight participants per distinct user group.[1] After five subjects have been tested, major usability problems will be observed repeatedly with successive subjects, and little additional usability information will be gained. For example, one study illustrated that doubling the number of participants from five to ten only increased the mean percentage of usability problems found from 85.6% to 94.7% (Table 1).[2]

However, whilst early-stage studies might be feasible, and indeed effective, with participant numbers as low as five, it is also advantageous to ensure wide representation to guarantee timely identification of use issues and allow for the design of any relevant mitigations. Further, as development progresses, prospective pharmaceutical partners will understandably seek assurance that their intended user has been adequately considered throughout the design process and iterative user testing. For validation testing, having 15 to 20 participants per user group is recommended by US and UK regulators. This number of test participants should be large enough to reasonably reflect the heterogeneity of device users.

INCLUSIVE USER EVALUATION

The second factor to consider is that samples must encompass a range of user characteristics and needs. To this end, Owen Mumford has adopted a practical and robust framework based on seven user groups (Table 2). These groups cover the widest possible range of characteristics that are likely to influence how users use devices. The US FDA states that caregivers, healthcare professionals, younger users and adults should be considered as distinct user types;[3] these categories have been included as four groups in the sampling plan. The remaining three groups cover aspects of user/device interaction: perception, cognition and action. These aspects encapsulate the user's ability to perform the required task correctly.

For the purposes of evaluation during development, it is useful to keep each use-impairment group mutually exclusive. This can be especially helpful in supporting the needs of prospective pharmaceutical partners, helping to illustrate the impact of different aspects of the user interface on a range of characteristics. A user evaluation strategy based on this sampling plan may be preceded by a less formal user evaluation with small groups of users that are easier

to access, such as participants from device designer's internal workforce. However, early objective user testing with more representative participants is recommended.

BROADENING REPRESENTATION

The user groups outlined above can be adjusted in size and makeup to incorporate a representative range of secondary characteristics, such as hand dominance, gender and ethnicity. Numbers per user group may also be increased to diversify the sample. For instance, the size of the "Action" group might be increased to accommodate a more in-depth examination of patients with biomechanical or neurological impairments as separate groups. This can help to ensure enough data is available to support root cause analysis where use difficulties and/or errors are identified. For commercial purposes, the size of each group can be adjusted in line with the projected needs of the business, such as by seeking to recruit a minimum representation of users with a specific diagnosis or comorbidity. This is especially useful where market trends and insights are available.

COVERING ALL BASES

The challenge with user evaluation is planning an effective number of studies, at the right time, and with the appropriate level of prototype fidelity. A further challenge with platform devices with an undefined intended therapy area is that the medical device developer must assume a hugely diverse target population. As such, it is therefore imperative to develop an effective sampling strategy to manage potential risks and use errors across as broad a range of patients as possible, as well as anticipate the needs of prospective pharmaceutical partners. To respond to these challenges, the human factors sampling strategy outlined in this article provides a framework for user evaluation planning in the absence of user data. This framework allows platform device manufacturers to satisfactorily assess a wide range of participants and meet best practices in a cost-effective manner.

"As such, it is therefore imperative to develop an effective sampling strategy to manage potential risks and use errors across a broad a range of patients as possible, as well as anticipate the needs of prospective pharmaceutical partners."

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. *"ISO, IEC/TR 62366-2:2016, Medical devices – Part 2: Guidance on the application of usability engineering to medical devices". ISO, published 2016.*
2. *Faulkner L, "Beyond the five-user assumption: Benefits of increased sample sizes in usability testing". Behav Res Methods Instrum Comput, 2003, Vol 35, pp 379–383.*
3. *"Guidance for Food and Drug administration Staff: Applying Human Factors and Usability Engineering to Medical Devices". US FDA, published 2016.*

ABOUT THE AUTHOR

Finola Austin is an experienced Human Factors Engineering Manager with 15 years' experience in mentorship and management of human factors services in safety-critical industries. Her career began in occupational therapy within acute, long-term and community settings, and her training in accessibility has given her special insight into the needs of impaired users. Since then, Ms Austin has successfully planned and delivered human factors activities for hundreds of handheld medical devices, including autoinjectors, emergency-use devices, inhalers, injection pens and lancets, and is proficient in the creation and review of documentation. She has executed numerous user evaluation studies in the UK and the US – including studies on safety-engineered devices, injection pens and colour differentiation.

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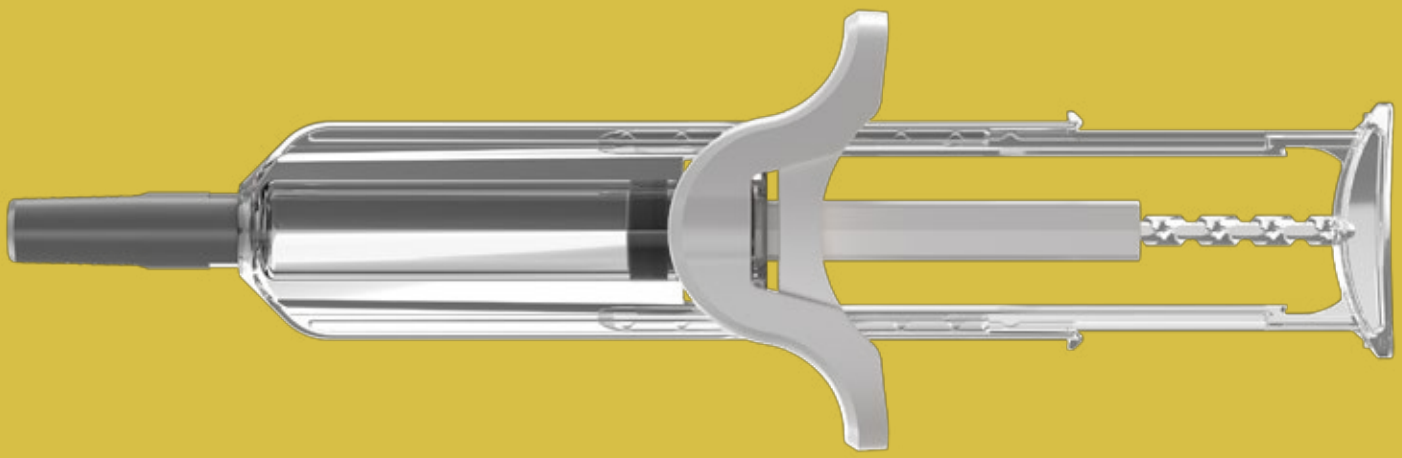

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NEW ENGINE FOR PRIMARY CONTAINER INJECTORS: A POWERFUL MICRO LINEAR ACTUATOR

In this article, Brian Li, PhD, Chief Executive Officer, Jiunn-Ru Lai, PhD Associate Professor, Tsung-Chieh Cheng, PhD, Professor, Kuang-Hsiang Cheng, Mechanical Engineer, Min-Ru Wang, Manufacturing Lead, Chia-Chi Tina Feng, Director of Business Development and Wen-Chi Huang, Specialist, all at MicroMED, introduce the company's new engine for primary container injectors, the Primary Actuator, which targets the unmet needs in the autoinjector and wearable injector market as the market shifts towards large injection volumes.

TREND OF CURRENT INJECTOR DEVICES

These days, product development for self-injectable devices is shifting towards large injection volumes. For example, the 2.25 mL autoinjector is one of the epicentres in recent market competition for cutting-edge drug delivery product development, along with many other creative products[1,2,3] under development. The other well-known biologics delivery product, the wearable injector,[4,5,6] is also moving towards large injection volumes such as 10–20 mL, or even more. Due to this new drug volume shift, the design of the primary containers used within the injectors also needs to be changed accordingly. For example, the prefilled syringe is moving from the ISO standard 1 mL to 2.25 mL, and the prefilled cartridge is moving from ISO 3 mL to 5, 10 and 20 mL. Stiction between the plunger of these large-volume glass containers is one of the key elements to maintain drug sterility, however, many engineering challenges, such as varying injection speed and risk of drug contamination, are associated with this larger container design and more complicated material interactions.

CHALLENGES IN LARGE-VOLUME INJECTION TECHNOLOGIES

Self-administration drug delivery products are limited in driving mechanism options, with springs and motors the most commonly used technologies. Within these driving technologies, spring offers large force and low cost, but comes with problems of varying flow rate (due to decrease of the spring force along with its relaxation) and high storage load (requiring more robust device housing structure making the device much bigger); motor, on the other hand, is usually quite noisy and with a limited driving force.[7] To improve device performance, many innovative driving mechanisms have been invented. Volute spring, compressed gas and linear motors are examples of the mechanisms used internally within those large-volume drug-injection devices mentioned above. These state-of-the-art delivery power sources (or "engines") offer quite large driving force, making it possible to drive large-volume, high-viscosity biologic medication fluids. However, drawbacks such as a bulky footprint and heavier weight still exist with these end products; the use of these engines as the system driving core lowers the convenience and usability of the injector systems for patient and healthcare professionals.

> "MicroMED has recently developed a novel microlinear actuator, the Primary Actuator, targeting the unmet needs for the current autoinjector and wearable injector market. The device is specifically designed to drive primary containers, such as a prefilled syringe or cartridge."

THE ENGINE

MicroMED has recently developed a novel microlinear actuator, the Primary Actuator (Figure 1), targeting the unmet needs for the current autoinjector and wearable injector market. The device is specifically designed to

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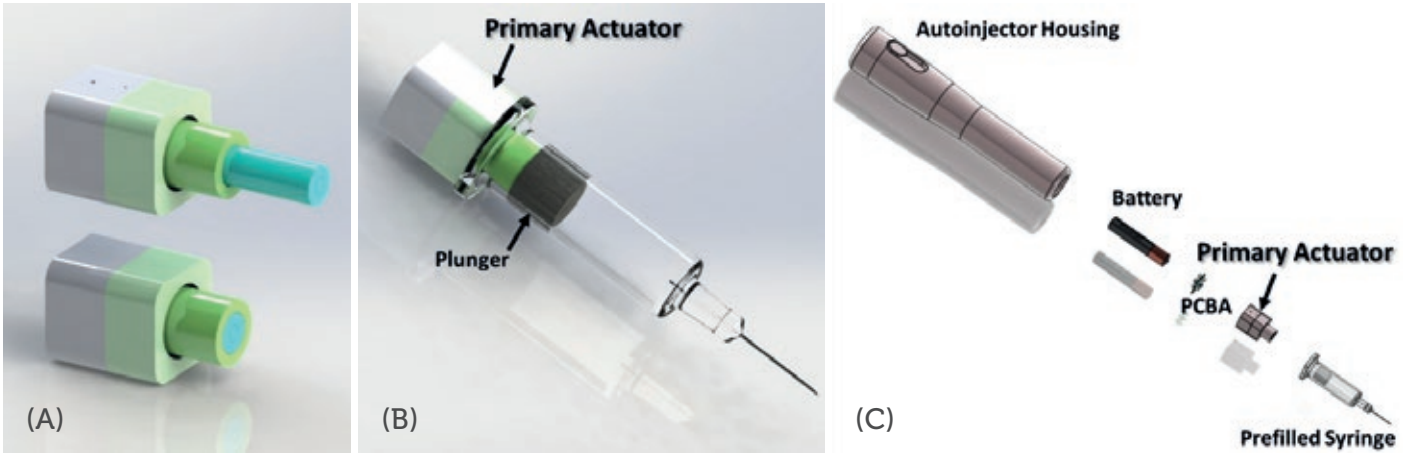

Figure 1: Device 3D photos showing: (a) working principle for the Primary Actuator, (b) an actuator assembled into the space behind the plunger of a prefilled syringe and (c) a simple modulisation design of the actuator with other autoinjector components.

drive primary containers, such as a prefilled syringe or cartridge. This small micro-electromechanical systems (MEMS) engine (22 mm in length, a small but powerful MEMS microchip and micro-integrated control circuitry inside) can provide the injection force/speed for the most challenging specifications required by high-viscosity, large-volume biologics injections. The real-time force output of MicroMED's actuator was measured using a load cell force sensor (Figure 2). The peak driving force exceeded 1,000 N at around three minutes (the data saturated at around 1,000 N due to the measurement limit of the sensor). The actuator can easily achieve higher force if required, but the 1,000 N force measured already surpasses most of the current driving technologies (springs or motors) by more than 10 times.

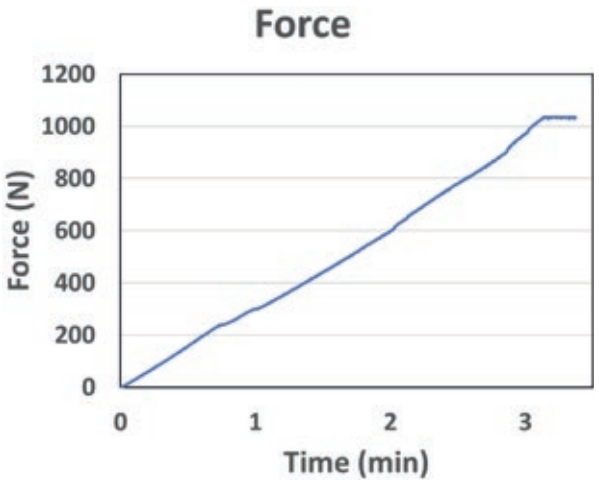

Figure 2: Real-time force output measured by a force sensor. The data saturated at around 1,000 N due to the measurement limit for the sensor, not the limit of the actuator.

MicroMED has also introduced a 2.25 mL prefilled syringe with 28 cP simulated fluid through a 26G needle with injection time of about nine seconds. Figure 3 shows this testing result measured by a commercial flow sensor. The flow rate was stable throughout the whole injection process and the injection volume increased steadily, demonstrating excellent delivery control of the primary drug container. The total capacity needed from the battery was about 5 mAh. This means a small lithium battery would be able to drive the microactuator, which also helps to lower the overall drug delivery device footprint (with this MEMS actuator as the core engine), making it superior to many current injection driving technologies such

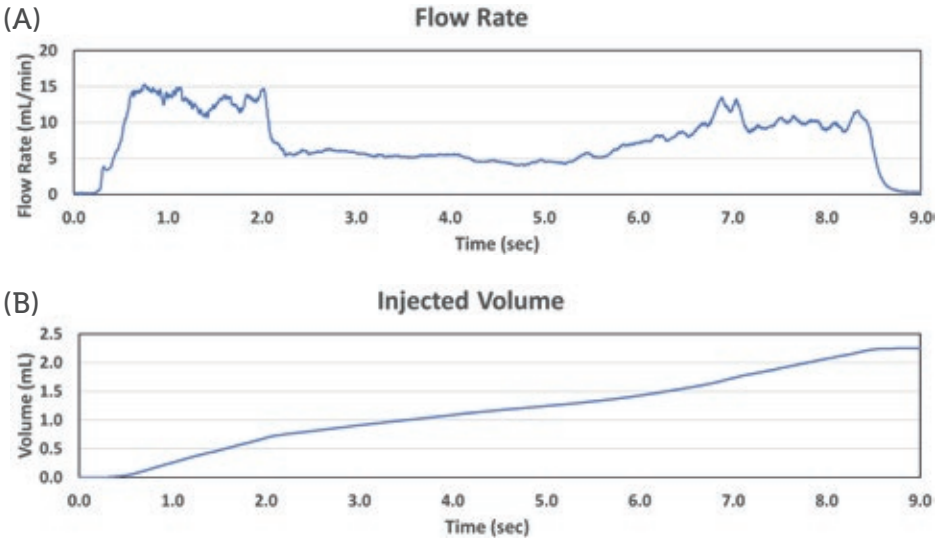

Figure 3: The injection performance (a: flow rate and b: injected volume) of the MicroMED Primary Actuator using a 2.25 mL prefilled syringe with 26G needle and 28 cP viscosity simulated fluid.

"The Primary Actuator is an innovative, small, low-cost engine solution for the application of large-volume, high-viscosity medication injection. This engine technology is well suited to address the growing needs for the subcutaneous protein drug therapies."

as spring, compressed gas and motor (see Table 1 for the performance comparison and Table 2 for the specifications of MicroMED's engine product).

The Primary Actuator is an innovative, small, low-cost engine solution for the application of large-volume, high-viscosity medication injection. This engine technology is well suited to address the growing needs for the subcutaneous protein drug therapies. The Primary Actuator has demonstrated its capability as a smart solution for drug delivery that will benefit all stakeholders in the subcutaneous injection market. A successful partnership between the strategic collaborators and MicroMED will enable this engine technology to be developed into a superb commercial injector product meeting the true needs for today's large-volume biotech injectables.

Large-Volume Engine Mechanism	Spring	Compressed Gas	Micro-Motor	Primary Actuator
Maximum Driving Force	✶✶	✶✶	✶	✶✶✶
Storage Load	✶	✶✶	✶✶✶	✶✶✶
Varying Injection Speed	✶	✶✶	✶✶	✶✶✶
Device Size	✶	✶	✶	✶✶✶
Leakage of Gas	✶✶✶	✶	✶✶✶	✶✶✶
Drug Contamination	✶✶✶	✶	✶✶✶	✶✶✶
Noise	✶✶	✶✶✶	✶	✶✶✶
Modular Design	✶✶	✶✶	✶✶✶	✶✶✶
Connectivity Integration	✶	✶	✶✶✶	✶✶✶
Cost	✶✶✶	✶✶	✶	✶✶

Table 1: Comparison of the current driving technologies for the large-volume primary container injectors. Performance scale: ✶✶✶ Excellent, ✶✶ Good, ✶ Normal.

Model #	PA-1W	PA-6W
Input Voltage (VDC)	3.0	3.0
Input Power (W)	1	6*
Max Load (N)	200	1200
Max speed (mL/min)**	1.5 mL/min	9 mL/min
Stroke (mm)	35	35
Ingress Rating	IP67	IP67
Weight (g)	15	20
Dimension Body Shaft	12 x 12 x 22 mm 25 (L) x 9.5 (D) mm	15 x 15 x 25 mm 25 (L) x 9 (D) mm

Table 2: Product specifications for the MicroMED Primary Actuator: (a) 1W model and (b) 6W model.

* Customisation engine with up to 24W is also available.
** The speeds were measured using a 2.25 mL prefilled syringe with 1 cP of saline and 30G needle.

ABOUT THE COMPANY

MicroMED is a MEMS microchip design house specialising in the development of microinjection devices targeting unmet needs in the most challenging drug delivery applications. MicroMED has established a proprietary high-precision MEMS drug delivery engine system, capable of delivering broad flow rate from 1 nL/min to 10 mL/min (eight orders of magnitude) with driving force up to 2,000 atm (29,000 psi) of pressure. MicroMED welcomes all types of business connections/relations in the PDA drug delivery value chain (pharma, biotech, medical injector developer and insurance payer) with the goals below (but not limited to):

- Purchasing of the current micro-engine products
- Co-development of advanced injector products
- Licensing of the micro-engine proprietaries/intellectual properties.

MicroMED has established a strong and experienced supply chain for the development of injection devices from raw material suppliers, semiconductor foundries and component providers to contract manufacturers in both the US and Taiwan. These valuable partners have required regulatory certifications and years of experience in supporting medical device design and manufacturing. MicroMED applies its quality management system, providing the necessary structure and controls to help its value-chain supplier team develop products that meet defined safety and performance requirements for high-value drug delivery customers.

REFERENCES

1. *Panting GRF, "Addressing Complex Biologics with Rational Drug Device*

Design". ONdrugDelivery Magazine, Issue 105 (Feb 2020), pp 8–12.
2. *Schneider A et al, "Hold the device against the skin: the impact of injection duration on user's force for handheld autoinjectors". Expert Opin Drug Deliv, 2020, Vol 17(2), pp 225–236.*
3. *Simpson I, "The New Emerging Needs Driving Autoinjector Development". ONdrugDelivery Magazine, Issue 113 (Oct 2020), pp 20–24.*
4. *Bedford T, "Emerging Trends in Wearable Drug Delivery". ONdrugDelivery Magazine, Issue 111 (September 2020), pp 17–20.*
5. *Shaked T, "Evolution of an On-Body Bolus Injector: From Drug-Specific Device to Platform Technology". ONdrugDelivery Magazine, Issue 100 (September 2019), pp 20–24.*
6. *De Hann S, "Company Showcase". ONdrugDelivery Magazine, Issue 100 (September 2019), pp 66–67.*
7. *Fiorini P, "Large-Volume Injectors: Rise in Biologics Brings Challenges". ONdrugDelivery Magazine, Issue 105 (February 2020), pp 47–50.*

ABOUT THE AUTHORS

Brian Li, PhD, Chief Executive Officer at MicroMED, has over 18 years of experience in both business and engineering development with medical device and drug delivery start-ups in ophthalmology and biotechnology in both the US and Taiwan. Dr Li has co-led fundraising activities and M&A deal negotiations resulting in successfully closed deals with leading pharmaceutical/biotech firms. Dr Li has 30+ technical articles and 40+ granted patents worldwide in biomedical microdevices. His research in ophthalmic implantable micropump was awarded Best Paper at a major MEMs conference.

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Kuang-Hsiang Cheng is a mechanical engineer and leads the medical device product design in MicroMED. His work involves early-stage research and development for design and manufacturing. Mr Cheng specialises in 3D modelling and is an expert in product development for medical device microcomponents. He graduated with a Bachelor's degree in mechanical engineering from National Yunlin University of Science and Technology, Taiwan.

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Wen-Chi Huang is responsible for the project management of the product development in MicroMED. She has over four years of experience in high-end tea branding and sales activities in the tea production industry and has a Bachelor's degree in economics from the National Central University, a top-ranking business school in Taiwan.

TACKLING PARENTERAL DRUG LABELLING'S SURGING COMPLEXITY

Lars Skole, Managing Director of LSS Labelling Systems Scandinavia, discusses emerging trends and challenges associated with growing parenteral packaging and labelling complexity – and how pharmaceutical developers and manufacturers can meet the challenges ahead.

Pharma and biotech development is expanding at a tremendous rate following sustained growth of pharmaceutical-based healthcare around the world. To maintain health and deal with chronic disease, more people are taking prescriptions and over-the-counter (OTC) medications than ever before.

Billions of doses will continue to be dispensed from basic packaging. But millions more doses will be delivered to patients in single-unit doses and specialised functional combinations that marry the drug with the delivery device – or the patient to a personalised therapy.

PACKAGING'S NEW ROLE IN THERAPEUTIC PERFORMANCE

For a long time, most consumer drug labelling involved mass-scale printing and application operations and the high-speed capacity to efficiently mark the packaging of large quantities of common products. Most drugs were packaged in very simple primary containers – essentially, jars and bottles for oral solid dose drugs and vials for liquid or parenteral medications.

A pharmaceutical packaging market study by Freedonia Group in 2020 notes the increasing importance of packaging as more sophisticated therapeutics penetrate the market.[1] Study data shows an expanding use of what was termed "high-value" containers, closures and accessories, with the goal of drug developers "to enhance drug delivery and security and promote better patient adherence with prescribed medication schedules".

> "Clearly labelled and marked primary drug packaging and devices help clinicians and patients accurately administer treatments and simplify delivery, especially for parenteral injectables."

PERSONALLY ADMINISTERED PARENTERALS GROWING

In its report "Pharmaceutical Packaging – Demand and Sales Forecasts, Market Share, Market Size, Market Leaders", Freedonia projects that parenteral containers (injectable, infusible liquid therapeutics) will post the fastest rate of growth among primary pharmaceutical packaging.

The analysts say advances in parenteral therapies for cancer, diabetes, viral diseases, neurological disorders and similar conditions will support gains in the segment. Accordingly, the report says the use of prefillable syringes – especially self-administering combinations like epipens – are expected to grow the fastest. However, vials will continue to be parenteral drugs' dominant package form for the foreseeable future.

CLEAR LABELLING HELPS SIMPLIFY DRUG DELIVERY

Clearly labelled and marked primary drug packaging and devices help clinicians and patients accurately administer treatments and simplify delivery, especially for parenteral injectables.

Many of these combination devices have limited label real estate and challenging surface characteristics and are tough to label. These circumstances explain why parenteral labelling, in particular, is growing more complex and technically challenging.[2]

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MORE INDIVIDUAL PRODUCT LABELLING REQUIREMENTS ON THE HORIZON

Freedonia notes trends favouring the use of smaller-sized medication containers and single-unit dosing will increase the overall number of labels pharmaceutical manufacturers will be processing for a given product. This number, according to Freedonia, will also be magnified by the increases in the overall quantities of drugs produced.[3]

All of these development trends are pointing to one thing: higher numbers of more discrete product lines and more frequent but smaller batch sizes – all of which drive vial and parenteral labelling operation complexity. Regardless, there is a desire from contract packagers and pharma manufacturers to have more flexible lines (Figure 1).

LABELLING KEY TO PATIENT CENTRICITY AND BETTER OUTCOMES

Driving the development of all drug products is the concept of patient centricity. Essentially, that means providing people with affordable access to safer, more effective drugs that deliver better results more efficiently than alternatives like surgery or a hospital stay.

> "Requirements for labelling prescription drugs are extensive because regulators want to provide both the prescriber and user with the best information in support of administering the medication effectively."

Requirements for labelling prescription drugs are extensive because regulators want to provide both the prescriber and user with the best information in support of administering the medication effectively.

Patients are increasingly administering their own parenteral treatments as well. To pharma and its regulators, that means clear markings, instructions and safety or administration guidance must appear on the label and be legible on the package at the point of care.

Labelling plays an even more critical role in dose compliance and is an inherently patient-centric strategy because it assures the precise prescription and dosing by physicians and accurate administration and delivery by clinicians and patients. Several studies have shown a clear correlation between dose compliance and improved health outcomes, as well as a lowering of the overall cost of care for a given condition.

Patients who can't or won't take their medications often get sicker, requiring expensive hospitalisations or surgeries.[4] When patients take their medications as prescribed, they get better faster and at significantly lower cost to payers.

SECURITY IN THE SPOTLIGHT

Among other things, the covid-19 pandemic has put parenteral drug supply chain security in the spotlight, so expect greater attention to labelling and labelling operations in support of supply chain integrity and resiliency in this area from all players.

For example, every primary package (vial or combination device) and label now carries information that assures both source and quality to global regulators. Label technology is also offering other security functionality to help assure supply chain integrity, including heat-sensitive and smart labels to thwart drug counterfeiting and diversion.

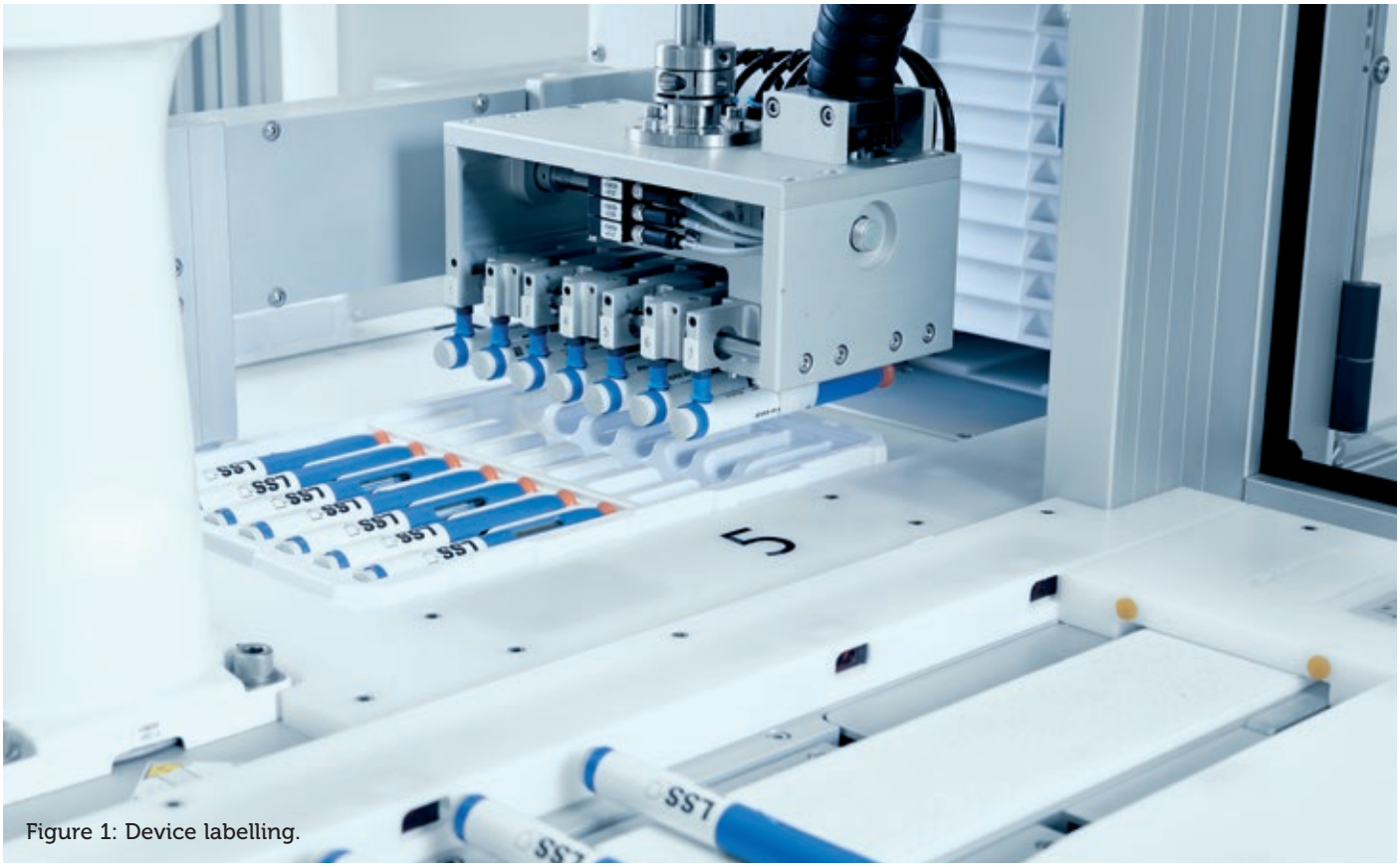

Figure 1: Device labelling.

Pharmaceutical companies, notes Freedonia analyst Mike Richardson, will be increasing their purchase of label technologies featuring high visibility and tamper-evident features, because the perception of safety enhances the perception of product value. He says these value-added labels are finding increased use in the OTC drug segment, where greater competition is boosting demand for labels that enhance the perceived value of products.

Freedonia says this trend will shift consumption towards label technologies with enhanced security features such as radio-frequency identification tags, serialisation codes, holograms, colour-shifting inks and other anti-piracy measures.

INDUSTRY 4.0 AND DATA INTENSITY

Serialising pharmaceutical packaging with an individual product identifier is now law in most established global pharma markets. This and a number of variables related to primary packaging – including its size and the product's data and physical handling requirements – are making labelling and marking operations more challenging to manage effectively.

In the face of Industry 4.0 and global serialisation compliance, companies are compelled to either develop and implement labelling operations that meet their products' packaging and labelling complexities or hire commercial partners who can. Either way, pharma and biotech manufacturers need access to sophisticated systems capable of integrating digital and information technologies currently disrupting pharma manufacturing and supporting data acquisition requirements.

MEETING REQUIREMENTS REQUIRES INTEGRATION AND EXPERTISE

Finding and integrating the capacity and capabilities to handle anticipated demand and meet emerging data requirements will likely be challenging manufacturers the most. Capable technologies are available but acquiring systems in high demand takes time, as buyers reserve their place in the production queue. Delivery time for new equipment and completing internal validation can impinge on timely access to processing and manufacturing systems.

Manufacturers are seeking faster, more flexible machines with increased throughput and integrated quality assurance technologies. Because many of the new biologic drugs are parenteral, including pandemic-fighting vaccines, they require processing in highly controlled cold environments (as low as -80°C in some cases). This is placing even more technical demands on labelling operations that require developed, integrated technologies to accomplish.

> "In the wake of the pandemic, and as current trends gain momentum, specialised vial and device labelling equipment procurement will become an imperative."

In the wake of the pandemic, and as current trends gain momentum, specialised vial and device labelling equipment procurement will become an imperative – all of which calls for defining the purchasing strategy.

When talking with suppliers, the dialogue needs to be open and forthcoming to determine optimal system specifications that create a comprehensive solution purchase and not just an equipment buy. Pharma's regulatory environment is one of the strictest there is – and that increases the need to develop a robust procurement strategy.

SPEED IS KEY, ACCURACY AND QUALITY ESSENTIAL

Pharma and biotech developers are under pressure to respond faster to market demands. That means timing the delivery of needed capability is critical. Details of the machine, the number of systems purchased and other variables also help set the timeline – as does the order book of the vendor. All of these variables can add weeks and months to delivery timing and clash with business plans if not sorted beforehand.

Purchasing capital equipment is a challenging process in its own right. It needs to be done with a straightforward, planned approach to ensure the investment is not wasted. Aligning manufacturing business interests with experienced vendors who have already considered the above will yield the best machine for the investment and meet the projected demands of global markets and the needs of patients around the world.

ABOUT THE COMPANY

For more than 40 years, LSS (Labelling Systems Scandinavia) has delivered automatic labelling solutions around the world and for all kinds of pharmaceutical products. Its individually designed and customised labelling solutions meet the unique requirements of the pharmaceutical industry. With decades of experience in developing, designing, manufacturing and installing pharmaceutical labelling machines, the company's versatile solutions range from simple offline systems and automatic label dispensers to integrated labelling systems that interface with other equipment and software. It has standard solutions for vials, ampoules, small bottles, syringes, autoinjectors, pens and boxes.

REFERENCES

1. *"Pharmaceutical Packaging – Demand and Sales Forecasts, Market Share, Market Size, Market Leaders". Report, Freedonia, April 2020.*
2. *"New Regulations And Safety Complicate Drug Labeling". Pharmaceutical Online, July 2, 2018.*
3. *"Pharmaceutical Label Demand to Grow Over 7 Percent Annually Through 2020". Pharmaceutical Processing World, February 8, 2017.*
4. *Claxton AJ, Cramer J, Pierce C, "A systematic review of the associations between dose regimens and medication compliance". Clin Ther, 2001, Vol 23(8), pp 1296–1310.*

ABOUT THE AUTHOR

After more than 15 years leading technology companies and 12 years devoted to the packaging industry, **Lars Skole**, Managing Director of LSS, has deep experience of integrating labelling technologies and systems to create high-performance packaging operations. He has an MSc degree in Technology Management from the University of Aalborg (Denmark) and international experience developing comprehensive labelling solutions for label manufacturing (converting) and marking and labelling primary pharmaceutical packaging, including parenterals, prefilled syringes, autoinjectors and combination devices.

INJAY: SIMPLE BY CHOICE, ADAPTABLE BY DESIGN

In this article, Arnaud Guillet, Vice-President Business Development at Biocorp, discusses Biocorp's Injay solution for adding connectivity to a wide variety of PFS devices, focusing on how Injay's designed-in simplicity and flexibility makes it easily applicable across the spectrum of PFS platforms on the market today.

INTRODUCTION

Traditionally used primarily for vaccines and anticoagulants, prefilled syringes (PFS) have now gained broad acceptance as delivery systems – especially for the delivery of biologics for the treatment of chronic conditions such as rheumatoid arthritis, multiple sclerosis and Crohn's disease – that require the repeated administration of medication. As a result, there has been a boom in the PFS market in the past few years. The global PFS market is expected to reach US$10.57 billion (£7.7 billion) by 2027. At the same time, the need for connected solutions in the drug delivery space is growing, especially because of the impact of the covid-19 pandemic and the increasing dependence on, and acceptance of, telemedicine.

But the application of digital connectivity to drug delivery devices isn't easy, specifically for PFSs, where costs and usability challenges are fierce. Besides, PFSs are available in various formats, sizes and materials, and they can be used in conjunction with different tools, such as finger flanges or safety systems, with strong consequences on their overall form factor and usability performance. In that context, simplicity, flexibility and adaptability are paramount to bring a successful connected solution for PFSs to market.

Injay has been designed with these challenges in mind. The technological proposal is extremely simple, based on the combination of two components that can be implemented in many different ways, while providing the same reliability and delivering the same benefits to end users (Figure 1).

"The application of digital connectivity to drug delivery devices isn't easy, specifically for PFSs, where costs and usability challenges are fierce."

Figure 1: Bicorp's Injay – a flexible solution for connected PFSs.

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SIMPLE BY CHOICE

The value proposal of Injay for patients and healthcare providers (HCPs) using PFSs is extremely simple, deliver the right product, the right way, at the right time:

- The Right Product: Critical product information (product reference, concentration, batch number, expiry date, syringe unique ID) are stored on an NFC tag located on the syringe piston rod. This information can be read before injection using a standard reader or a smartphone equipped with NFC-reading capabilities to check the characteristics of the product.
- The Right Way: Injay detects a complete injection when the piston rod is pushed down to the stopping point, thanks to an activator located in the syringe finger flange.
- The Right Time: After injection, users scan the data with the NFC reader to register the complete injection with a specific time stamp and link the information with the treatment plan.

Injay follows basic requirements to make it easily implementable:

- Injay must not require any modification of the syringe barrel or any other critical components of the syringe (RNS, stopper, needle, etc.).
- Injay must not affect drug filling.
- Injay must not modify regular user experience and impact injection process.

The technological proposal is even simpler, based on two components: an NFC tag and an activator. In the standard Injay configuration, the NFC tag is located on the syringe piston rod and the activator on the finger flange, which makes it by design compatible with all standard PFSs, regardless of their materials (plastic, glass), needle formats (staked needles, luer lock, luer cone) or size (0.5 mL, 1 mL long and short, 2.25 mL or other specific sizes). But other configurations can be explored to meet specific requirements, such as compatibility with certain safety systems.

ADAPTABLE BY DESIGN

Safety systems have slowly become a must. From the regulatory standpoint, both EU and US authorities have implemented specific requirements around needlestick protection, EU Directive 2010/32/EU – "Prevention from Sharp Injuries in the Hospital and Healthcare Sector" and the US Needlestick Safety and Prevention Act (2000). From a user standpoint, this issue has become critical, not only in hospital settings, where the frequency and repetition of injections performed by doctors and nurses increase the risks of needlestick injuries, but also for patients delivering their treatment at home, for whom safety has become a primary concern. As a result, the syringe safety-systems market is booming and market penetration of these devices is rapidly growing. Delivering a connected solution compatible with those systems has therefore become a must.

Compatibility of Injay with integrated passive safety systems, such as Biocorp's Newguard, Stevanato Group's EZ-fill® (Padua, Italy) or Gerresheimer's Gx InnoSafe® (Düsseldorf, Germany), is obvious and the standard format can perfectly apply in this configuration. Compatibility with add-on options, such as BD Medical – Pharmaceutical Systems' UltraSafe Plus™ (Le Pont-de-Claix, France) or Nemera's Safe'n'Sound® (La Verpillière, France) is significantly more challenging, specifically when such systems feature their own specific piston rod, which is entirely part of their technical dossier. In that configuration, the standard format of Injay cannot apply as any modification on the piston rod will impact the safety-system regulatory dossier and the ability to implement an activator in the finger flange component is highly dependent on the add-on form factor.

> "Injay is designed around an NFC tag for product ID and an activator to detect a complete injection. The location, position and interactions of these components is not carved in stone, and could be designed in many different ways."

This is where the simplicity and adaptability of Injay comes into play. Injay is designed around an NFC tag for product ID and an activator to detect a complete injection. The location, position and interactions of these components is not carved in stone, and could be designed in many different ways. The intellectual property (IP) filed on this technology actually allows this flexibility and protects different configurations. Thanks to the inherent flexibility of the technology, the scope of IP protection and Biocorp's strong delivery device engineering capacities, Injay's design can be adapted to a variety of safety devices, while guaranteeing the same value proposal for end users and complying with the same industrial constraints.

CONCLUSION

When it comes to connected options for drug delivery devices, Biocorp wants to keep ease of implementation as one of its primary requirements. Injay is very much in line with this principle, thanks to its design simplicity. Injay is an effective, economically viable solution applicable for any PFS, whatever the use case.

ABOUT THE COMPANY

Recognised for its expertise in the development and manufacture of medical devices and delivery systems, Biocorp has acquired a leading position in the connected medical device market, thanks to Mallya. This intelligent sensor for insulin injection pens allows reliable monitoring of injected doses and thus offers better compliance in the treatment of diabetics.

ABOUT THE AUTHOR

Arnaud Guillet is Vice-President Business Development at Biocorp, in charge of finding partnerships and licence opportunities for Biocorp's range of connected devices. Previously, Mr Guillet worked for a healthcare consulting firm with a strong focus on connected health strategies for pharma and insurance companies and has additional past experience in the pharmaceutical industry with Sanofi and the insurance industry with AXA (Paris, France). He graduated from HEC Paris (France), a major European business school.


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