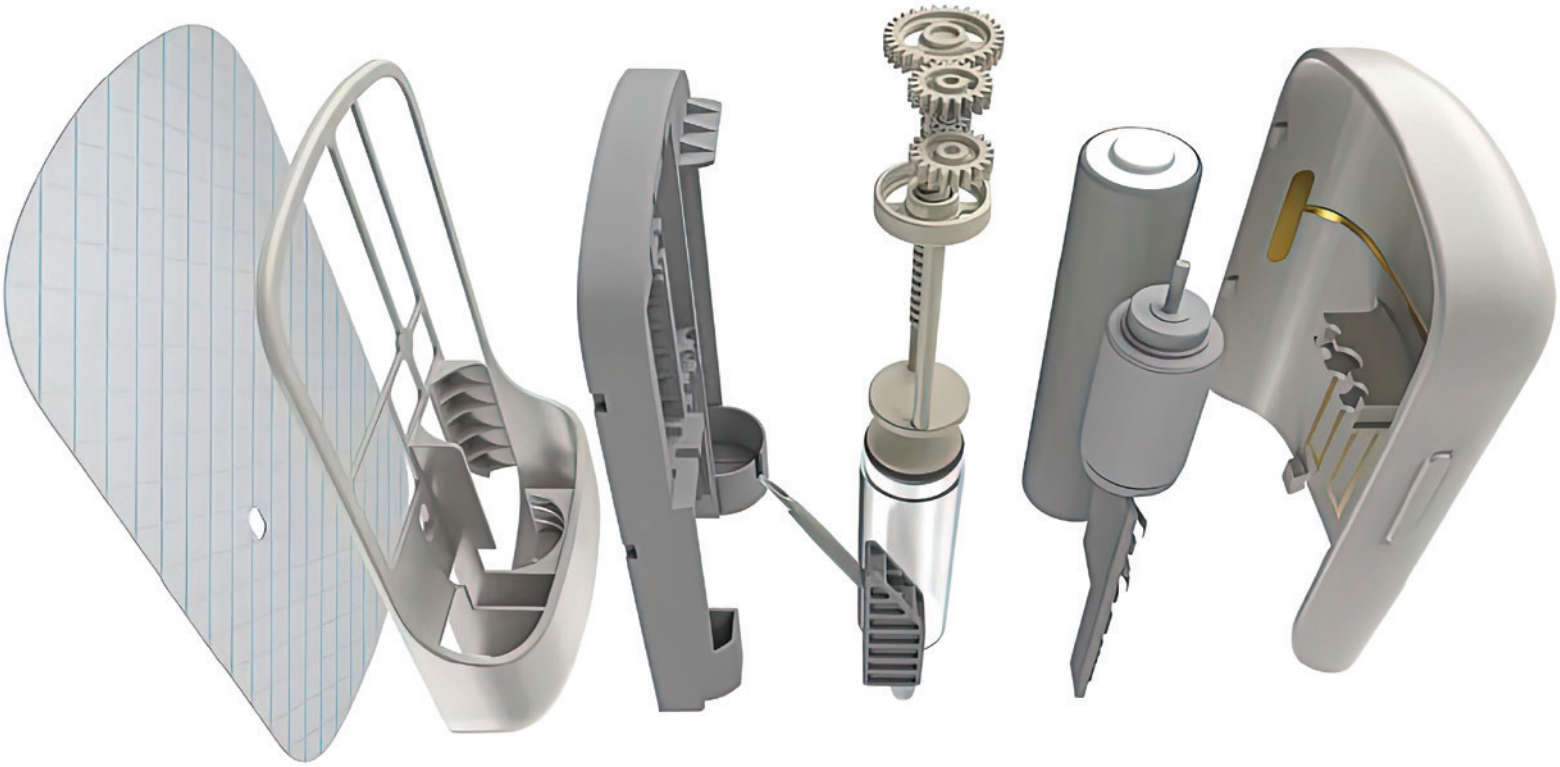
WEARABLE INJECTORS

ON drugDELIVERY



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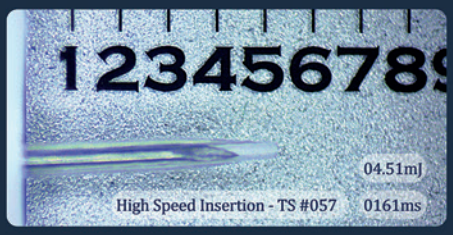

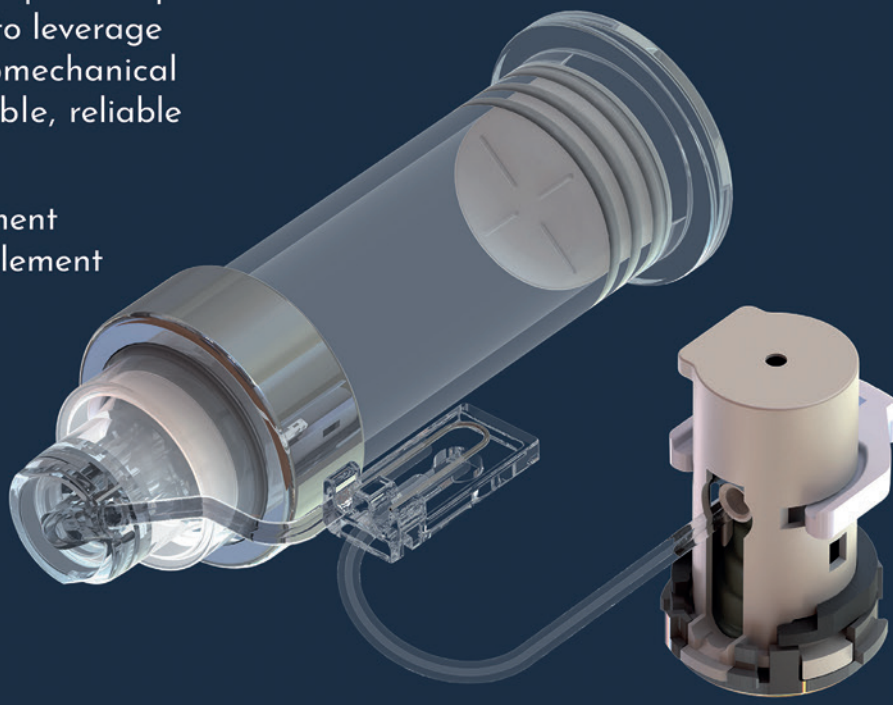

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ONdrugDelivery Issue N° 124, September 14th, 2021

WEARABLE INJECTORS

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YPSOMED SELFCARE SOLUTIONS

YPSODOSE – SIMPLIFYING LARGE-VOLUME PATCH INJECTIONS

In this article, Ian Thompson, Vice-President Business Development at Ypsomed, provides the latest insights into the YpsoDose prefilled and pre-assembled patch injector as it moves into the industrialisation phase for clinical trials.

PREPARING A NEW PLATFORM FOR CLINICAL TRIALS

The YpsoDose patch injector has been developed in response to the significant increase in demand for new large-volume subcutaneous therapies. These new therapies are usually antibody-based and have payloads of up to 1000 mg that require a 5–10 mL fill volume. Therapies in this category include treatments for autoimmune diseases and orphan and rare diseases, as well as for the delivery of immuno-oncology drugs.

Various comparative studies have confirmed that patients and healthcare providers (HCPs) prefer a prefilled and pre-assembled device that increases convenience. Beyond the immediate advantages of convenience, safety, correct dosing and time saving, pharma customers particularly like that the user is unable to manipulate the drug container before or after the injection event. Ypsomed has drawn on its experience with prefilled pen injectors and autoinjectors to develop a modular and customisable platform to speed up time-to-clinic, lower up-front investment costs and lower project risks for pharma partners.

INNOVATIVE SOLUTIONS FOR SAFE AND SIMPLE HANDLING

For very infrequent injections, the number of use steps, and thus complexity, must be minimised to ensure that all users will remember the correct handling for their device even with a lengthy timespan between injections. Accordingly, simplicity and safety are key requirements for a patch injector, and this is reflected in the YpsoDose design. Being prefilled and pre-assembled, handling is reduced to two simple steps – patch and inject.

> "Simplicity and safety are key requirements for a patch injector, and this is reflected in the YpsoDose design."

The innovative solutions that are core to the YpsoDose platform are all very closely linked:

- **10 mL Cartridge:** The drug is filled into a 10 mL glass cartridge, cartriQ® from SCHOTT (Mainz, Germany), that uses standard-dimensioned components, including a standard 13 mm coated stopper and a coated plunger. The stopper is protected by a sterile barrier during storage, which is removed immediately before use when the patch release liner is removed.
- **Needle Unit:** The needle unit contains the fluid path, including the cartridge needle and injection needle that allow the drug to be administered. Customisation of the injection needle is an important option to accommodate more viscous drugs or faster injection times. The needle unit is fully mechanical, and its functionality is controlled by the electromechanical drive mechanism.

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- **Sensing Patch:** The capacitive sensing patch ensures that YpsoDose is correctly attached to the skin during the injection process and signals if YpsoDose is removed prematurely. Most importantly, immediately prior to injection, during the removal of the patch release liner, the needle unit's sterile barriers are also removed.
- **Electromechanical Drive:** Above all, the drive mechanism and electronics provide safety, reassurance and flexibility. Safety due to direct links to the needle unit and sensing patch; reassurance to the user based on clear feedback; and flexibility to accommodate different drug fill volumes, viscosities and injection times.

YpsoDose's functionality has been fully tested according to the relevant parts of the current draft of "ISO/FDIS 11608 Needle-based Injection Systems for Medical Use – Requirements and Test Methods", including "Part 6: On-body Delivery Systems".

COLLABORATIVE APPROACH WITH EXPERIENCED PARTNERS

In order to develop a ready-to-use 10 mL glass cartridge, it was important to build up the requisite know-how with experienced partners. In 2020 Ypsomed, SCHOTT and Lonza (Basel, Switzerland) announced the YpsoDose patch injector collaboration (Figure 1). The three companies are co-operating closely to develop all the necessary components and manufacturing processes. The comprehensive solution includes the ready-to-use cartriQ® glass cartridge from SCHOTT as the primary packaging for the drug, the YpsoDose patch injector platform from Ypsomed and the processes for filling, assembly and testing of the final product by Lonza Drug Product Services (Figure 1).

Figure 1: YpsoDose represents a collaboration between Ypsomed, for the patch injector design, SCHOTT, for the ready-to-use glass cartridge, and Lonza, for filling, characterisation and final assembly services.

This collaboration brings together three experts in their respective fields. All the processes and components of the solution are predeveloped, co-ordinated and tested. The 10 mL ready-to-use cartriQ® from SCHOTT requires fewer process steps during filling than conventional cartridges. Lonza Drug Product Services applies its expertise in process development, testing and characterisation, and provides filling and assembly services for YpsoDose in Stein (Switzerland) to provide short implementation times for customers. Pharma customers thus receive a tested and documented overall solution and can concentrate on their core business.

BOX 1: YPSODOSE PATCH INJECTOR OVERVIEW

Designing and developing a wearable patch injector is a demanding task, requiring a broad range of technology and medical device competencies. Ideally, the infrequently used patch injector should be as easy, if not easier, to use as a disposable two-step autoinjector, which is why the prefilled YpsoDose format (Figure 2) incorporates the following key technical features and benefits:

- Prefilled and pre-assembled to avoid any need for the patient or HCP to assemble or fill the drug reservoir and device
- Adheres to the skin during injection and is easy to remove after injection
- Capacitive sensing patch only allows initiation of the injection after the skin sensor has confirmed skin contact
- Automatic needle insertion at the start and retraction at the end of the injection process, and the needle is also retracted if the device is removed from the skin before the end of injection
- Electromechanical drive accommodates a range of fill volumes and viscosities, and provides a programmable and reproducible injection time and volume for each drug
- Audible and visual feedback to clearly communicate with the user before, during and after the injection
- Integrated electronics allow wireless connectivity to provide additional patient or HCP therapy support.

Figure 2: YpsoDose, the prefilled electromechanical motor-driven patch injector.

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TRIED AND TESTED HUMAN FACTORS

Current patch injectors are generally HCP- or patient-filled or -assembled; no prefilled, ready-to-use wearable devices have been approved for use by patients to date. To ensure that patch injector therapies are widely adopted for biological therapies, usability is the most important aspect that needs to be successfully tested with patients and HCPs. During the development process, YpsoDose has gone through a number of iterations and various rounds of usability and human factors (HF) testing. The final formative HF evaluation was successfully performed in early 2021, the detailed results of which will be published shortly. The main focus of the study was to test the remaining minor product changes linked to the patch/release liner functionality and the electronic user interface.

YPSODOSE – THE LATEST SELF-INJECTION PRODUCT PLATFORM

For pharma companies to consider and invest in patch injectors, they need to be able to access reliable device technology and implement standard filling and final assembly processes that provide a solution that fulfils the needs of patients and HCPs.

> "For pharma companies to consider and invest in patch injectors, they need to be able to access reliable device technology and implement standard filling and final assembly processes that provide a solution that fulfils the needs of patients and HCPs."

> "To ensure that patch injector therapies are widely adopted for biological therapies, usability is the most important aspect that needs to be successfully tested with patients and HCPs."

Fulfilling these requirements with well thought-out device technology will allow the patch injector market to grow significantly over the coming years and to become established as the third self-injection device class, complementing the maturing markets for pen injectors and autoinjectors. The 10 mL YpsoDose has undergone thorough internal testing and comparative studies with pharma customers and Ypsomed is committed to the successful industrialisation and commercialisation of YpsoDose as a new state-of-the-art patch injector.

ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms consist of autoinjectors for prefilled syringes in 1 and 2.25 mL formats, disposable pens for 3 and 1.5 mL cartridges, re-usable pen injectors, ready-to-use prefilled wearable patch injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio.

With over 35 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases, and integrating these insights with third-party digital ecosystems.

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

ABOUT THE AUTHOR

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

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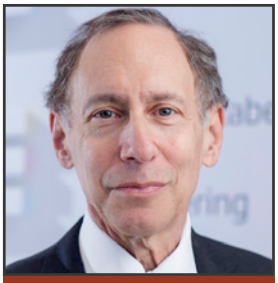

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DRUG DELIVERY: WHAT DO PATIENTS AND PROVIDERS WANT?

In this article, Matthew Huddleston, Executive Vice-President and Chief Technology Officer, and Jennifer Estep, Senior Director, Marketing & Strategy, both of Enable Injections, discuss current drug delivery options and the value of convenient care.

Worldwide, patient and provider preferences are changing due to the covid-19 pandemic. The need to reduce patient exposure to the virus and free up healthcare resources is driving unprecedented change.

For patients, providers and healthcare systems, the need for more flexible, convenient medical treatment has never been greater. While innovations that improve patient access to care evolve, understanding the needs and wants of patients and providers is more important than ever.

CURRENT DRUG DELIVERY OPTIONS

IV Administration

Consider these facts:

- The average time required to place an IV line is 13 minutes[1]
- IV placement attempts fail 26% of the time in adults and 54% of the time in paediatrics[2]
- More than one billion IV lines are used annually, worldwide[3]

Not only are patients unwilling to spend hours in a healthcare facility receiving IV infusions, covid-19 is preventing patients from going into the hospital or clinic. Creative solutions can help improve patient access to care. For example, one provider in Florida (US) has made infusions more accessible to cancer patients by creating a drive-through IV clinic. However, given the amount of time required per IV placement and the IV placement failure rate, it is not surprising that patients prefer subcutaneous (SC) delivery over IV infusion.[4]

The Step Forward With SC Administration

SC administration enables more flexible delivery options for both the patient and the provider. Current approved delivery options include syringes, autoinjectors, syringe pumps and bolus injectors, which may allow for patient self-administration. However, the full potential of SC delivery has been held back.

Availability of SC Therapeutics – To date, the number of therapeutics marketed for SC administration is limited despite the advantages SC has over IV administration.

Volume Limitations – Autoinjectors and syringes traditionally have limits on the volume of therapeutic which can be delivered, typically less than 1.5 mL. This small volume presents formulation challenges to pharmaceutical companies.

Administration Challenges – Larger volumes delivered with a syringe often require administration by a healthcare professional (HCP). Syringe pumps and bolus injectors allow delivery of greater volumes but require tubing sets, exposed needles and large, cumbersome systems.

In addition to limited therapeutics and delivery volume challenges, several myths plague SC delivery, presenting challenges to its widespread acceptance.

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THREE SUBCUTANEOUS DELIVERY MYTHS

1. Injection Time

There is a belief that the quicker the administration, the better for a patient, caregiver and provider. However, this is often not the case. If the person receiving the treatment is mobile, untethered and not feeling like a patient during an administration,[5] delivery time becomes irrelevant.

2. Number of Needles

Recent preference studies have asked patients about the number of needles that they will tolerate per dose. In the studies, patients were questioned about their preference using two different methods: one method being the completion of a questionnaire and the second method involving the administration and receipt of a dose. Upon evaluation of the results, a difference in patient response was identified. When required to administer several needlesticks for a dose, patients in the survey preferred fewer needlesticks and were less likely to state they prefer SC administration with autoinjectors or syringes.[6] In general, patients do not like to see or handle needles[7] and prefer fewer needlesticks for a single dose.

3. Need for a Permeation Enhancer

While the use of permeation enhancers has provided valuable efficiencies for in-clinic compared with traditional IV administration, multiple studies demonstrate that large volumes[8,9,10] administered into the SC tissue with the right delivery technology do not require an enhancer. The use of an enhancer requires addition of further formulation work, clinical trials, packaging and administration steps to the original therapeutic. Lastly, these permeation-enhanced products are typically delivered with a needle and syringe, relegating them to hospital/in-clinic, HCP-supervised use.

In order to deliver volumes necessary to gain therapeutic benefit and allow patients to self-administer therapies on their own, innovative new SC delivery alternatives are needed.

Figure 1: Meet enFuse – a wearable drug delivery solution.

"To deliver volumes necessary to gain therapeutic benefit and allow patients to self-administer therapies on their own, innovative new SC delivery alternatives are needed."

THE VALUE OF CONVENIENT CARE

Convenience and access to care have an impact on patient adherence to prescribed treatments – but how impactful is convenience on patient adherence? Consider the following:

- Patients want convenience. NRC Health's Market Insights[11] surveyed more than 223,000 healthcare consumers and found that 51% said convenience and access to care are the most important factors in their decision making. That's above insurance coverage (46%), doctor/nurse conduct (44%), brand reputation (40%) and quality of care (35%)[12,13]
- The US Congressional Budget Office estimates that a 1% increase in the number of prescriptions filled by beneficiaries would cause Medicare's spending on medical services to fall by roughly 0.2%[14]
- In a systemic review assessing the cost of non-adherence across 14 diseases, the annual adjusted disease-specific economic cost of non-adherence per person ranged from US$949 (£691) to $44,190[15]
- Medication adherence leads to lower healthcare use and costs despite increased drug spending.[16]

MEET ENFUSE: ENABLING ENYWHERECARE™

"The most important benefit of the enFuse platform would be the improvement of the quality of life – keeping patients out of the clinic and infusion chair." – KOL, Scientific Advisory Board of three top-10 pharmaceutical companies.

The enFuse® is perfectly suited for flexible care (Figure 1). Enable's flexible delivery model, EnywhereCare with enFuse, enables a range of delivery options for patients and providers, from in-clinic to at-home self-administration of therapeutics.

The focus at Enable Injections is on the patient (Figure 2). In the past year, the company has had the ability to learn from patients' actual experiences with the enFuse. Two clinical trials with partners have concluded successfully, and it has received an overwhelming positive response from both patients and providers. In these clinical trials, Enable Injections proved that subcutaneous delivery of large volumes – 50 mL and more – can be delivered successfully via the enFuse without the use of permeation enhancers.

For patients currently receiving care with large-volume SC delivery systems, 100% of the patients in a clinical trial reported they prefer the enFuse over their current method of SC delivery.

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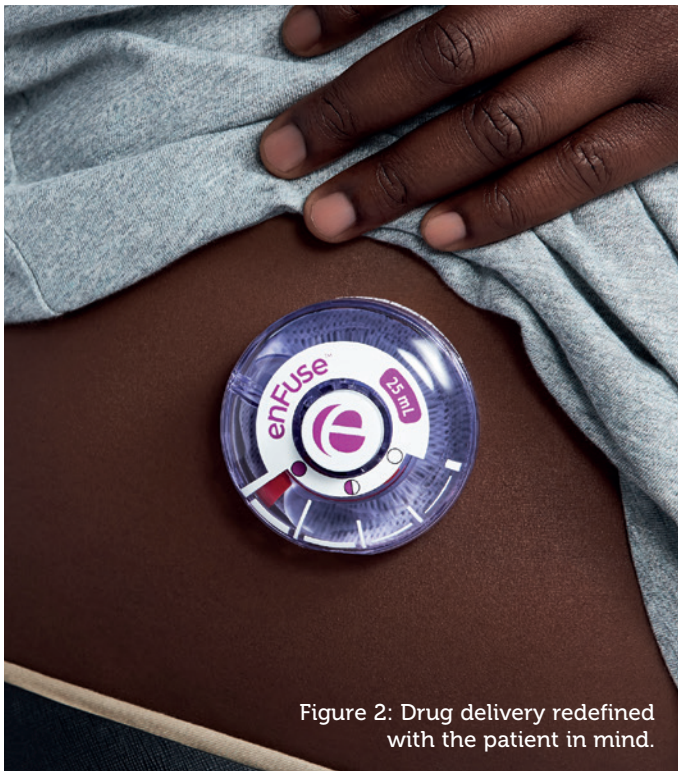

Figure 2: Drug delivery redefined with the patient in mind.

As patient care transitions to the home in a flexible care model, patients will increasingly rely on delivery technology to provide solutions to connect with their physicians and other patients, as well as provide training, reminders and validation of injection success. One of the many ways in which Enable is working to provide this type of flexibility is through the development of the Smart enFuse (Figure 3). The Smart enFuse is being developed to support next-generation patient-HCP connections and enables increased flexibility in the site of care. The enFuse allows flexibility for the patient and provider – enabling administration of therapeutics both inside and outside the clinic, including self-administration at home.

Administration with enFuse does not require a permeation enhancer. Thus, enFuse may provide advantages for pharma partners over SC products paired with permeation enhancers, including potential reduced risk, cost and time to market (Table 1). The mission of Enable Injections is to enable convenience for the patient, with the goal of making a positive difference in patient compliance and adherence.

WHAT DO PATIENTS SAY?

"It is difficult for me as a patient to feel as though someone making the decisions in pharma grasps the various intricacies of patient care. The ease of flowing back and forth between different types of applications – clinic versus home and back again – is such a key insight! The treatment centre I go to tries to model this concept – being flexible based on patient needs – but the one restriction has always been the drugs and which ones are available for administration outside the clinic. I've tried SC, but the way it had to be administered in large volumes with pre-admin of hyaluronic acid and using multiple needles, etcetera, was just impossible. enFuse is a game changer." – Patient, after education on enFuse.

CONCLUSION

Patients often say they want to feel less like a patient and more like a healthy human being. In a study of patients participating in studies during the pandemic, the option to participate in trials at home increased the respondents' likelihood of participating in trials, which helped improve the overall patient experience.[17]

The pandemic has thrown a spotlight on the need to improve the patient convenience aspects of treatment and allow for flexibility in the setting of administration, based on the physician's and patient's preferences and needs. Enable plans to continue to focus on delivering enFuse technology for its pharma partners, and on improving the patient and provider experience.

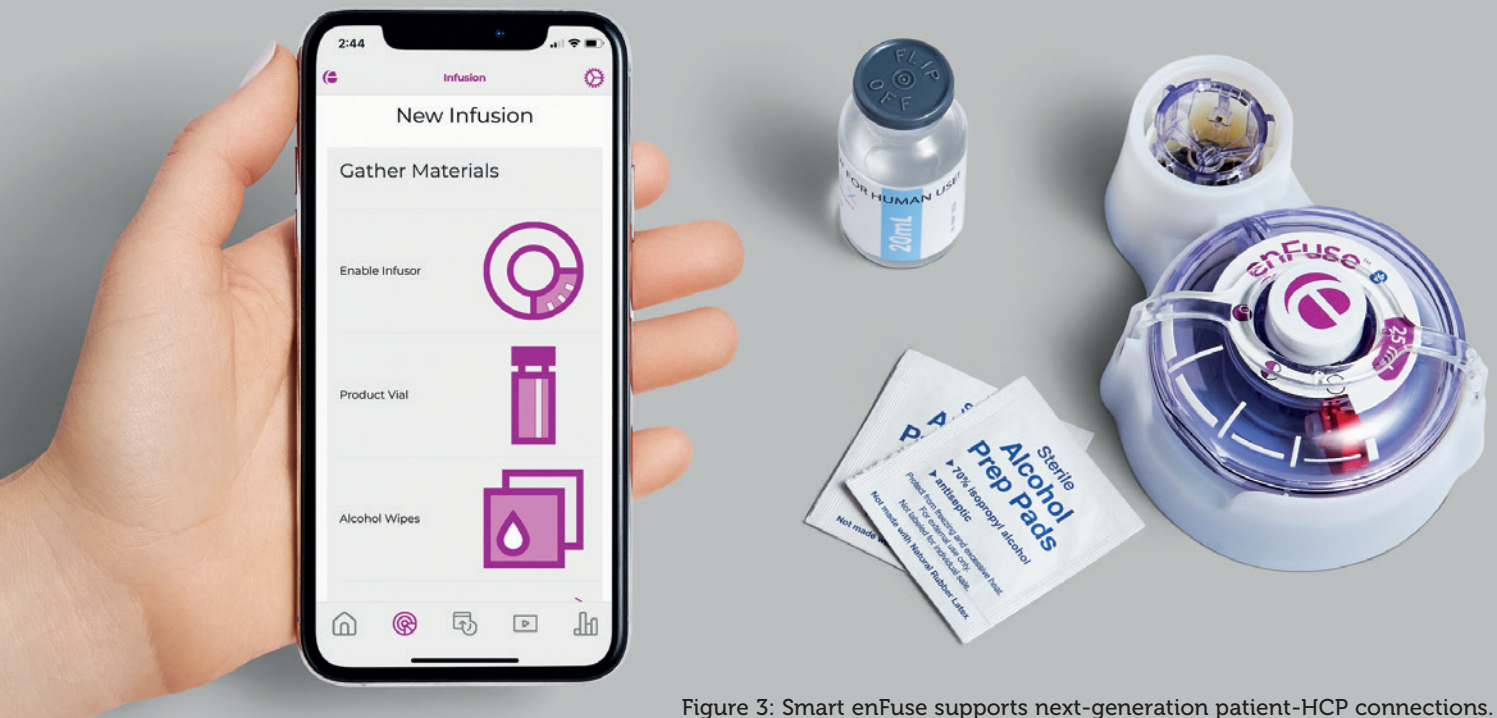

Figure 3: Smart enFuse supports next-generation patient-HCP connections.

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Route of Administration	Benefits	Disadvantages	Limitations
IV	Large volume, low-pressure delivery, extended delivery time possible	HCP required, exposed needle/catheter, difficult administration	Site of care, venous access, number of ports in patient lifetime
SC via autoinjector	Portable	Limited delivery volume, large needle, multiple injections needed for a single high dose, discomfort	Volume, high-pressure delivery
SC via syringe + permeation enhancer	Duration for in-clinic injection may be shorter than IV infusion	Must be in-clinic. May not reduce HCP time per patient – long-held injection, angle, HCPs do not prefer, additional clinical trials required, additional formulation required, large needle	Requires continuous HCP time to introduce enhancer, high-pressure delivery
SC via syringe pump	User self-administration possible, precise and extended delivery time possible	Cumbersome, patient immobile for long period of time, numerous user steps required, exposed needle sets, tubing	Difficulty of administration and steps involved, high-pressure delivery
SC via enFuse	Wearable, simple, flexible, not exposed to needle, large-volume, low-pressure delivery, small needle	Not yet available	Not an extended or precision delivery profile

Table 1: Drug delivery at a glance.

ABOUT THE COMPANY

Enable Injections is an investigational-stage company, based in Cincinnati (OH, US), developing and manufacturing on-body delivery systems designed to improve the patient experience. Enable's enFuse system delivers large volumes of up to 50 mL of high-viscosity therapeutics.

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ABOUT THE AUTHORS

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VECTRA® MT® LCP BRINGS THE ADVANTAGES OF LIQUID CRYSTAL POLYMERS TO WEARABLE INJECTORS

Here, Wim Vos, Principal Field Development Engineer, Dave Pellegrino, Principal Field Development Engineer, and Rob Haley, Global Marketing Director for Medical & Drug Delivery Devices, all of Celanese, discuss the myriad benefits of Vectra® MT® LCP, Celanese's medical-grade liquid crystal polymer, for wearable injection devices, including improved patient comfort, greater design flexibility and reduced processing costs.

Over the past several years, thinking in the drug delivery industry has seen a shift away from traditional clinic-based practices and towards a patient-centric model. This shift in thinking manifests in a multitude of ways, from an increasing focus on human factors in device design to a push towards introducing digital connectivity functionality, such as smartphone companion apps, to the world of drug delivery devices. A major result of this shift has been the rise of wearable on-body injection devices.

With a goal of increased patient convenience, whilst also tackling the conundrum of delivering high-dose, high-viscosity biologic drug formulations, wearable injectors have proven capable of delivering high volumes of formulation over an extended period of time. This method of injection offers a number of advantages, including significantly reducing the frequency of injections that a patient requires and enabling patients to self-administer at home.

However, designing an injection device to be worn on a patient's body poses its own unique design challenges. Wearable devices must be evaluated for patient comfort because, unlike any other drug delivery device, a wearable injector is adhered to a patient's body during use, often for extended periods of time. As such, these devices must be made from material that is strong and lightweight to impose a minimum of burden on the patient, and preferably be as small and discrete as possible to minimise any disruption of their daily lives. A solution presents itself in the form of liquid crystal polymers (LCPs), a polymer material perfect for the device miniaturisation desirable for wearable injectors.

> "These characteristics allow LCPs to be used to reliably and accurately produce highly complex designs. Couple this with the ability to produce thin, lightweight, high-stiffness components, and using LCPs for wearable injectors becomes a sensible and attractive option."

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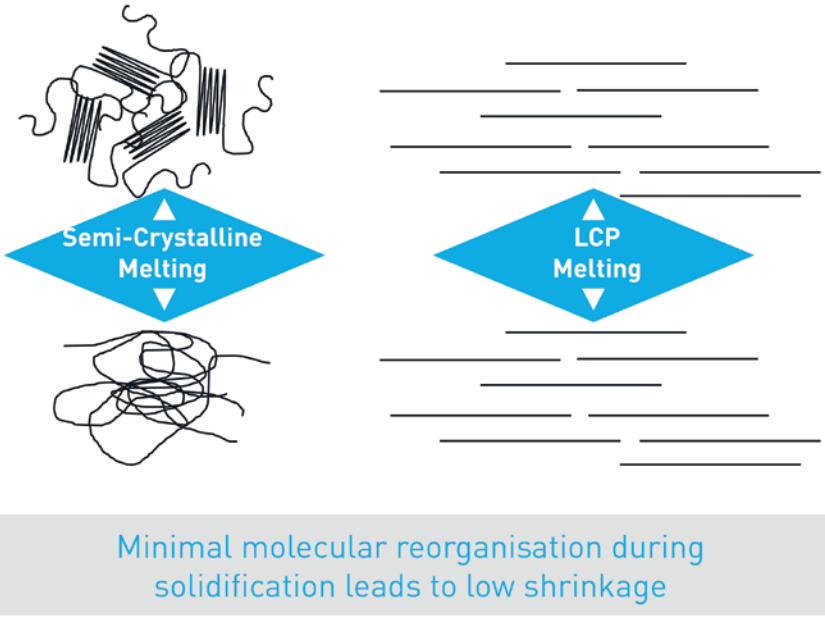

Figure 1: LCP molecules form fibrils that align in the flow direction of the material.

WHAT IS LCP?

LCPs are a family of high-performance polymers formed of rigid, self-aligning molecules. LCP molecules are shaped like a crankshaft and align with each other in concentrated bundles, resulting in fibrils that orient themselves in the direction of flow while in a liquid state and present only a small change in structure when transitioning between liquid and solid (Figure 1). This leads LCPs to act as a self-reinforcing resin or "liquid wood". LCPs retain this highly crystalline structure until they reach their decomposition temperature.

This property of LCPs results in material properties that make it ideal for use in wearable injectors. Of key significance is that the stiffness of an LCP component increases as the material is made thinner (Figure 2). This means that components can be made as thin as 0.3 mm without sacrificing stiffness; in fact, thinner walls result in stiffer parts.

LCPs also boast exceptional flowability when compared with amorphous or semi-crystalline polymers. This ultra-low viscosity has numerous benefits for the production of polymer parts. Additionally, the low latent heat of fusion of LCPs provides three key benefits:

- Fast processing
- High accuracy
- Very low tendency to flash.

These characteristics allow LCPs to be used to reliably and accurately produce highly complex designs. Couple this with the ability to produce thin, lightweight, high-stiffness components, and using LCPs for wearable injectors becomes a sensible and attractive option.

Also of note is that LCPs are remarkably stable. They are environmentally resistant to heat, chemicals, weather and radiation; have low moisture absorption (0.03–0.1%); are inherently flame retardant; have excellent barrier properties to both oxygen and moisture; and operate with a long-term service temperature of -196 – +240°C (340°C in the short term). Furthermore, LCPs have excellent dimensional stability with low shrinkage.

Figure 2: LCP is stiffest when the material is thinner than 1 mm.

Celanese is able to bring these benefits to the drug delivery device industry with its Vectra® MT® LCP. With decades of experience in the industry, Celanese can provide expert advice on its Vectra MT portfolio to best match the LCP grade to a customer's requirements, including varying viscosity and tribology, and offer a keen understanding of how using an LCP rather than a more traditional "default" polymer would best benefit a project.

BENEFITS OF LCPS FOR WEARABLE INJECTORS

Strong, Lightweight Material

First and foremost, Vectra MT LCP enables wearable device designers to get the most out of their design while prioritising patient comfort. The tight tolerances and ability to use thinner components without sacrificing stiffness means devices can be made smaller and lighter while maximising the space available inside the device for the necessary injector components and primary drug container. This provides the dual benefit of increased patient comfort and greater design freedom.

Celanese has a broad portfolio of grades of Vectra MT LCP to suit the particular needs of a project, varying the mechanical, dimensional, thermal and tribological properties of the material as necessary. This makes Vectra MT LCP the material of choice for wearable device designers looking to miniaturise their devices, making them more comfortable and discrete for the patient, without sacrificing the quality of the device or compromising the design.

Easy Integration of Electronics

Integrating electronics and connectivity is a widespread trend in the drug delivery industry, and wearable devices are no exception. Many innovative wearable devices integrate connectivity, but even those that don't frequently incorporate an electronic component to control various aspects of the injection. LCPs are already a widely used material in the consumer electronics industry, as they have humidity-stable dielectric properties, making them the material of choice for micro-connectors and precision optics.

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> "The material properties of LCPs provide significant advantages over other traditional thermoplastics when it comes to processing the material."

Vectra MT LCP combines Celanese's MT portfolio service package with a medical grade version of the LCP that has been tried and tested in the consumer electronics sector. Celanese discussed the value of LCPs for the integration of electronics into connected medical devices in greater detail in ONdrugDelivery's June 2021 issue on Connecting Drug Delivery, and that value can be readily applied to wearable injectors.

Tight Tolerances for Micro-Moulding

As mentioned previously, miniaturisation is a key consideration for wearable injectors, so complex micro-moulded parts can be critical to developing such devices. Material choice makes all the difference for manufacturing small, complex parts, as the material needs to be suitable for fine detail and strong enough to be reliable in use. As such, the tight tolerances and high stiffness at low thickness of Vectra MT LCP make it ideal for use in these complex micro-moulded parts.

High Processability

The material properties of LCPs provide significant advantages over other traditional thermoplastics when it comes to processing the material. LCPs flow exceptionally well under high shear without degrading their mechanical properties. This high flowability allows LCP to be moulded into very thin, highly complex parts with relative ease; depending on grade, Vectra MT LCP can achieve a flow length of 65 mm at a wall thickness of 0.2 mm.

LCPs also have a low heat of fusion due to their highly ordered molecular structure. As discussed previously, the structure of an LCP changes relatively little between the liquid and solid phases. This means that not only is LCP easy to process, it is fast as well. By using an LCP, the cycle time from melt injection to part ejection can be significantly reduced.

The rapid solidification of LCPs allows for minimal part flashing, which significantly increases the efficiency and reliability of processing. The low flash is also critical when producing small, complex components that are often key to wearable injector designs; low flash means fewer parts rejected for not meeting the precise dimensional requirements.

Typically, LCPs solidify very fast, meaning the injection moulding cycle is commonly 5–15 seconds for small part moulding, depending on the number of cavities in the mould. This leads to higher productivity, as rapid cycling means more parts can be produced in a single mould per unit of time, reducing the number of moulds necessary for the same output. The high flowability of LCPs means that there can be a greater number of cavities per mould, further enhancing productivity.

In contrast with other commonly used thermoplastics, LCPs render high mould temperatures unnecessary, since high shear is used to thin the resin and make it flow better. LCPs can be processed at mould temperatures below 100°C and only require water-based cooling.

Lower Production Costs and Improved Sustainability Profile

The factors that make LCPs so much easier to process naturally result in lower costs and improved sustainability. Rapid cycling of the injection moulding process and higher number of cavities per mould mean that the production rate per tool is significantly higher with LCPs than with traditional thermoplastics. The lower temperatures reduce the energy required for running the process, which, in turn, reduces costs and makes production using hot runners more feasible, which reduces waste, reduces cycle time and provides greater design flexibility.

These advantages mean that, despite the higher cost of the material itself, Vectra MT LCP can be the lower-cost option overall, compared with commonly used polycarbonates (Figure 3) while also providing the myriad benefits to processability and product quality already discussed.

Naturally, many of these cost-savings translate into an improved sustainability profile for parts made using Vectra MT LCP. For example, the lower energy cost per part directly reduces the carbon footprint of devices made using Vectra MT LCP. The high flowability and lower number of moulds required also allows for smaller machines with lower material requirements, which can, coupled with the reduced material waste from the low flash tendency and ready use of hot runners, further reduce the environmental impact of a device using Vectra MT LCP over other thermoplastics.

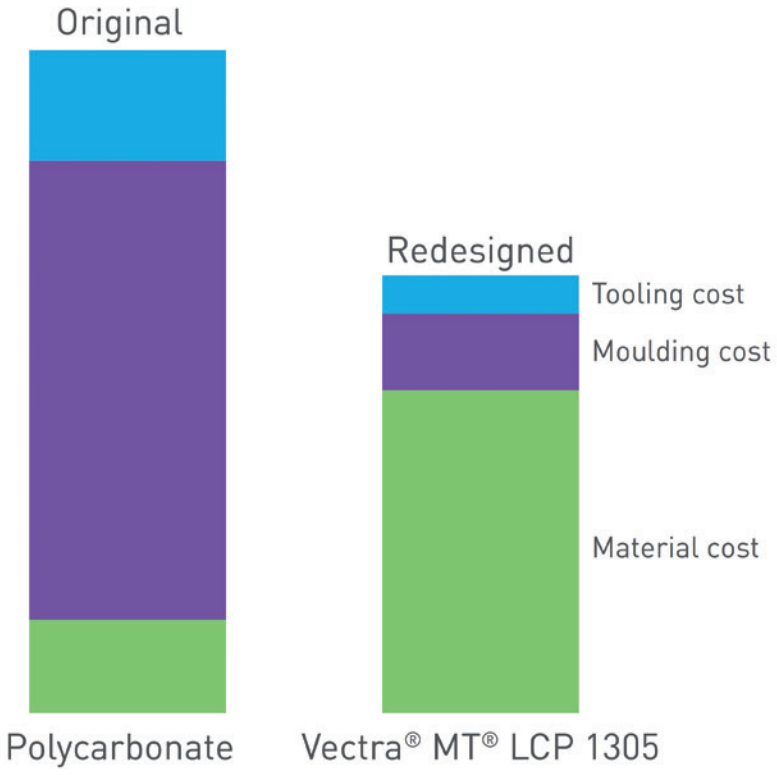

Figure 3: While the material cost of Vectra MT LCP is higher than commonly used polycarbonates, the significant cost savings resulting from its superior processability make it the lower-cost option overall.

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"The factors that make LCPs so much easier to process naturally result in lower costs and improved sustainability. Rapid cycling of the injection moulding process and higher number of cavities per mould mean that the production rate per tool is significantly higher with LCPs than with traditional thermoplastics."

CONCLUSION

It is critical in drug delivery device design to use the right plastic for the right product. When it comes to the growing field of wearable injectors, an advanced LCP polymer provides a host of benefits over the traditional thermoplastics that designers may default to simply because that is what they have always worked with in the past. As such, it's important to consult with a materials specialist to take advantage of a more suitable polymer for your product development process. The benefits that using an LCP can provide include:

- Excellent dimensional stability and tight tolerances
- Fine detail frequently unachievable with other materials
- High stiffness at material thickness of less than 1 mm
- High environmental resistances
- Strong barrier properties to both oxygen and moisture
- High processability
- Low flash tendency
- Tried and tested value for integrated electronics
- Significantly reduced processing costs
- Improved sustainability profile.

Celanese is able to provide that expertise and work with device designers to ensure that they're using the optimal polymer for their device. The company's MT portfolio service package guarantees material compliance with US FDA and EU requirements, assurance of long-term supply without a change to material formulation and support with regulatory approval. Vectra MT LCP brings together all these advantages, making it the natural fit for any wearable device designer looking to miniaturise their device, improve patient comfort, increase design flexibility and reduce processing costs.

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.

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ABOUT THE AUTHORS

Wim Vos is Principal Field Development Engineer within the Medical Group at Celanese, specialising in injection devices and wearable/on-body pump systems. He has worked within the plastic industry for over 35 years across quality assurance, R&D, technical services, Six Sigma and application development, supporting large global OEMs to develop and launch new products. Mr Vos joined Celanese in 2014 where he works closely with brand owners, designers and moulders, who, together, create new, life-saving products using Celanese's engineered polymer technologies and solutions with a focus on design and human factors.

David Pellegrino is a Principal Field Development Engineer within the Americas Medical Group for Celanese specialising in drug delivery and medical devices. He has over 35 years of experience in plastic injection moulding for the medical industry and has worked in all facets of the industry, including computer-aided engineering, design for manufacture, finite element analysis, mould flow, mould making, mould design, material selection, process development, business development, engineering and operations management. Mr Pellegrino joined Celanese in 2020 and works closely with product design firms, original equipment manufacturers and moulders to support troubleshooting of existing applications and the development of new designs using Celanese's engineered materials to ensure successful product launch.

Rob Haley is the Global Marketing Director for Medical and Drug Delivery Devices at Celanese. In this role, he helps develop and lead the strategic vision of the Celanese medical organisation to keep the team positioned with high-value products, clearly defined value propositions and opportunities to realise a healthy growth plan. He has been working in the medical device, pharmaceutical and drug delivery device space for over 14 years, serving in a range of technical and commercial leadership roles. He holds a BS in Business Management from Salem State University (MA, US) and is currently completing an MBA from the same institution.

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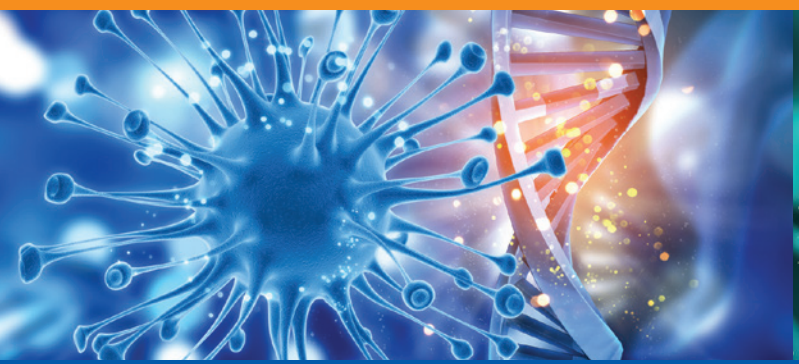

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LIFE SCIENCES

COMPLEXITY OF PATCH PUMP **ASSEMBLY** AND CONSIDERATIONS FOR MASTERING IT

In this article, Roger Nordy, Key Account Manager at ATS Automation, discusses the complexities of patch pump assembly and explains how ATS has been mastering the intricacies of the automation process to take on the growing industry demand.

According to a May 2021 report published by Fortune Business Insights, the patch pump market is expected to grow from US$3.62 billion (£2.64 billion) in 2020 to nearly $11.86 billion by 2028 – representing a 16 % compound annual growth rate (CAGR) from 2021-2028.[1] While a rise in the number of diabetic patients globally factors into this anticipated increase in demand, so too does the high degree of convenience and peace of mind patch pumps bring to users.

Instead of the traditional multiple daily injections (MDI) method of insulin delivery to maintain blood sugar levels, there is now an alternative. Patch pumps that are filled by the user, adhered to the skin and paired to a specific customised diabetes management device (much like a handheld device or mobile phone) can provide insulin delivery for more than two days.

This means patch pump wearers no longer experience several needle pricks daily, providing huge relief not only for the user, but also for the caregivers of infants, children or other patients incapable of self-administering insulin. Furthermore, when paired with a suitable glucose monitoring device, blood sugar levels can be continuously monitored. And, while

Figure 1: Patient using a patch pump for insulin delivery.

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a device that can act as an "artificial pancreas" may still be years away, patch pumps could play a key role in the development of this technology.

While the patch pump market is certainly expanding, the process of getting a patch pump (Figure 1) from the drawing board into the end-user's hands is quite lengthy. Today's patch pumps are easy to use, quite discrete, smaller than a minicomputer mouse and contain dozens of internal components that need to work harmoniously together every single time they are adhered to the patient's body. They are life-saving devices and could result in tragic consequences if they aren't functioning properly.

SIZE MATTERS

Patch pumps, while relatively small devices, are highly complex – and when a company looks to assemble and test these devices on their own production floor using automation, they must partner with a company that can manage and execute these huge programmes from beginning to end. As a result, automating the assembly, testing and pack-out is equally complex. Often, very large, integrated automation programmes occupy an entire production plant's floor space.

Putting together dozens of components in one single device requires multiple systems cascading finished sub-assemblies from one assembly cell to the next. Essentially, what you are doing is building sub-assemblies and

> "Patch pumps, while relatively small devices, are highly complex."

those sub-assemblies need to then be routed and introduced into the next system – and even the smallest nuances of change within each sub-assembly need to translate to the next sub-assembly. The entire system needs to be thoughtfully engineered and material flow must be co-ordinated perfectly, but it also needs to be flexible enough to minimise downtimes across the entire production system. Simply stated, with a highly complex system like this, a single poorly performing cell can bring the whole production line to a halt.

Imagine Zone 1 is building Widget A, Zone 2 is building Widget B and Zone 3 is building Widget C. All three of those widgets are then input into Zone 4, which is building Widget D and which then feeds into another zone and so on. For any number of reasons, when there is variability within Zone 1, the output of widget A is affected which, in turn, will affect Zone 4's performance. If you must make an adjustment in Zone 1, you might also then have to deal with the outcome of that adjustment in Zone 4 because of the newly introduced variation. This leads to a continuum of back and forth to dial in the process.

INTEGRATION CONTINUITY IS PARAMOUNT

If you were to look at a sub-assembly's flow through the system, it would quickly become apparent that the likelihood of success is linked to an integrator's ability to design, build and integrate the entire programme on their floor prior to shipment. If the integration of the equipment is attempted on-site at the production facility, the programme will likely be stalled – perhaps even to the point that you may never get the production line running.

Due to the complex nature of these types of systems, their massive footprint and the sheer number of some of the industry's brightest minds required to integrate them, ATS is a logical fit for patch pump manufacturers. Its production floor is staffed with over 1,500 people in the Life Sciences division alone, with a global network of suppliers and services.

VALIDATION STARTS AT THE DESIGN PHASE

A well-organised and comprehensive validation package is of paramount importance – and is something that regulatory agencies around the world expect. Equipment validation begins with the user requirements specification (URS). With a programme as complex as a patch pump, continuing the equipment validation effort through from the very first steps of the design phase is only logical.

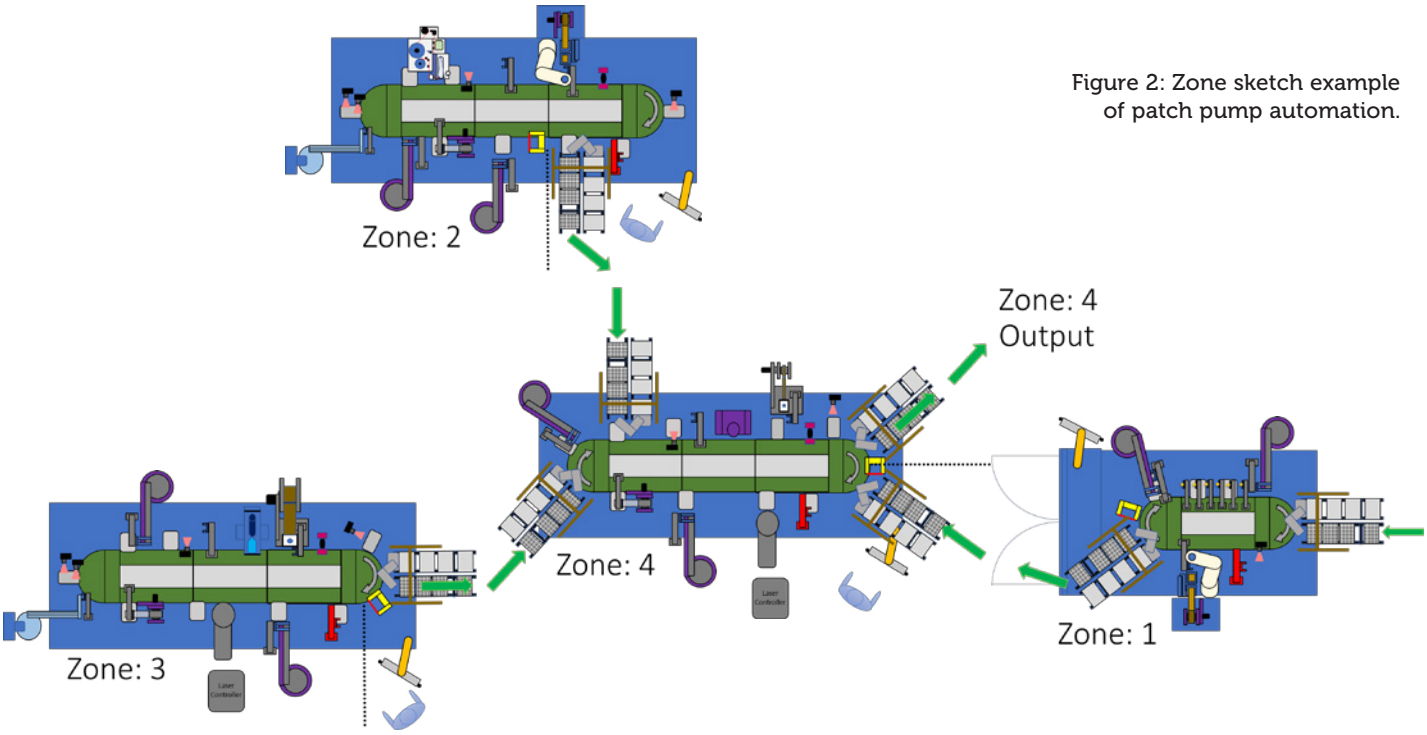

Figure 2: Zone sketch example of patch pump automation.

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It ensures that overall programme continuity is maintained, simplifying the process by gathering the relevant information along the way, and saving costs and efforts in the end. Engaging the dedicated ATS validation team at the programme's conception, even if it is just for a risk-based validation approach, puts the customer on a time- and cost-saving path to production.

FEEDING AND PART CONSISTENCY IS KEY

To state the obvious, automation will not work if you can't get the parts to the line. There are a plethora of different feeding technologies, each of which can and does take on many different form factors and commercial profiles. Effective feeding systems are essential to the success of any automation programme. The more complex the programme, the more influence (good or bad) that feeding will ultimately bring to the production floor.

Whether the parts are introduced to the line in trays, reel format, from bulk or by some other means, you must find a way to consistently get each part isolated so that it can be picked up reliably and be ready for further processing. As an example, if one of the multiple dozens of parts changes, even only slightly, it could cause performance issues within that station.

Consider the diagram in Figure 2 – a part inconsistency within Zone 1 may cause Zone 1 to struggle to run and, as a result, it will have a cascading ripple effect of struggles that will be passed along to Zone 4 and each subsequent zone after that, and therefore will affect the entire assembly and test system. Bottom line, if parts aren't consistent, it will likely have a profound effect on overall manufacturing efficiencies.

> "If parts aren't consistent, it will likely have a profound effect on overall manufacturing efficiencies."

To address some of the incoming material inconsistencies and mitigate those risks, ATS recommends a series of proof of principal (POP) tests and a customer component tolerance stack-up/ review by looping in different suppliers for the different components. It is about understanding how the components work together while learning what works and eliminating early what doesn't.

THE RIGHT TECHNOLOGIES

Over the last few years in the life sciences space, ATS has received automation requests for devices that are becoming more and more complicated. To address these challenges, innovative turnkey solutions with high modularity, scalability and customisation have been the key to the company's success. This starts with special feeding and handling technologies that move parts through flexible conveyance platforms and high-end assembly solutions to effective tray/pallet handling and packaging automation.

For patch pumps with 40 or more components, continuous functional and vision testing stations after almost every process step are essential. Due to the large footprint of these programmes, which can stretch out over various production halls, material transport also needs to be innovative. And, last but not least, manufacturing intelligence is required that is able to capture subassembly, finished product, and machine performance data over the entire production system – with artificial intelligence to avoid downtimes, react flexibly, recognise real-time risks, carry out predictive maintenance and capture all kinds of analytics from each station (Figure 3).

COLLABORATION FROM DAY ONE

While ATS has the tools and technologies to successfully complete a patch pump programme, it's not enough. The reality is projects don't finish themselves. You must

> "A successful patch pump programme is a true partnership between the customer and the automation supplier."

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Figure 3: The ATS SuperTrak CONVEYANCE™ platform (A) and the Illuminate™ Manufacturing Intelligence software (B).

drive them to completion.

A successful patch pump programme is a true partnership between the customer (or end user) and the automation supplier. ATS's project management team leverages PMI PMBOK-based principles and is a group that is focused on success. The team works in tandem with the customer on a daily basis, combing through multiple design reviews of each part of the automation. A transparent cross-company project management tool with hundreds of tasks and subtasks tracks the project's progress and any upcoming risks, delays or issues – making everything visible for everybody and defining exact responsibilities.

The customer plays a huge role in the programme's success. These programmes are a true collaboration, with each team bringing their own knowledge, tools, answers and experiences, and then openly sharing this knowledge. Over the many months of a project like patch pump assembly, the lines between the teams may become a bit blurred, but that begins to tell the story of the collective single path to success.

INSULET'S AUTOMATION PARTNER

In September 2016, Insulet publicly announced that ATS was its automation partner for its OmniPod pump.[2] This was part of a multi-year, multi-million-dollar programme.

"Utilising cutting edge technology, we will produce our product at the highest quality, and lowest cost in the industry," said Insulet in a promotional video for its new, world-class manufacturing facility in Acton (MA, US).[3] "These new unrivalled, automated production lines will directly address many current challenges in production. The automation will also drastically reduce needed labour resources and mitigate the risks associated with having a single source supply chain.

"Our product is highly complex and, as such, we need to utilise the most advanced and capable technology and talent," the video continues. "Our highly automated operation will accelerate the efficiency of our global manufacturing operations and supply chain and allow us to adapt to market conditions and innovate faster than our competitors."

ATS continues to work with Insulet today.

ABOUT THE COMPANY

The ATS Group is an automation solutions provider across various industries including life sciences, chemicals, consumer products, electronics, food, beverage, transportation, energy, and oil and gas. Its offering includes custom automation products and value-added services, including pre-automation and after-sales services, to address the sophisticated manufacturing automation systems and service needs of multinational customers. The ATS Life Sciences division develops and builds innovative automation solutions for the world´s most successful medical and pharmaceutical manufacturers. It offers end-to-end services for its premium customised turnkey solutions for medical devices, medical diagnostics and pharmaceuticals.

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ABOUT THE AUTHOR

Roger Nordy is a Key Account Manager with over 45 years of hands-on industry experience. He has a rich history of equipment design and applications engineering which he leverages every day in his selling of bespoke life sciences automation systems.

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WEIDMANN

HIGH PRECISION IN PLASTICS IMPROVES THE QUALITY OF LIFE OF DIABETES PATIENTS

In this article, Steffen Reuter, Director Engineering at Weidmann Medical Technology, discusses the importance of high precision when manufacturing injection moulded components for wearable insulin delivery devices, with particular reference to three such parts from a recent project as a case study for Weidmann Medical Technology's approach.

Today, there are more than 460 million people living with diabetes, and the number is increasing day by day.[1] As such, medical scientists and the drug delivery industry are looking for new solutions to improve the user-friendliness of insulin injections, and thus the quality of life of millions of diabetics. This is why the current trend is moving away from conventional methods of treatment – injecting long-acting and rapid-acting insulin infusions by using a pen injector – and more towards the use of automated insulin delivery (AID) devices worn on the body.[2] Such devices are preferable because they provide a continuous subcutaneous insulin infusion that attempts to simulate the natural function of the pancreas.

This therapeutic use of insulin pumps is to balance a patient's blood glucose level so that it remains as constant as possible within the required target corridor. Correct insulin management prevents major fluctuations in blood glucose levels, thus significantly reducing the risk of damage due to hypoglycaemia or hyperglycaemia. Furthermore, additional burdens on the patient's day-to-day life due to their condition are avoided, and the increased comfort of using an AID leads to greater freedom for those affected.

HIGH-PRECISION COMPONENTS

Successful diabetes therapy via continuous subcutaneous insulin infusion not only requires continuous measurement of blood glucose levels and an excellent algorithm for calculating the necessary dose of insulin according to the patient's state of stress but also a highly precise pump for delivering an accurate dose (Figure 1).

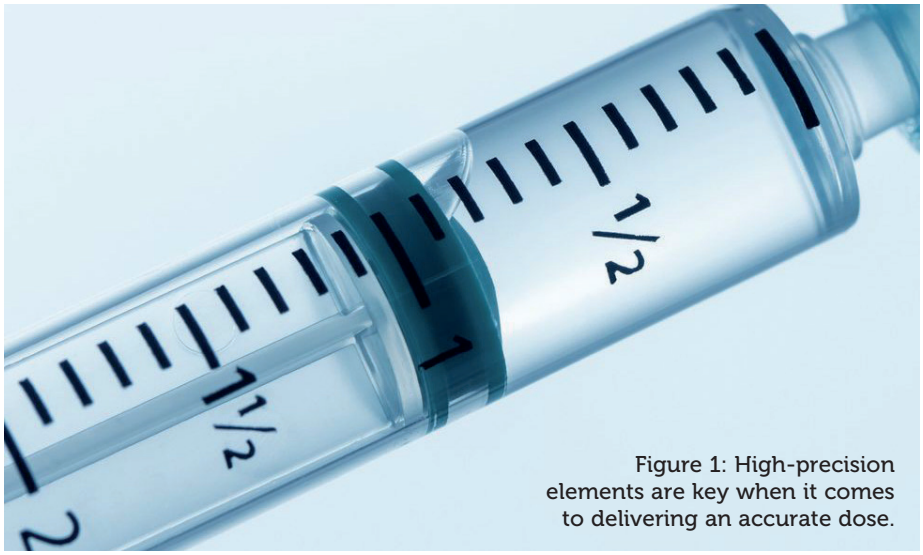

Figure 1: High-precision elements are key when it comes to delivering an accurate dose.

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"Plastic injection moulding plays a crucial role in the manufacture of such highly sophisticated components – injection moulding processes can be used to produce precise parts to a high degree of accuracy in high volumes and at low cost."

Plastic injection moulding plays a crucial role in the manufacture of such highly sophisticated components – injection moulding processes can be used to produce precise parts to a high degree of accuracy in high volumes and at low cost. Designing the right production concept, consisting of an injection moulding machine, injection mould and production periphery, is mandatory for success.

Weidmann Medical Technology supports its customers with in-house know-how in the development of production solutions for highly precise and sophisticated plastic components, applying the ISO 13485 based "Stage and Gate" development process (Figure 2). Such expertise is a requirement for realising the components needed for an AID pump.

DEVELOPING PRECISION PARTS FOR AN INSULIN DELIVERY DEVICE

Using the example of three key components for insulin delivery – the fluid reservoir, dispenser piston and dosing spindle – this article briefly presents Weidmann Medical Technology's development approach, as well as the challenges faced during product realisation.

Because the design responsibility for the product rests with the customer, the first step of good design for manufacturing (DFM) is to recognise and identify the key requirements at the beginning of the project. At this stage, it is crucial to provide the drawings and specifications from a detailed feasibility study based on computer-aided design data. Any critical requirement should be addressed, jointly discussed and agreed with the customer. If possible, all optimisations necessary for stable and robust serial production should be implemented to the part design at this point in the development cycle. The next important step is to translate those results into individual user requirement specifications for the injection moulds and production equipment.

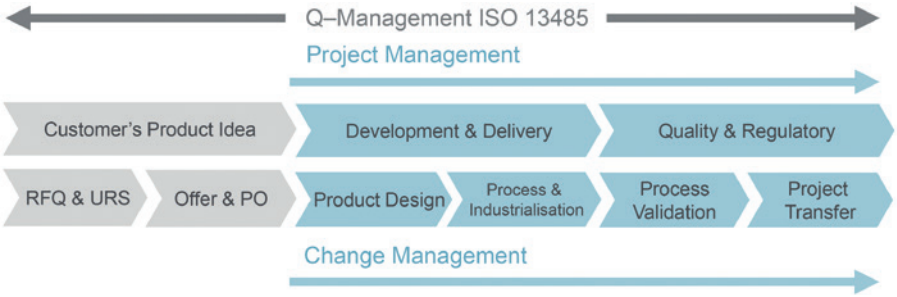

Figure 2: Stage and Gate process at Weidmann Medical Technology. Overview of the process steps for handling a client's project from the product idea to industrialisation.

Dispenser Piston

Of the key components discussed in this article, the interface of the plunger with the reservoir is the most sensitive to imprecise manufacturing. In this case, an elliptical cross-section was selected for the reservoir design in order to maximise simultaneously the level of comfort for the patient wearing the device, the size of the insulin tank and the ability for the device to be worn as inconspicuously as possible on the body. This required that the components have the tightest shape and position tolerances possible in order to position the seal precisely in the piston mechanism. On the one hand, there cannot be any leakage due to excessive play between the two components, and on the other, the sealing forces must not unduly influence the metering accuracy. The great challenge was in realising the geometric specifications and the tolerances on the component – as well the compliance with those requirements during series production.

For the reasons outlined so far, a manufacturing concept for the piston consisting of a three-plate mould with multiple cavities produced on a micro injection moulding machine was selected. Because of the low shot volumes required, such an injection moulding machine offers many advantages for achieving the maximum possible component quality – for example, through the injection of thermally homogeneous material, low-stress metering, the possibility for short flow paths, and high process and repeat accuracy.

The high-performance plastic selected for the component needed to be processed at a very high melt temperature, as well as a very high mould temperature. The knowledge in design and experience in building such high temperature moulds is of limited availability on the market. Therefore, carefully selecting a supplier is highly recommended to get the right one for the project's needs.

The complex geometry of the component required a sophisticated mould with several moving components and sliders. The moulding components needed to be precisely matched to each other in order to prevent over-moulding and burrs. To maintain the required tolerances of a few thousandths of a millimetre, it was necessary in this case to carry out the final matching of the mould on the injection moulding machine at its operating temperature. In this way, burr build-up could be significantly reduced even further.

In addition to the quality of the mould, a robust production process is equally important in order to deliver the required quality during serial production. For this reason, process development is of the utmost importance. Systematic process variations were carried out and several loops have to be performed until the "right" process had been found. Based on this, in the final step, the potential standard variations

"The knowledge in design and experience in building such high temperature moulds is of limited availability on the market. Therefore, carefully selecting a supplier is highly recommended to get the right one for the project's needs."

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Figure 3: Metal screw over-moulded with plastic.

"In the future, digitisation will make even greater inroads into medical technology. The integration of electronics in plastic components is already playing a major role, and the combination of high-precision plastic with inserted and over-moulded components will only evolve further."

of the most important process parameters were run in so-called "process windows". All parts produced in this way were measured and found to be within the required specification of the multi-stage approval process according to ISO 13485 (design, installation, operational and performance qualifications), at which point the product validation was considered complete.

Fluid Reservoir

In addition to compliance with the geometric requirements for guiding the dosing piston, the challenges with the fluid reservoir were the integration of an additional sealing lip to seal the entire system, as well as the high optical requirements of the transparent insulin tank. There are multiple different mould concepts for the production of multi-component parts such as this. When a concept is decided on, it is mounted on an injection moulding machine with plasticisation units for each resin in order to be able to produce it in the required quantities.

In this case, a multi-cavity mould was selected using core back technology. In the first process step, the cavity of the transparent insulin container is injected with polypropylene. Once that step is complete, the sealing geometry is created by pulling back a slider and then filling the reveal with a thermoplastic elastomer as a second process step. Due to the good adhesion between the two plastics, a durable seal is created. Particular attention had to be paid to the injection gate geometry of the soft component to ensure that the gate "rubs off" cleanly and that there are no unwanted protrusions.

Another important quality feature concerns the inner surface of the tank. This influenced the sliding properties of the piston seal, and therefore the metering accuracy. For this reason, a high-gloss surface is generally desirable. However, this can lead to demoulding problems – severe deformation when the component is removed from the open injection mould. To avoid this effect, which is similar to two sheets of "sticky" glass, the cores are withdrawn before the mould is actually opened. In this way, the injection-moulded insulin reservoirs can be easily removed from the mould by means of a gripper and placed on the cooling conveyor belt. From there, they are packaged in blisters ready for shipment.

Dosing Spindle

The third sophisticated component of an insulin pump referred to in this article is the helical dosing spindle. The interface between the dosing spindle and the driving element that was designed by the customer was as a plastic head. This meant that the metal screw had to be inserted into the injection mould and then over-moulded with plastic resin (Figure 3). The shot weights required for this also lent themselves well to the use of another micro injection moulding machine. However, the associated automation required so much space that it would only fit on a standard injection moulding machine. One reason for this was that was the metal screws were delivered in blisters and then had to be placed back into blisters after over-moulding, a process that required a significant amount of machinery to automate.

Because of the need to use a standard injection moulding machine, the use of a very small metering screw for plasticisation was required. Additionally, in order to achieve the necessary injection shot volume, the mould inserts of the ball heads were filled using a cold runner manifold and the mould needed to have a large number of cavities. In turn, this further increased the effort and space required for automation!

Key to implementing automation for the process was ensuring the exact alignment and pre-positioning of the screw, so that the threaded screws were inserted precisely into the mould to prevent any unwanted over-moulding of the mould cavities. Furthermore, the screws had to be inserted and fixed in the designated cavities in such a way that they would not lose their position when the mould was closed, otherwise severe damage to the mould cavities, or even a total failure of the mould, could occur – an outcome that needed to be avoided at all costs.

To ensure the insulin pump's high dosing accuracy, the screw was designed as a fine thread. It was imperative that it was not damaged during the multi-stage handling process under any circumstances, otherwise it could result in the insulin pump malfunctioning. Extensive tests with different grippers were conducted for removal from the blister, insertion into and removal from the tool, and storage in order to find the right design. In this way, it was possible to realise the required fast movement speed of the handling robots, which was necessary to achieve the desired cycle time, without losing the inserts or damaging the spindle's thread.

CONCLUSION & FUTURE OUTLOOK

In the future, digitisation will make even greater inroads into medical technology. The integration of electronics in plastic

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components is already playing a major role, and the combination of high-precision plastic with inserted and over-moulded components will only evolve further. The experience already gained in projects, such as the one discussed in this article, will help to industrialise high-precision components in future implementations.

Weidmann Medical Technology offers solutions from a single source. This is because the company uses a holistic approach to find the right balance between the necessary complexity (a combination of injection moulds and automation systems) and economic efficiency in the industrialisation of highly demanding products. A great deal of experience and passion in implementation are necessary to correctly assess the complexity of a project and to find sophisticated, tailor-made solutions for the customer, as demonstrated by the examples outlined here.

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; and high-volume plastic consumables. It has production sites with ISO Class 7/8 clean rooms in Switzerland and Mexico.

Weidmann Medical Technology is part of the Weidmann Group, a major global supplier of technical products with a history spanning more than 140 years. The Group employs almost 3,000 people across 30 production sites and service centres worldwide.

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ABOUT THE AUTHOR

Steffen Reuter has over 18 years' leadership experience in medium-sized companies in the plastic industry. He is very well experienced in project and product development and refers to himself as a mechanical engineer with a passion for plastics. Mr Reuter holds a degree from the University of Munich (Germany) and is member of the "VDI Fachausschuss Spritzgiessen" (VDI Injection Moulding Technical Committee).

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Publication Month	Issue Topic	Materials Deadline
October 2021	Prefilled Syringes & Injection Devices	DEADLINE PASSED
October/November	Drug Delivery & Environmental Sustainability	Oct 1, 2021
November	Pulmonary & Nasal Drug Delivery	Oct 7, 2021
December	Connecting Drug Delivery	Nov 4, 2021
January 2022	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 9, 2021
February	Prefilled Syringes & Injection Devices	Jan 6, 2022
March	Ophthalmic Drug Delivery	Feb 3, 2022
April	Pulmonary & Nasal Drug Delivery	Mar 3, 2022
April/May	Drug Delivery & Environmental Sustainability	Mar 17, 2022
May	Delivering Injectables: Devices & Formulations	Apr 7, 2022
June	Connecting Drug Delivery	May 5, 2022
July	Novel Oral Delivery Systems	Jun 2, 2022
August	Industrialising Drug Delivery	Jul 7, 2022
September	Wearable Injectors	Aug 4, 2022

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EXTENDING CONTAINER CLOSURE INTEGRITY TO WEARABLE INJECTORS

In this article, Shaun Devitt, Director at Neuma, looks at how the principles and methods of container closure integrity might be adapted for wearable injectors.

For many in the drug delivery and pharmaceutical industry, container closure integrity (CCI) is understood to be a major – even foundational – element of product quality. For newcomers and innovators, its scope and achievement can be a mystery. As we move into a new paradigm of complexity and capability with wearable injectors, how will the principles and methods of CCI be adapted and incorporated to enable a new generation of therapies?

CCI: A KEYSTONE ASPECT

To develop a systematic understanding of CCI, it is best to start with a definition. From the US Pharmacopeia (USP) Chapter 1207, "Container closure integrity is the ability of a package to prevent product loss, to block micro-organism ingress, and to limit entry of detrimental gasses or other substances".[1] To break that down further, CCI is a characteristic of a container regarding its function of containing and protecting the product it holds. Of note, the requirements expected of the container are driven by the product and what is a detrimental level of product loss or product exposure for that specific application. Therefore, no container can universally "meet CCI" without a product context and, indeed, some container formats are fundamentally incapable of meeting particularly stringent product needs.

Furthermore, these requirements defining CCI draw from the full span of quality attributes, embodying both product safety (block microorganism ingress) and efficacy (prevent product loss and limit entry of detrimental substances). When expressed in this fashion, the rationale for CCI to have high and ever-growing importance for both manufacturers and regulators becomes self-evident.

CCI AND TRADITIONAL CONTAINER FORMATS

Maximising container integrity at all costs is not without its drawbacks, however. An idealised "perfectly integral" container subsequently has the functional issue of ease of access to the product. Consequently, the industry has actually moved away from the ideal over time to provide more usable and accessible modes of delivery. This progression of products is depicted in Figure 1.

Figure 1: Trajectory of traditional drug containers – ampoules, vials and syringes – sustaining CCI, improving usability.

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"Leak test methods should be selected based on an appropriate sensitivity and means of challenge relative to the requirements."

What could be a more ideal container closure than a single-component glass ampoule? And yet, the only way to access the drug is to snap off the glass cap, with the risk of introducing glass particles and thus possibly compromising safety or efficacy. While ampoules retain their place in many applications, vials and, more recently, syringes have come to dominate new product containment.

Now multiple components create the container, with increased potential for ingress at the sealing interface. In the case of syringes, there are also multiple locations of ingress as well as a dynamic (sliding) seal. With each step of increasing complexity, the requirement for maintaining CCI does not change, but the demonstration of its fulfilment (both in development and in routine manufacturing) becomes more extensive. This has included the CCI testing of seals at the edges of specification for dimensions as well as environmental conditions (such as storage of vials under cryogenic temperatures for some covid-19 vaccines). And since CCI is defined by the drug product and not the container, evaluations and verifications for these well-established formats are still ongoing as new products with greater needs are developed.

CCI TEST METHODS

How then is CCI measured or verified through testing? Many test methods have been developed to meet the needs of the wide range of container formats and integrity requirements now present. All containers leak at some level, but the purpose of an integrity test is to discern if a leak rate can occur that would violate the CCI requirements of a particular product. So the leak test methods should be selected based on an appropriate sensitivity and means of challenge relative to the requirements.

Many guidance documents have now been produced describing the available methods and their suitable applications, such as USP <1207>.[1] Traditionally, the focus was on directly proving that the container was blocking microorganism ingress, with the test approach being microbial exposure through forced air or liquid exposure followed by a sterility test. Subsequently, testing has moved to physical leak tests, such as vacuum decay or mass extraction, which can give the same assurance faster and with greater repeatability and reproducibility.

But, in many cases, the product requirements for limiting entry of detrimental substances can result in different or stricter criteria for test methods. In these cases (for example, oxygen-sensitive products) other test methods such as tracer gas detection or laser headspace analysis must be employed. Through the accounting of the full scope of CCI, it is atypical that any single test method will be sufficient for a combination product. So the objective in selection should be method suitability for a requirement rather than a universal "best" CCI test method.

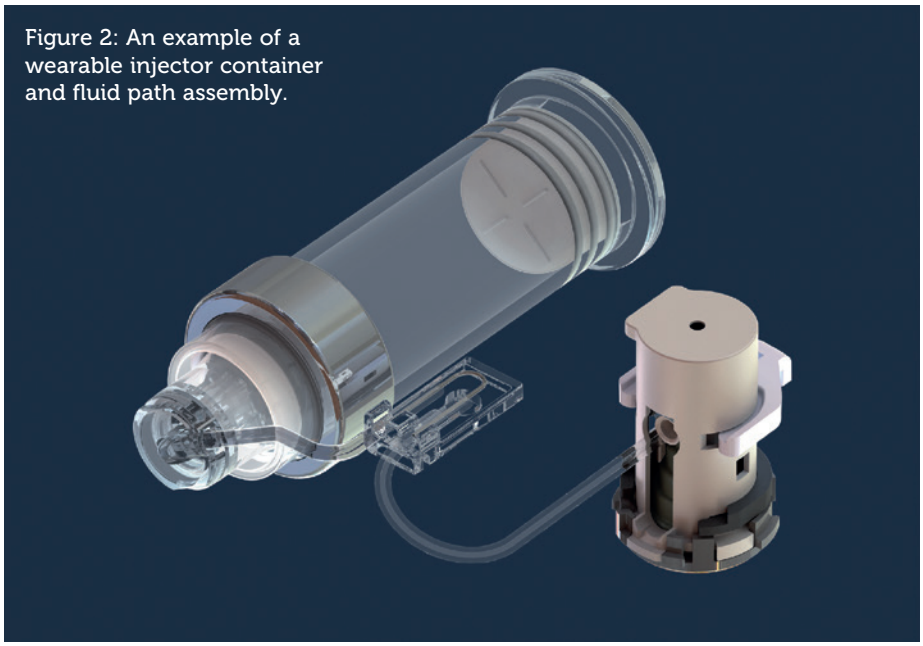

Figure 2: An example of a wearable injector container and fluid path assembly.

WEARABLE INJECTORS: A MENAGERIE OF CONTAINERS

Wearable injectors represent a large part of the next generation of drug delivery devices after syringes/cartridges and the devices that use them (such as autoinjectors and pen injectors). They promise a new degree of accessibility and usability, delivering larger volumes over longer durations and even controlling the time of start and finish – and possibly even communicating all this back to a monitoring system.

To achieve these varied aims, manufacturers have elected a wide range of container sizes, materials and formats. The sheer variety can be seen through a quick perusal of this very edition of *ONdrugDelivery*. Some wearable injector systems are based around traditional containers such as vials and cartridges. Some use elements of syringes or syringe components. Others seek inspiration from large-volume parenteral containers such as IV bags, form/fill/seal packages or other flexible pouches. And others still have elected entirely novel packaging and sealing constructions – or at least novel for drug delivery systems.

Just like in the expansion to prefilled syringes, these new containers will have to demonstrate fulfilment of CCI even as that requires significant alteration or extension of the established test methods. Even where the primary containers have hewed closely to established container forms, such as the cartridge shown in Figure 2, the additional functionality of the wearable injector system can create new requirements for evaluation.

Like many other wearable injectors, the system shown in Figure 2 has a fluid path assembly between the container and the patient needle. This new assembly is not the primary container (as drug is not stored long term within it) but it is still, however briefly, a drug container; certainly, the element of CCI for "preventing product loss" must apply to the fluid path. Thus, wearable injectors are bringing not only forms of containers to combination products but also new dimensions of the extent of the container system.

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WEARABLE CCI: SAME PRINCIPLES, MORE CONSIDERATIONS

While the novelty of most implementations of wearable injector containers has been noted, this does not portend a massive revolution in CCI standards or testing methodologies. While many test methods will need to be revised or extended to accommodate new geometries and materials, the core test principles (whether vacuum decay, laser headspace, dye penetration, etc) will retain their particular effectiveness. As containers get larger, there will be a shift in the test sensitivity, with some methods affected more than others. In some cases, where the container is particularly novel, the specific deterministic test methods now in force for standard containers may not readily apply.

For example, some materials of construction may have outgassing or permeation characteristics that incorrectly impute leaks in tracer gas or vacuum decay tests. Or extreme aspect ratios or container mechanical properties may prohibit adequate repeatability and reliability at the necessary sensitivity. In these cases, the fallback remains of "direct proofs" of CCI through microbial challenge and liquid dye immersion. However, in these cases, a container redesign should be strongly considered, since these test methods have known limitations, and this is quite possibly just one of several areas where product design, however elegant, is inhibiting quality assurance and quality control.

However, the most significant area of change is the further multiplication of considerations to be accounted for in a holistic reckoning of CCI. Many wearable injectors introduce new sub-assemblies that qualify as containers even if they are not primary containers. Depending on the conditions and duration of use, these sub-assemblies may need to meet requirements for not only product loss but also microbial ingress and contaminant ingress.

Wearable injectors can also be exposed to a wider range of environmental exposures up to and through end of use, including potentially long periods of on-body wear. Wherever feasible, suitable simulated-use testing can demonstrate CCI while mitigating the testing burden. In every case, it is critical to manage each element of CCI separately so that the aims are met for the new system without adding undue burden.

"Many wearable injectors introduce new sub-assemblies that qualify as containers even if they are not primary containers."

CONCLUSION

CCI is a foundational aspect of combination products that impacts assurance of both product safety and efficacy. Over decades, many tests have been developed for the various parenteral containers today – there is no "best test" or one-size-fits-all solution. As wearable injectors expand drug delivery therapies, they bring new dimensions to this established field: modified test methods, new classification of containers and more complicated conditions for CCI assurance. This greater sophistication in container requirements only highlights the irony that CCI is not about containers at all: it is about patients and products, and what is necessary to ensure their successful interaction. Wearable injectors are poised to offer new levels of functionality, usability and patient outcomes to make this extension of testing and assurance more than worthwhile.

"CCI is not about containers at all: it is about patients and products, and what is necessary to ensure their successful interaction."

ABOUT THE COMPANY

Neuma is an engineering services company focused on the development of robust, verifiable, reliable and manufacturable drug delivery devices. Experience includes work on novel, custom and platform adaptations across prefillable syringes, autoinjectors, reconstitution devices and wearable injectors. In July 2021, Neuma was acquired by Kymanox Corporation – a professional services company providing extensive services offerings with a focus on pharmaceuticals and combination products.

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ABOUT THE AUTHOR

Shaun Devitt is a product development engineer with nearly a decade of experience in developing drug delivery devices and related processes. He has worked on the product and process development of novel parenteral packaging, including reconstitution systems and wearable injectors. This work has extended to a focus on sterilisation and sterility assurance process development, especially for new forms of products and packages where traditional approaches were not feasible. Mr Devitt co-founded Neuma in 2017, where he has worked with a skilled team of mechanical, electrical and container science experts to transform innovative technologies into viable drug delivery solutions.

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TACKLING HIGH-VOLUME ADMINISTRATION CHALLENGES WITH A SMART, SUSTAINABLE ON-BODY INJECTOR PLATFORM

In this article, Séverine Duband, Marketing Director, Drug Delivery Devices at Nemera, introduces Symbioze, Nemera's novel on-body injector platform device, comprising a reusable main unit and disposable prefilled drug container, and offering a balance between the need to deliver advanced formulations at high volumes and the desire for patient-centric ease-of-use that enables patients to self-administer their therapies at home.

Over the last decade – driven by significant innovations in APIs, drug compounds, formulation technologies and manufacturing processes – drug administration has become increasingly complex, with significant changes in pharmacokinetic profiles (viscosity, volumes, physiological properties, stability, etc), and, based on the current outlook, this is an accelerating trend. This rising complexity has generated several challenges from both the perspective of both the drug and the device side.

In parallel, major market trends have emerged,[1] such as:

- Rising prevalence of chronic diseases
- Shift towards at-home care
- Growth in the biologics market
- Connected health technologies
- Shift towards value-based care.

All of which are opening the pathway for a new generation of injectable devices (Figure 1).

CHALLENGES FACING MODERN DRUG DELIVERY DEVICES

Within this continually evolving environment, a recurring issue that generates a need for innovation in drug delivery systems is the increasing volume of drug required for each administration. Whereas the gold standard for self-administration used to be the 1–3 mL range, more and

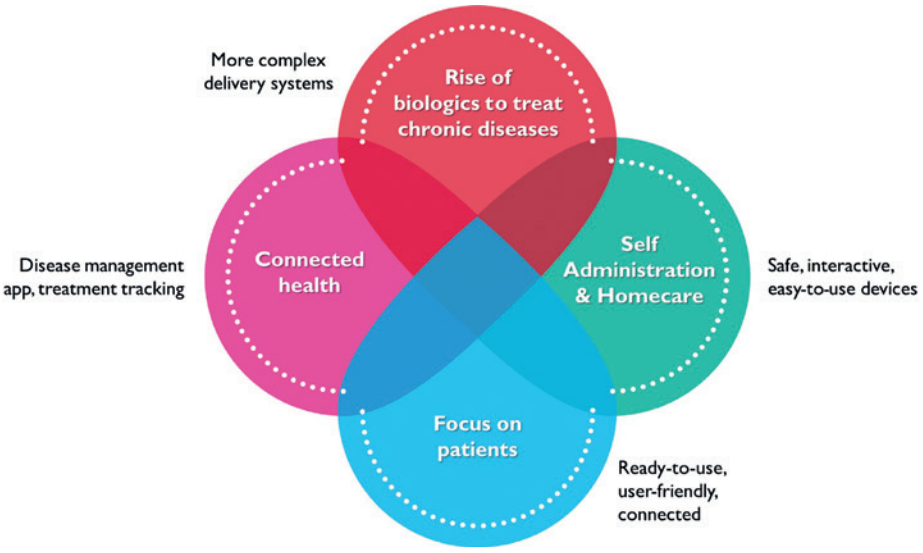

Figure 1: Major market trends impacting the parenteral space.

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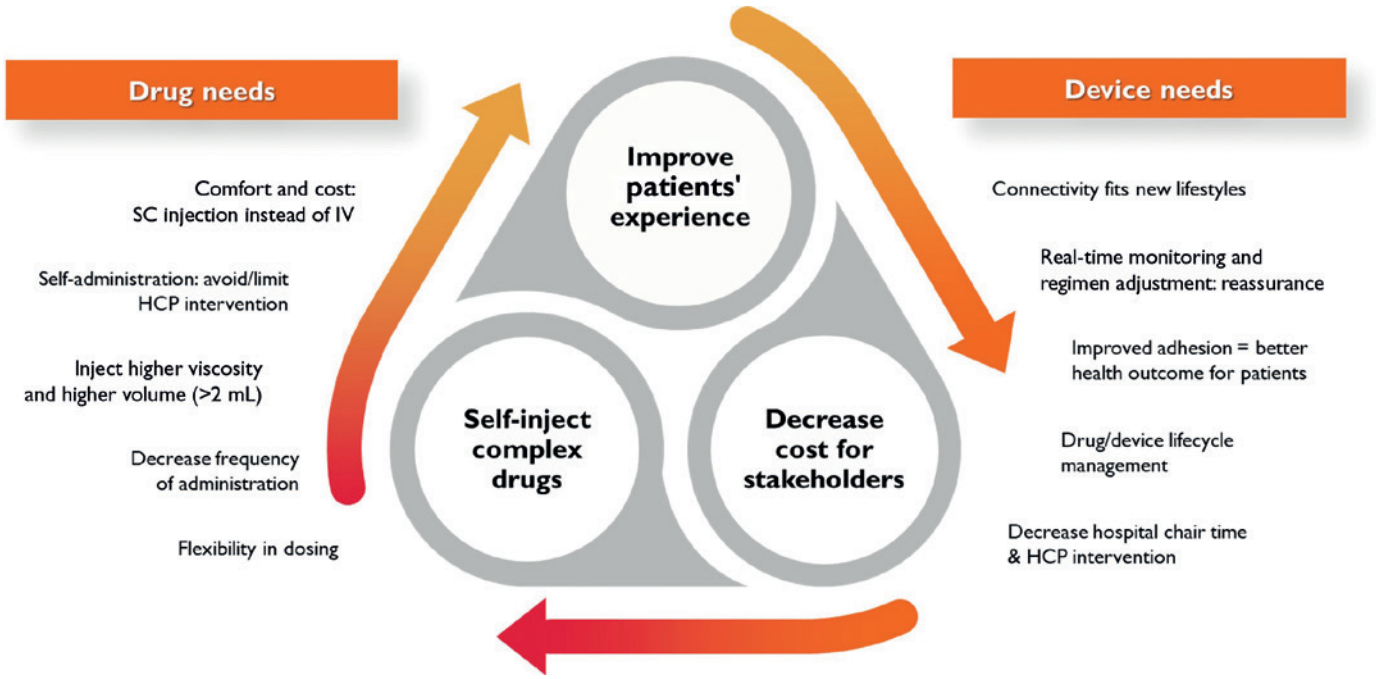

Figure 2: OBDSs are often the only option to tackle drug administration and device delivery constraints.

more treatments now require volumes of over 5 mL per injection, with some even requiring volumes as high as 20 mL. This is driven mainly by:

- The high molecular mass of certain drugs, especially monoclonal antibodies (mAbs).[2]
- Manufacturing challenges on fill-finish lines, leading to the need to dilute the formulation, thus increasing its volume
- Increased concentration of formulations in order to decrease the required frequency of administration.[3]
- New treatments requiring high dose volume linked to patients' body weight, such as immunoglobulins.

Another substantial advance in the injectable space is the ongoing shift from intravenous (IV) to subcutaneous (SC) delivery routes.[3,4] This move from IV to SC brings many benefits, including:

- Reducing time spent in hospital, or avoiding the need for a healthcare professional altogether, which relieves patients from the burden of frequent visits to clinics and decreases cost for payers.
- Decreasing the risk of adverse events, such as systemic infections, blood clots and air embolisms.
- Allowing a less-invasive procedure, increasing patient acceptance of and adherence to their treatment.
- Offering the option of self-administration, which gives greater control to patients in managing their therapies.

This shift has been further accelerated by the covid-19 pandemic, with a strong push for medications that can be administered at home to avoid unnecessary exposure to the virus at healthcare facilities and to free up medical care resources. With a growing number of patients seeking independence and convenience in managing their treatment, the push for self-administration is inevitably growing stronger.

Finally, the frequent use of self-injection devices, combined with the adoption of "smart" connected devices, is adding a further layer of complexity and increasingly raising concerns around their environmental impact. With the majority of marketed connected devices today being fully disposable, electronic waste management and device disposal are creating safety and sustainability issues for the industry.

> "Within this continually evolving environment, a recurring issue that generates a need for innovation in drug delivery systems is the increasing volume of drug required for each administration."

Therefore, the question that presents itself is how best to answer these challenges while still providing patients with the best possible care? Is there a solution capable of accommodating a high-volume SC injection with a seamless, sustainable and successful self-injection device?

DELIVERING LARGE VOLUMES AT HOME IN A SUSTAINABLE AND USER-FRIENDLY WAY

Even with the variety of injectable devices already developed and commercialised, it is no easy task to select a suitable solution for the delivery of complex, large-volume drugs that also enables patient self-administration, or at least at-home administration. Whilst there are several easy and ready-to-use offers available for patients to choose from to self-administer their medication,[4] these are very often limited in the drug volume that can be injected:

- The largest standard size of prefilled syringes (PFS) is limited to 2.25 mL
- Injection pen devices can usually only deliver drugs in cartridges up to 3 mL
- Autoinjectors are usually based on either a cartridge (1–3 mL) or a PFS (1–2.25 mL).

Therefore, if the drug volume needs to be above 3 mL, then the only available option is an on-body delivery system (OBDS). However, OBDSs usually involve a pump-based administration, which comes with its own set of challenges, mostly user- and environment-related (Figure 2).

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Traditional pump-based systems are complex devices and often come with a difficult set-up process involving a drug transfer operation, lots of tubing and requiring a sterile setting. As such, their use often requires the involvement of a healthcare professional or ends up being a real burden if the patient attempts to regularly self-administer.

More recently, a new generation of patch-pump devices has been launched, demonstrating significant progress in miniaturising components and making the use steps easier. These devices help to enable deported devices to be self-administered at home. However, these solutions still suffer from some limitations:

- Drug volumes are often limited to 5–10 mL
- Device set-up frequently involves a drug transfer operation or inserting a prefilled primary drug container into the device
- Electro-mechanical components (pump engine, sensors, connectivity) are embedded in the device and must be disposed as hazardous waste, which is neither cost-effective nor sustainable.

In short, even current wearable device options are creating hurdles for both patients (risk of use errors with drug container manipulation, complexity limiting adherence and therefore treatment efficacy) and for pharmaceutical companies (complex manufacturing processes, poor sustainability footprint), which could limit the adoption of such devices. Nemera has been striving to find ways to answer these needs, and has recently developed an innovative solution to reconcile the need for large-volume injections with the desire for self-administration in a user-friendly and sustainable platform.

Figure 3: Symbioze – Nemera's on-body injector platform.

"The Symbioze smart wearable platform is Nemera's latest development in injectable devices, designed to reconcile the injection of complex drugs with stakeholders' most demanding needs."

NEMERA'S SYMBIOZE ON-BODY DELIVERY SYSTEM

A Differentiated Approach in the Wearables' Landscape

The Symbioze smart wearable platform (Figure 3) is Nemera's latest development in injectable devices, designed to reconcile the injection of complex drugs with stakeholders' (patients, healthcare provider and payers) most demanding needs. Combining a robust design with ease-of-use, connectivity and sustainability, Symbioze fosters patient adherence by way of a seamless and enhanced injection experience. This innovation is specifically tailored for the administration of complex drugs, such as biologics, by means of a highly engineered, reliable drug delivery system. It is suitable for very large volumes, up to 20 mL and beyond, while preserving formulation integrity – critical for mAbs.

Another major differentiator for Symbioze in today's landscape is the choice to go with a disposable unit and a reusable system housing the main drive module (Figure 4). The benefits of a reusable part are two-fold:

- **Sustainability:** OBDSs usually involve electro-mechanical components, for both injection control and connectivity purposes. Embedding those into a reusable unit offers a more favourable environmental footprint, especially with regard to the device's waste management profile.
- **Cost efficiency:** As it is designed to be used multiple times, using Symbioze is a profitable choice, especially in a value-based care environment that often involves expensive therapies. This is even more beneficial when targeting medications requiring large administration volumes.

The drug product is contained in the disposable part, with the drug container already prefilled and preloaded for patient safety and ready-to-use convenience. An embedded recognition system ensures that drug information verification is shared between the reusable and disposable elements.

As the target of Nemera's OBDS is to be able to accommodate a wide range of applications, adopting a platform approach was a must. Symbioze is designed with enough flexibility to be adjusted to meet the needs of any pathology, targeted patient population and drug posology. This also enables multiple uses of the device with a portfolio of therapies, leveraging its reusable benefit for pharmaceutical players.

Symbioze offers a unique drug delivery system including following benefits:

- Adaptable to several drug volumes and viscosities
- Adjustable injection speed
- Injection control and failure mode control
- Fully integrated engine in reusable core system.

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Figure 4: Symbioze consists of a reusable main unit and a prefilled, preloaded disposable module containing the drug.

At the Crossroads of Industry and Patient Needs

From the start, the Symbioze OBDS was developed with the goal of finding the best possible compromise between meeting pharmaceutical industry standards and patient needs. OBDSs are both highly complex devices and still novel to the healthcare industry, with only a few drug/device combination products registered and marketed. Therefore, it is critical to stay within the industry manufacturing standards, in respect of both processes and components, to decrease global risk profile and limit investment requirements. Some of Symbioze's features include:

- A standard primary drug container (PDC), a glass cartridge, in a nest-and-tub configuration. This allows the use of standard filling equipment, either by the customer or a contract filler.
- An innovative, patent-protected design allowing prefilled PDC assembly in the disposable unit in a non-aseptic environment. An embedded sterile connection between the drug container and the fluid path enables both a ready-to-use solution for patients and a seamless filling and assembly process for manufacturers.

Finally, Nemera needed to ensure that, throughout the development, no compromise was made on the injection experience from a patient's perspective. The company leveraged its Insight Innovation Center expertise to map out the envisioned patient journey, which is an even more critical process when considering new, complex devices. This process includes the development of a human factors task analysis, which identifies the demands placed on the user, assuming the general workflow and system components, and notes potential use errors. This effort sets the foundation for the human factors programme for potential applications.

Integrated task analysis allows for the mapping of key user needs at each step of the workflow, identifying potential challenges or errors, and for appropriate prioritisation of development activities. This allowed Nemera to set a foundation for Symbioze to ensure that the device is optimised across all aspects of device use from set up and wear to removal and storage in a home-use context (Figure 5).

This effort was translated by Nemera's team of experts into a concept development framework (CDF) that outlined a list of user needs that needed to be met by the design of the device and provided a clear priority order of tasks for achieving that aim, based on acquired knowledge. The CDF was used to guide the development process and ensure alignment with a hierarchy of user needs related to technical challenges. This methodology drove development of a platform that is as broadly applicable to potential patient populations and drug

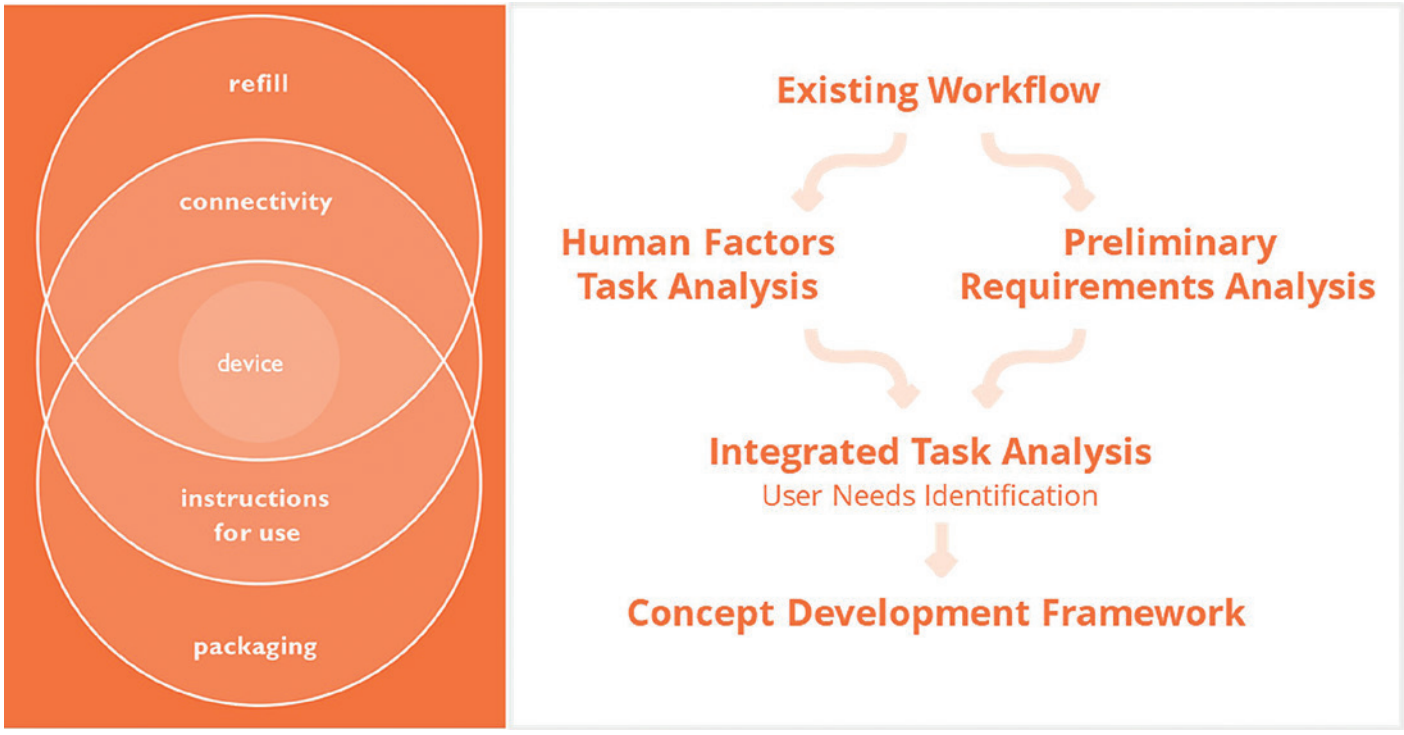

Figure 5: Supporting the combination product ecosystem from the earliest stages of developing a device strategy.

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product characteristics as possible. This foundation will be supported by multiple studies that are planned to take place over the course of the development of Symbioze. A key aspect to assess at the current stage of development is how the combination of size, weight and adhesive for a 20 mL device impacts on "wearability" during use, given a wide variety of potential wearing times.

By applying a thorough understanding of the patient journey and the broader healthcare ecosystem to the development of Nemera's device strategy for Symbioze, the company has established a foundation that can be applied to its customers' specific applications. Nemera can work with customers to adapt Symbioze to their specific needs, as well as provide services to support their combination product development requirements – including differentiation of the user experience and support of clinical trials from a device supply perspective, as well as the rest of Nemera's broader capabilities.

The Right Balance Between Drug Delivery Technology and Patient-Centricity

The right balance between simplicity and robustness of an OBDS is crucial for ensuring seamless self-administration, without adding unnecessary complexity and thereby compromising the patient experience. Symbioze offers sustainability, provides extra protection to users and ease-of-use, which are some of the most important characteristics in modern advanced parenteral devices. Nemera's extensive end-to-end capabilities in design, development and manufacture, coupled with Symbioze's platform approach, embraces the need for specific combination product solutions tailored to unique patient populations.

ABOUT THE COMPANY

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

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Séverine Duband is Marketing Director for drug delivery Devices at Nemera, steering overall category strategy, product portfolio and innovation development for five key delivery routes. She has been leading the parenteral segment at Nemera since 2018, focusing on proprietary products such as safety systems, pen injectors and on-body injectors. Ms Duband graduated from Emlyon Business School (Lyon, France) in 2004, and joined Nemera's Global Marketing team in 2018 as a Global Category Manager, focusing on the parenteral segment.

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SONCEBOZ

REPOSITIONING FROM IV TO VIAL-BASED SC FOR LARGE-VOLUME BIOLOGICS

In this article, Tom Mayer, Business Development Manager at Sonceboz, discusses the growing trend of moving away from intravenous drugs administered in clinical and hospital settings to at-home, self-administered vial-based subcutaneous delivery for cost savings, better lifecycle management and improved care.

The covid-19 pandemic has highlighted a weak spot in drug delivery – care for patients with chronic conditions can be easily affected, as many have chosen not to visit healthcare settings during the crisis. A March 25, 2020 survey by the American Cancer Society Cancer Action Network found that 27% of cancer patients in active treatment experienced some delay in treatment associated with covid-19.[1] This has led drug delivery manufacturers to seek alternatives, such as transitioning from intravenous (IV) drugs given in clinics and hospitals to at-home, self-administered vial based subcutaneous (SC) delivery for cost savings, better lifecycle management and improved care.

IV-to-SC drug repositioning is the strategy of positioning therapies currently requiring IV infusion by a qualified clinician as SC injectables in prefilled devices that are safe and efficacious when self-administered by the patient. Recent advances in the development of anti-cancer medicines in the form of SC drugs could be key to pandemic-era attempts to minimise cancer patients' exposure to coronavirus during active treatment.

As the pace of competition increases within the pharmaceutical and biotech industries, the concept of lifecycle management is becoming a key component of drug product management. While reformulation is an important approach, efforts to prolong IP benefits have only recently involved IV-to-SC drug re-engineering. This migration is now becoming a significant pathway in the lifecycle of many parenteral drugs. A number of technology approaches are currently being employed to accomplish this migration. By pursuing IV-to-SC strategies, drug patent holders are finding they can achieve a number of competitive advantages.[2]

> "The concept of lifecycle management is becoming a key component of drug product management."

For companies with IV products in their portfolio, a transition to an SC formulation can make sense as measures of lifecycle management and differentiation. In other instances, large-volume injection might be advantageous from a pharmacokinetic point of view.

A VIAL-COMPATIBLE DEVICE MEANS A FASTER TRACK TO MARKET

Pharma can ease into the transition from IV to SC delivery by moving to a vial-based solution. Vials remain the container of choice for pharma because most companies have vial-filling capabilities. In fact, 90–95% of liquid drug formulations rely on vials as

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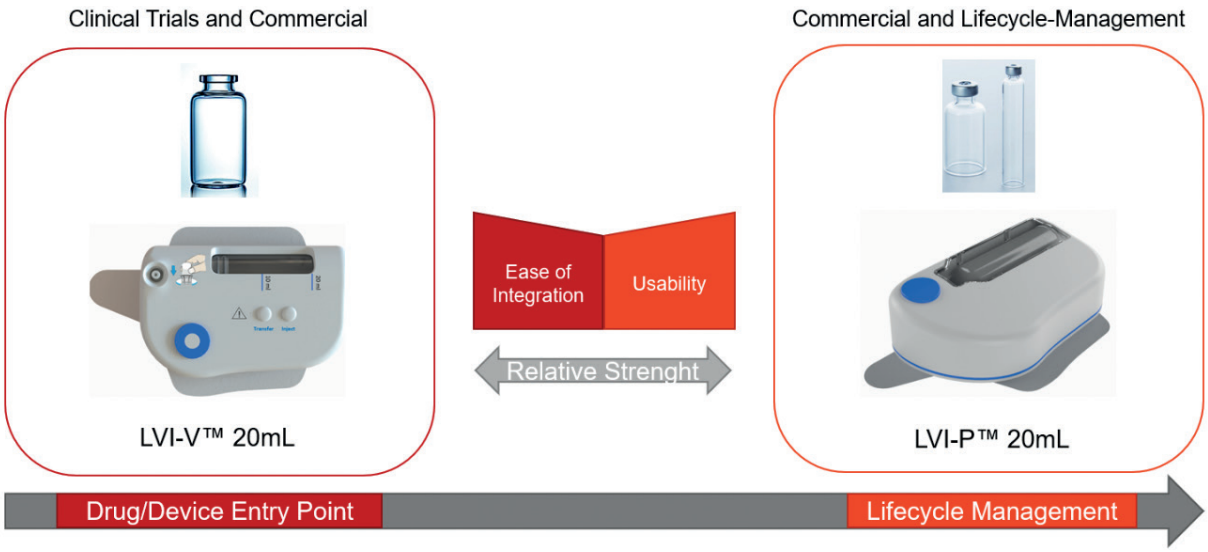

Figure 1: Starting with a vial-based product provides both a fast-track to clinical trials and a seamless transition to a cartridge-based solution for at-home use.

> "The advantage of a vial-compatible solution is the relative ease of integration into existing and proven pharma processes."

the primary container. As such, vials are easier to adopt from a drug stability and compatibility perspective.

A large-volume, vial-based SC solution like the LVI-V20 also enables a faster time to market as it is well suited to move from clinical trials to commercialisation. LVI-V20 features an internal reservoir and, with the help of a standard vial adapter, automatically transfers the contents of the vial into the device prior to injection. A temporary drug container inside the device is designed for short-term storage. This device is suitable for both clinical trials and commercial applications, depending on the use case. The LVI-V20 is designed for operation with standard vials up to 20 mL.

The advantage of a vial-compatible solution is the relative ease of integration into existing and proven pharma processes. Pharma companies can keep using existing primary containers and do not have to develop a specific container and create stability data.

Additionally, LVI-V20 provides flexibility from a payload point of view, able to be filled from 1 mL to 20 mL. Often, in early development phases, it's unclear what the final dose volume will need to be, so something that provides more headroom offers more flexibility to the overall process. LVI-V20 offers the ability to go to clinic without having final dose volume determined and, because it can be filled with less than 20 mL, provides pharma companies with a great deal of flexibility.

Ideally, a pharma company would start with the LVI vial-based solution in clinical trials or early commercial development and then, in cases where home use or self-care is intended, transition to a solution with a prefilled and preassembled cartridge, such as the Sonceboz LVI-P.

SUBCUTANEOUS DELIVERY EMPOWERS PATIENTS

An increasing number of people with chronic diseases, along with the availability of self-administered drug delivery devices, have propelled the growth of global subcutaneous drug delivery devices market – valued at US$22.4 billion (£16.3 billion) in 2019 and expected to reach $71 billion by 2030.[3] SC drug delivery refers to the medication being injected in the SC layer (between the skin and muscle) of an individual. These injections are less invasive than IV and, in many cases, manageable by patients themselves.

Depending on the drug, SC drug delivery devices make it possible for patients with diabetes, cancer, autoimmune diseases or rare diseases to self-medicate anywhere and at any time without professional help. SC drug administration has proved to be safe, well-tolerated, effective – and often preferred by healthcare providers and patients, resulting in optimised drug delivery costs.[4]

Traditional SC injection devices, such as prefilled syringes or autoinjectors, are limited to a maximum delivery volume of 3 mL. Strategies for overcoming this problem are crucial to widening the scope of drugs that may be administered subcutaneously.

To achieve IV-equivalent efficacy, SC formulations often require higher volumes or higher concentrations – in some cases, a combination of both. To meet this challenge, Sonceboz developed the LVI-V20 as a vial-compatible solution and LVI-P20 as a prefilled, preloaded cartridge solution, both of which can handle drug payloads up to 20 mL (Figure 1). The LVI-P acts similarly to an autoinjector: the device is placed on the skin and activated by the touch of a single button – the remaining steps, such as placing the injection cannula and initiating the injection, are done by the device and the user is informed about the current state of operation, including when the procedure is completed and the full intended dose received. This process is monitored by a series of embedded sensors.

WEARABLE, SMART SC INJECTORS

The rise in the number of biologic drugs, such as monoclonal antibodies, has increased the desire for and awareness of injection devices in general. While the market today is dominated by devices like autoinjectors, higher dosage volumes and viscous formulations of certain drugs are further emphasising the need for alternative injection methods, including wearable injectors. This is often due to reformulation efforts, where a trade-off between efficacy and drug stability must be found.

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Figure 2: The Sonceboz wearable injector platform offers different delivery volumes, programmable pump delivery profiles and container options.

"Empowering the patient with a wearable injector to be used at home eases administration, improves compliance and eliminates costly healthcare visits."

Empowering the patient with a wearable injector to be used at home eases administration, improves compliance and eliminates costly healthcare visits. Aside from the home-use scenario, devices like the LVI-V20 can also improve care in injection clinics or hospitals, since the automated injection/infusion process allows for higher patient throughput in a less-invasive fashion. Done right, this can have a substantial impact through healthcare cost reduction.

The increasing prevalence of diabetes, chronic pain, cancer and autoimmune diseases, such as rheumatoid arthritis, is driving the use of wearable injectors. This is expected to create a lucrative opportunity for advanced drug delivery device manufacturers to make wearable devices for administering larger dose volumes or enabling self-medication in the comfort of a patient's home. This is being witnessed by a global market for wearable injectors estimated at $4.8 billion in 2020, and that could reach upwards of $18.3 billion by 2028.[5]

The Sonceboz wearable injector platform (Figure 2) comes with built-in connectivity using Bluetooth Low Energy as the communications standard. Information such as time and volume of delivered dose can be transmitted to relevant stakeholders such as healthcare providers. If the device simplifies the overall treatment experience, it will most likely have a positive impact on compliance. Thanks to connectivity, the device provides feedback to the patient that the treatment regimen has been followed correctly. Pairing this information with elements of gamification can most likely improve compliance and thereby help solve one big challenge in healthcare – non-compliance. Thus, in the coming years, the adoption of connected device technology is expected to accelerate significantly.

While vials are the go-to container for large-volume drugs, they are not ideal for wearable devices use due to their non-compressible/collapsible nature. This means that, for successful drug retrieval, one needs to manage vial orientation to avoid incomplete injection. There are different approaches to this challenge. One is to monitor orientation with digital orientation sensors – another is to first transfer the drug into a collapsible container. Sonceboz follows the latter approach since it believes this is the only way to guarantee that the full dose of drug is delivered every time. While there are devices that need to be aligned on the body in a certain way so that the pump can access the drug, Sonceboz's devices pump drug regardless of the spatial orientation of the device on the skin – whether upside down, sideways or tilted.

The Sonceboz wearable SC devices, like the LVI (Figure 3), are designed with an electronic drive system which can be programmed to give pharma and healthcare providers options as to how the drug will actually be delivered. The pump system is independent of the drug container so one can connect both small and very large containers. Additionally, the pump is constructed with materials and coatings that are compatible with large-molecule biologics.

Whether a drug manufacturer chooses a vial- or prefilled cartridge-based SC delivery device, improved patient care, options for lifecycle management and potential

"While vials are the go-to container for large-volume drugs, they are not ideal for wearable devices use due to their non-compressible/collapsible nature."

Figure 3: The large volume injector (LVI™).

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cost savings are potential benefits of reformulating an IV-based delivery method. While the past 10 years have been fairly slow, the next 10 will be clearly different, with many active programmes for drug-device combinations in development and many programmes of IV-to-SC reformulation underway. IV to SC is where Sonceboz's technology will have an impact.

ABOUT THE COMPANY

Sonceboz's core competencies consist of design, development and production of mechatronic drive systems. Since 1936, the company's focus has been on innovation, and best-in-class quality and service. Sonceboz is ISO 13485 certified and active in wearable drug delivery, medical devices and laboratory industry. Customised technology modules like motor drives, electronics, pumps and needle insertion systems are available for medical device manufacturers. Sonceboz's activity in medical devices is based on long experience in the automotive sector, where top quality, reliability and cost effectiveness is key.

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Subcuject

MEETING EMERGING STAKEHOLDER NEEDS WITH THE SUBCUJECT WEARABLE BOLUS INJECTOR

Here, Tony Bedford, Director, Front-End Innovation, at Phillips-Medisize, looks at the emerging market for on-body injectors coupled with stakeholder needs and introduces the Subcuject wearable bolus injector, which is designed to accommodate these requirements.

In *ONdrugDelivery*'s previous issue on Wearable Injectors (Issue 111, Sep 2020), we wrote about emerging trends that could shape the market for on-body injectors (OBIs). At that time, these were the potential erosion of OBI market share by autoinjectors at lower volumes, the switching of already marketed intravenous drugs to subcutaneous formulations, the long-term impact of covid-19 and a tendency towards prefilled device configurations.

> "The prospect for OBIs remains promising, driven by new biologic drugs, the reformulation of intravenous drugs for subcutaneous routes of administration and the continued push for more widespread self-administration."

The prospect for OBIs remains promising, driven by new biologic drugs, the reformulation of intravenous drugs for subcutaneous routes of administration and the continued push for more widespread self-administration. Stakeholders are starting to demand simpler, more cost effective devices and, in this article, we will look at some of the evolving stakeholder needs and introduce the Subcuject wearable bolus injector (WBI) designed to meet those needs.

VOLUME-BASED SCENARIOS

Subcutaneous formulation research allows us to assemble a set of volume-based scenarios that can be used to determine the optimal device configuration, including where the drug might be administered and what drives these positions.

To reduce dosing frequency, a new breed of biologic drugs is being formulated for subcutaneous administration. Formulation teams are trying to pack higher concentrations of active ingredients into their product, which increases viscosity and/or results in larger delivery volumes to balance the need for higher concentrations with a product that can be injected without damaging the molecules or causing discomfort for the patient. We can, therefore, expect to see an increase in subcutaneously administered drugs with volumes of 2–5 mL and beyond begin to appear, and it is within this volume bracket that competition between delivery devices will intensify.

Anecdotally, it is feasible for a patient to receive a dose made up of two consecutive injections from 2.25 mL autoinjectors (which are already launched

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on the market and successfully delivering doses), and we fully expect even larger volume autoinjectors to reach the market. However, questions remain over the practicalities and patient comfort of administering injections in this way – for example, ensuring patients are sufficiently trained to use both autoinjectors (in the case of a pack of two equalling a single dose) rather than mistakenly considering one to be a spare, avoiding under-dosing through wet injections (where the autoinjector is lifted away from the skin prior to completion of delivery) and dealing with the absorption and pain issues caused by repeated injection at the same site or the need to hold the autoinjector still for a longer time period.

Consequently, the 2–5 mL volume range is a good starting point for wearable devices to establish a market position as it provides an alternative to multiple or larger autoinjectors and can offer a slower delivery rate that may be better suited to more viscous and larger volume drugs. Perhaps even better is the next range, 5–10 mL, which is likely to be beyond the reach of larger embodiments of autoinjectors and seems ideal for cost-effective single-use and reusable OBIs alike. With the knowledge that a number of OBIs with different configurations are in development, formulation teams may relax a little instead of striving for the highest possible concentration and the lowest possible volume, particularly in cases where packing the drug into a prefilled syringe or autoinjector is not a realistic target.

The last group is the 10 mL and above range, already populated by "switched" products such as Janssen's DARZALEX Faspro® (daratumumab and hyaluronidase-fihj) and Roche's MabThera SC (rituximab), which are currently delivered from syringes as fixed doses of 15 mL and 11 mL, respectively. Both of these were originally (and still are) marketed for the intravenous route of administration and herald the start of an expected rush of "switching", particularly in the immuno-oncology space – for example, Merck & Co's top-selling Keytruda® (pembrolizumab) is currently in clinical trials in subcutaneous form. We expect to see drugs such as these being delivered via some form of on-body delivery system in due course.

Figure 1 illustrates these groupings, with the formulation of smaller volume biologics driven by the need for less frequent (and most likely self-) administration, and the reformulation of larger volume products driven by the need for decreasing cost, with significant savings made possible by reducing time in the clinic, hands-on involvement by a healthcare practitioner and, potentially, moving administration away from the clinic altogether.

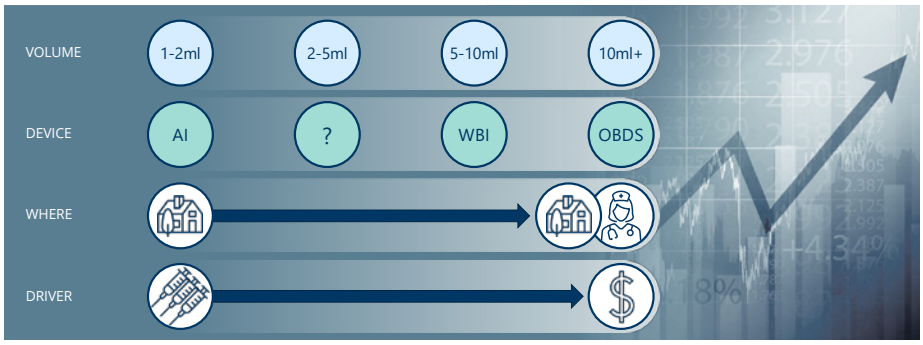

Figure 1: Subcutaneous volume groupings, devices and drivers.

EVOLVING STANDARDS

Certainly, it appears as though regulators believe that there is potential for a significant increase in the number of OBIs reaching the market and, presumably derived from some of the learnings from devices that are already commercialised, a number of changes are being drafted for the latest update of the ISO 11608 series, which are expected to be published during 2022.[1] This is understood to include moving some of the elements specific to ISO 11608-6[2] to ISO 11608-1[3] and the addition of fluid lines and paths to ISO 11608-3,[4] signalling intent with regard to the arrival of OBIs.

STAKEHOLDER NEEDS

In order to succeed in this emerging market, a number of stakeholder needs must be met. Given the relatively low market penetration of OBIs thus far, we do not yet know for sure if patients will accept these body-worn devices, so that is a good place to start.

Autoinjectors offer a simple, two- or three-step process for delivering a dose; OBIs must compete with this as it is unlikely that patients will be satisfied with anything that increases the burden. Perhaps the need we hear about the most is for devices that are prefilled and preloaded – this minimises the need for user involvement or increased patient burden, but interestingly, none of the wearable devices currently on the market adopt a prefilled and preloaded format. With this configuration, all that is required of the user is to remove the device from the primary packaging, apply the device and activate it.

> "Perhaps the most influential stakeholder group is the pharmaceutical or biotech company whose drug is contained within the device."

Patients also need to know the status of the device – Is it working? Has it completed the dose? – and these are issues that are being increasingly scrutinised by the regulators, so high-quality design and user feedback are of paramount importance.

The patient needs are likely echoed by healthcare practitioners too. This stakeholder group should be considered as a gatekeeper, or at the very least an influencer, when it comes to the adoption of devices as they reach the market; if choice is available, the option that works reliably and can be trusted in the hands of the patient will emerge as the winner – but also anything that reduces healthcare practitioner burden (e.g. replacing a large volume syringe) should be warmly received.

Perhaps the most influential stakeholder group is the pharmaceutical or biotech company whose drug is contained within the device. With the uptake of drug delivery devices on the increase, drug companies have become increasingly savvy and sensitive to the needs of their customers and, in addition to their own needs, will also look to ensure that those of other stakeholders are being met. Gone are the days of the device and patient comfort being disregarded, if ever that was really the case.

Pharmaceutical and biotech companies need to be certain of the efficacy of any device. Put simply, they have to work reliably and accurately, all the time, without risking the stability of the drug through, for example, shear damage, material compatibility or temperature-related issues.

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Cost Effective	Ease of Use	Efficacy	Standard Processes
• Cost per injection • Development / licensing fees • Differentiation	• Simple to apply and activate • Comfortable in use • Clear feedback	• Free of drug stability issues • Cold chain compatibility • Customisable	• Standard primary container • Fill and finish • Sterilisation

Figure 2: Stakeholder needs for OBIs.

Add to those needs the requirement for fill and finish (and sterilisation) without disruption or significant investment in new processes, and an overwhelming desire to use trusted primary containers to minimise stability and handling issues, and the blueprint for the specification of any OBI development is already partially drafted. These example needs across stakeholders are summarised in Figure 2.

"Combining the elements of larger volume and ease of use together results in a device that readily crosses from self-administration to clinic-based use – easily applied and used by patients and healthcare practitioners alike."

THE SUBCUJECT WEARABLE BOLUS INJECTOR

Phillips-Medisize is collaborating with Subcuject in order to bring the Subcuject WBI to market (Figure 3). The Subcuject WBI has been designed with stakeholder needs in mind and offers a cost-effective, pharma-friendly and patient-friendly solution.

The Subcuject WBI is currently configured to deliver up to 5 mL from a prefilled standard glass cartridge to allow ease of integration into filling lines without deviation from industry-standard stopper or container materials. The design allows for flexibility in terms of delivery volume (the device is a fixed-dose bolus injector) – either by underfilling or by employing a smaller cartridge – and is a scalable platform design, which in-laboratory bench tests have already demonstrated can deliver up to 15 mL from a larger primary container.

It is also preloaded, meeting the needs of the end-user by minimising the steps required to use the device – once removed from the primary packaging, it is a simple three-step "peel, place, press" process to complete the dose (Figure 4).

Figure 3: The Subcuject WBI.

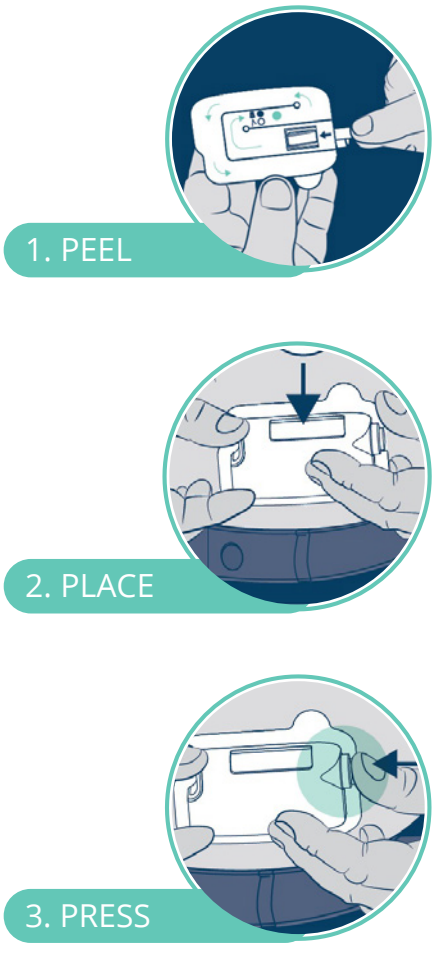

Figure 4: Three-step use of the Subcuject WBI.

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With built-in needle insertion and retraction, the user has control at the beginning of the treatment and safety at the end, with feedback to suit the usability requirements.

Furthermore, the device is conveniently small compared with other OBIs and is noiseless during operation, apart from "click" sounds at activation and at end of dose.

Combining the elements of larger volume and ease of use together results in a device that readily crosses from self-administration to clinic-based use – easily applied and used by patients and healthcare practitioners alike. The Subcuject WBI can also be used in scenarios where the patient continues with their daily tasks or is observed during use (for example, some immuno-oncology drugs require patient supervision and availability of resuscitation equipment upon first dose).

A COST-EFFICIENT, NATURE-INSPIRED SOLUTION

What is really compelling about this technology is the novel drive system, which is free of batteries, electronics and motors, maintaining simplicity and facilitates a much lower cost of goods than electromechanical devices. Whilst sustainability credentials are a challenge for any single-use disposable device, the Subcuject WBI offers an alternative to throwing away a greater number of (smaller volume) devices by way of its larger payload and/or reduced frequency of use, while also eliminating the need for the disposal of battery chemicals and numerous metallic components.

By using forward osmosis, the device creates a hydraulic pressure internally once it has been activated by allowing salt and freshwater to mix (Figure 5). The hydraulics replace the need for lead screws, plunger rods or other mechanical solutions and drive the stopper along, expelling the drug. This is all done naturally, requiring just the simple press of a button to start the process. This provides a unique solution free of superfluous functionality and complexity.

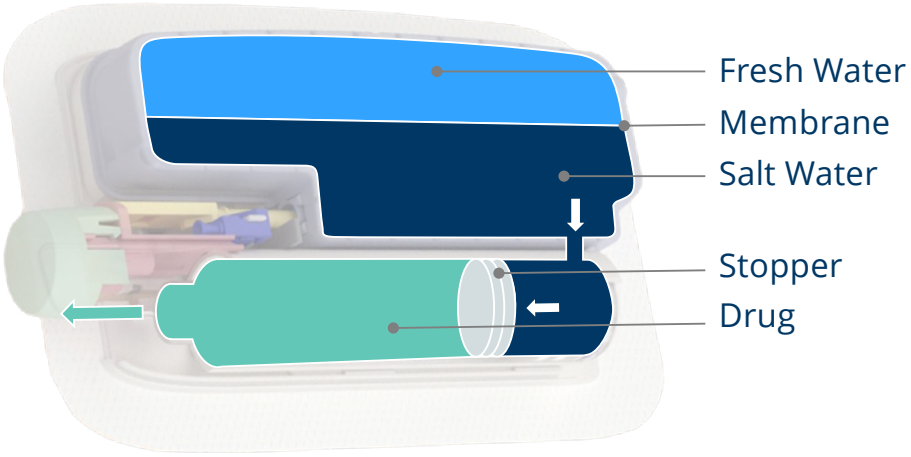

Figure 5: Forward osmosis delivery of drugs from a standard cartridge.

ACCURATE AND VERSATILE

As previously noted, the expected new breed of biologic drugs is likely to see increasing viscosities and these pose no issue for the Subcuject WBI. A characteristic of osmosis is that it will build up a higher pressure when meeting a counterforce, and initial tests have successfully and repeatedly delivered liquids up to 100 cP via a 27G needle, the trade-off being a slight decrease in flow-rate (at 1 cP the Subcuject WBI delivers at a rate of approximately 1 mL per minute), with a high degree of dose delivery accuracy. This makes for an incredibly versatile platform.

With 5 mL demonstration devices expected to be available during the last quarter of 2021, Phillips-Medisize and Subcuject are ready for engagement into drug-specific feasibility and development programmes with pharmaceutical and biotech companies.

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ABOUT THE COMPANIES

Phillips-Medisize, a Molex company, is an end-to-end provider of innovation, development, manufacturing and post-launch services to the pharmaceutical, diagnostics, medical device and speciality commercial markets. Post-launch services include a connected health app and data services. Backed by the combined global resources of Molex and its parent company Koch Industries, Phillips-Medisize's core advantage is the knowledge of its employees to integrate design, moulding, electronics and automation, providing innovative high-quality manufacturing solutions.

Founded in 2017, Denmark-based **Subcuject** is a privately held technology development company focused on developing an innovative and proprietary device platform for wearable bolus injection, the Subcuject WBI. The founder of Subcuject, Claus Schmidt Moeller, is the inventor of multiple innovative injection devices, including a number of the injection pens from Novo Nordisk. The Subcuject board of directors includes substantial drug delivery industry expertise, including Paul Jansen (ex-Sanofi and Eli Lilly) and Lars Guldbaek Karlsen (ex-Novo Nordisk).

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ABOUT THE AUTHOR

Tony Bedford is Director, Front-End Innovation at Phillips-Medisize and has been involved in the design and development of medical devices for over 25 years. With a background in product design, his broad experience covers everything from innovation and market strategy to clinical research and product launch, with a focus on understanding market, stakeholder and user needs. Prior to joining Phillips-Medisize, Mr Bedford held project management and business development roles in the consulting industry, working on a wide range of device programmes. He has specialised in drug delivery devices for a number of years.

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DESIGNING DRUG DELIVERY DEVICES THROUGH COLLABORATIVE USABILITY TESTING

Alice Bogrash, Product and Human Factors Specialist at Eitan Medical, examines how the company uses human factors studies to design drug delivery devices that respond to user needs, while providing a competitive advantage for pharmaceutical companies looking to introduce innovative combination products to the market.

Human factors – or "usability engineering" – is the science focused on the interaction between people and devices. Specifically, human factors is a key focus for medical device manufacturers, as they seek not only to optimise their device design through iterative user testing sessions but also to comply with regulators' mandatory requirements and guidelines throughout the device development process.

The purpose of these guidelines, which have been developed, published and updated over recent years, is to assist medical device manufacturers with following "appropriate human factors and usability engineering processes to maximise the likelihood that new medical devices will be safe and effective for the intended users, uses and use environments."[1] Usability testing is an important aspect of any medical device design process but, when looking at devices used in home-care settings, usability engineering's importance is further highlighted.

One of the primary purposes of wearable drug delivery devices (Figure 1) is to simplify the process of self-administration for patients, making home-care treatments more feasible. With a strong preference for "hospital at home" and patient demands for greater involvement in the care process, wearable drug delivery devices provide a

Figure 1: The Sorrel wearable injector.

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"The wearable injectors that are expected to win strong market share will be those that are reliable, comfortable and easiest for the patient to use."

solution for both healthcare providers and patients, increasing patient throughput in the clinical setting while also enhancing the user experience for patients, enabling them to receive their prescribed therapy in the comfort of their own home. The challenge is making wearable injectors that are easy to use and intuitive enough that a wide range of use groups and patient populations can use them, regardless of age, tech-savviness, dexterity and other factors generally influenced by the specific indication the drug product is looking to address.

Although there are not many wearable injectors on the market as of yet – or even too many in clinical stages – they differ from each other significantly in terms of *how* the device is to be used; the number of steps they require to be activated, the method by which the drug is filled into the device, the reusable versus disposable aspects of each device and so on.

The wearable injectors that are expected to win strong market share will be those that are reliable, comfortable and easiest for the patient to use. It is therefore essential to examine the key human factors that must be considered throughout the development of self-administration devices – from basic design to final commercial product – to ensure that they provide a safe, intuitive and seamless user experience, empowering users to take control of their health, all in a home-care setting.

HUMAN FACTORS TESTING FROM INITIAL DESIGN

The process of human factors testing is, and indeed must be, an iterative one. From the initial design stage, it is imperative to eliminate all use-related risks via a robust and comprehensive risk analysis and mitigation process. A multidisciplinary evaluation will reveal any design issues that must be addressed before moving on to the first device prototype for further in-house testing and evaluation.

"From the initial design stage, it is imperative to eliminate all use-related risks via a robust and comprehensive risk analysis and mitigation process."

At Eitan Medical, each product line has its own in-house team for human factors and usability engineering. Whether they be wearable devices intended for self-administration or infusion pumps intended for both hospital and home-care use, a dedicated product management team has specific expertise and experience with human factors. That said, usability and human factors testing are not activities managed solely within the company, as the Eitan Medical human factors team partners externally with pharmaceutical companies and third-party vendors to support, plan and execute human factors studies throughout the product development lifecycle.

PLATFORM APPROACH FOR USABILITY TESTING

For the Sorrel wearable platform, it is important to differentiate between the generic Sorrel-branded platform devices and the specific device configurations customised as part of a partner-specific development programme. As part of the initial design and development of the Sorrel platform, testing was conducted on a wide variety of key aspects of device usability. These studies were conducted primarily on a general population of test subjects, with a wide range of ages, ethnicities, body mass indices (BMIs) and health conditions.

When Eitan Medical partners with a pharmaceutical company, the project is focused on a specific drug product, resulting in a clinical, then commercial, drug/biologic-device combination product. In such a case, the pharma partner is generally responsible for testing the customised Sorrel device for the specific and relevant patient population, use case and use environment, with the Eitan Medical human factors team supporting, or at times even running parallel studies, to provide a robust set of usability testing data as an output.

The combined human factors team, with representatives from both the device and the pharma side, is an integrated unit bringing together the best of both worlds – the knowledge and experience from the pharma world with a specific indication and patient population on the one hand, and the device expertise on the other. The full set of human factors studies conducted throughout a joint programme ranges from smaller internal studies to local medium-sized studies to larger studies conducted in a variety of geographies run by third-party human factors firms.

DESIGN FLEXIBILITY TO ACCOMMODATE DIFFERENT USE CASES AND PATIENT POPULATIONS

The Sorrel wearable injectors were developed with inherent flexibility, as part of an overarching platform approach. What this means is that, as part of a molecule-specific development project, a Sorrel device can be customised and optimised for a specific drug product, use case and patient population (Figure 2).

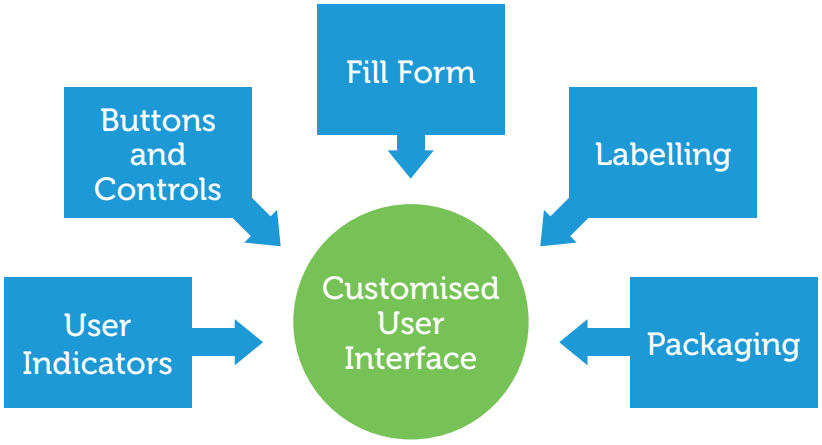

Figure 2: Customised features of a smart wearable drug delivery device.

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These customised features include several aspects affecting the user's interaction with the final combination product:

- **User Indicators:** For self-administration devices, indicators are essential for guiding the user through their drug delivery experience – providing the user with positive feedback throughout the treatment and alerting them if there is an issue. Indicators are important in that they point out the critical steps for using the device, as outlined during the user risk analysis (Figure 3). For example, if it is imperative that the user comprehends when the treatment has started, an indicator will be designed to signal that point in time to the user. The Sorrel devices include audio, visual and tactile feedback, which can be easily customised and quickly tested, as the device is software controlled. This means that not only can the sequence and duration of each indication be customised but it can easily be changed between one human factors study iteration and the next – allowing for ideal comparison throughout testing and quick optimisation of user indications. Further customisation can be performed for specific patient populations – increasing the strength of the light indicators or buzzer sounds for those suffering from visual or aural impairments, respectively.

Figure 3: Critical use steps that may require dedicated indication sequencing.

- **Buttons and Controls:** Drug delivery devices may require some form of push button or switch, whether to activate the device, initiate drug delivery, administer a bolus or pause and resume treatment. The Sorrel devices include a software-controlled hard key that can be configured for one or several actions. As an example, a long press can mean treatment initiation, while two consecutive button presses may mean a bolus administration. Alternatively, with the use of the proprietary on-body sensing mechanism – consisting of a trigger and supporting algorithm – the device can forgo a button altogether and the treatment can begin automatically once the device has been adhered to the skin properly. These decisions are made on a case-by-case basis, as part of the joint usability evaluation between the Eitan Medical team and the pharmaceutical partner.
- **Fill From:** A key parameter affecting the user experience in drug delivery devices is the way in which the drug is filled or loaded into the device. A drug-administration process that entails the least number of user steps will inevitably reduce the probability of use errors, as each additional step is a potential point of failure. Not only does the drug filling or loading aspect of the combination product need to be assessed as part of the overall human factors testing plan (Figure 4), but the device design should be optimised in a way that the overall steps for the user are kept to a minimum. The Sorrel platform includes unique technology solutions to enable a prefilled and preloaded device configuration, whether using a cartridge or vial, enabling the ideal user interface where – essentially as simple as using a plaster – all the user needs to do is peel the adhesive liner and stick the device on their body.
- **Labelling:** Effective labelling is a key element in directing patients towards safe and effective use of a device, while mitigating any potential use-related hazards. Labelling includes the information on the device itself, as well as labelling on the packaging of each device and the overall combination product, together with the instructions for use. These graphics and guides are jointly developed between the device manufacturer and the pharmaceutical partner and are included in the iterative human factors review process. The general approach at Eitan Medical is to reduce dependency on the user reading the instructions for use by using graphics and text on the device itself, on the adhesive liner and on the packaging as an effective way of guiding the user through their use of the Sorrel devices.
- **Packaging:** As with labelling, significant investigation must be conducted into the design of the device packaging. Key considerations will include the user experience when opening packaging, the ease with which users can extract the device from the package, and the packaging design's ability to protect the device integrity in various conditions and during transportation.

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Figure 4: For a manually filled device, emphasis must be placed on testing the filling or loading process.

USER ACCEPTANCE OF NEW DEVICE CONCEPTS AND DESIGNS

Not only can specific device features be tested, analysed and optimised through human factors testing, but similar studies can be used as a way of initial assessment of new device concepts. Groups of individuals, representing the target patient population demographics, can be interviewed to understand their acceptance of a new product, concept, feature or design.

For example, before initiating a study moving a treatment from hospital-based intravenous infusion to at-home subcutaneous administration, potential users can be asked if they believe a wearable injector is something they can manage on their own – or if they would prefer having a healthcare professional present during their injection. Another question that can be targeted as part of a user preference study is if potential users would accept a 50 mL on-body drug delivery device as an alternative to several lower volume injections or a trip to the clinic.

These types of studies are regularly conducted at the start of joint ventures between Eitan Medical and pharmaceutical companies partnering with the Sorrel platform, as a way to receive early feedback from user groups – reducing risk and increasing the overall probability of success in a development project. Over the years, Eitan Medical's team has gained valuable insight throughout user preference studies as a way of determining areas of focus for the company's product pipeline.

DESIGNING WEARABLES TO HELP PHARMA COMPANIES ACHIEVE THEIR COMMERCIAL GOALS

Pharmaceutical companies today seek to provide more value to their customers, with friendly devices that enable at-home administration of large-volume and high-viscosity medications. They are looking for partners that are able to support this goal, with innovative device technologies that enable patient self-administration. Eitan Medical's pharmaceutical solutions business unit aims to help pharmaceutical companies appeal to the largest possible demographic and make the devices as easy to use as possible, de-risking market entry (Figure 5).

Designing a wearable drug delivery device with the patient in mind from the start, together with proven design capabilities, flexible platforms and a collaborative approach throughout human factors testing, ensures that the final device will be optimised from a usability perspective. This can, in turn, have a

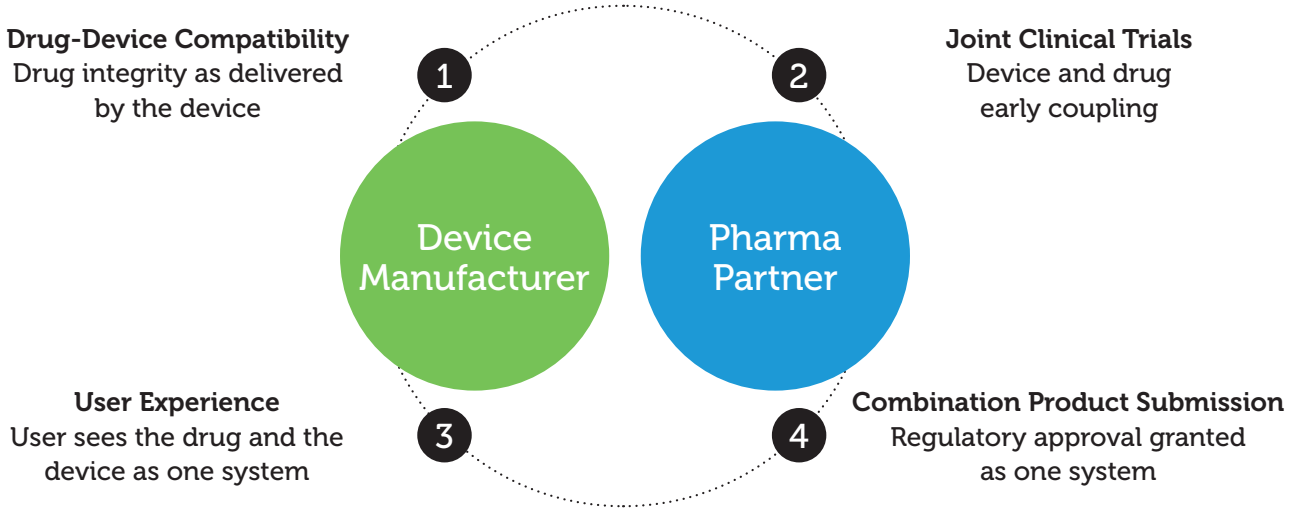

Figure 5: Collaborative approach throughout device development.

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positive impact on adherence to treatment regimens, ensuring users receive medication in a safe, easy to use way, delivering competitive advantage, and helping both patients and pharma providers.

ABOUT THE COMPANY

Eitan Medical develops innovative drug delivery devices – wearable injectors and infusion solutions, including connected devices – that put patients at the centre of care, making drug delivery easier and safer. The devices are applied across the continuum of care, including hospital, ambulatory and home-care environments. 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, a prefilled and preloaded patient-centric on-body injector for delivery of biologic treatments; and Avoset, connected infusion systems for the home-care market.

> "Not only can specific device features be tested, analysed and optimised through human factors testing, but similar studies can be used as a way of initial assessment of new device concepts."

ABOUT THE AUTHOR

Alice Bogrash is Product and Human Factors Specialist, Pharmaceutical Solutions, at Eitan Medical, where she supports product management activities and oversees independent and collaborative human factor efforts for the Pharmaceutical Solutions business unit. Ms Bogrash has contributed to a range of combination products including cartridge-based, vial-based and filled-at-point-of-care drug delivery solutions. She worked across multiple customer-facing projects with pharmaceutical companies to develop customised and efficient drug delivery solutions catering to specific user populations. She holds a BSc in Medical Engineering from the Afeka College of Engineering (Tel Aviv, Israel), with a specialisation in mechanics and physiological fluid dynamics.

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THE PATH TO COMMERCIALISATION FOR WEARABLE DRUG DELIVERY DEVICES

In this article, Atul Patel, Vice-President, Devices & Delivery Systems at West Pharmaceutical Services, looks at the evolution of the wearable drug delivery market, including the route to commercialisation and the challenges faced.

Wearable medical devices have transformed healthcare. Ever since the US FDA granted Cygnus (ID, US) approval to market for its GlucoWatch Biographer as a prescription device for adults with diabetes in 2001,[1] the wearables market has continued to evolve and now includes a variety of wearable injectors – devices designed to deliver drugs in large volumes subcutaneously.

Some analysts predict that the global wearable injectors market will reach US$18.3 billion (£13.2 billion) by 2028.[2] This growth is being driven by the benefits these devices deliver to various stakeholders. For pharmaceutical and biopharmaceutical companies, wearables offer the opportunity to grow market share and reduce competition. For payers and providers, wearables can reduce costs associated with in-clinic treatment and, potentially, improve outcomes due to better medication adherence. And for patients, wearables offer the convenience of taking medication at home, avoiding the time and effort of visiting a clinic, thereby improving quality of life.

The home care end-use segment of the wearables market grew significantly in 2020, reflecting a preference for self-administration that was growing even before the covid-19 pandemic. In a 2018 study conducted in Belgian hospitals, for instance, the majority of patients surveyed said they would prefer to self-administer medication, and they had a positive attitude towards self-administration of medication.[3]

To capitalise on this trend, the pharmaceutical and biopharmaceutical industries have responded by introducing next-generation therapies that combine a medicine with a delivery system conducive to self-administration. These combination products, as designated by the FDA, can take several different configurations: a drug and a device; a biologic and a device; a drug and a biologic; or a drug, a biologic and a device. These products also include combinations that are physically, chemically or otherwise mixed and produced as a single product; two or more products contained in a single package; or separate products that are cross-labelled to be used together.[4] For most wearable injectors, their designation as a combination product seems clear, but even a prefilled syringe – a relatively simple drug-device combination – is viewed by the FDA as a combination product. It should be no surprise, then, that combination products account for approximately one-third of all medical products under development today.

> "For patients, wearables offer the convenience of taking medication at home, avoiding the time and effort of visiting a clinic, thereby improving quality of life."

What is not apparent in this statistic are the enormous challenges that must be overcome when commercialising any combination product. A more typical approach – one in which early development

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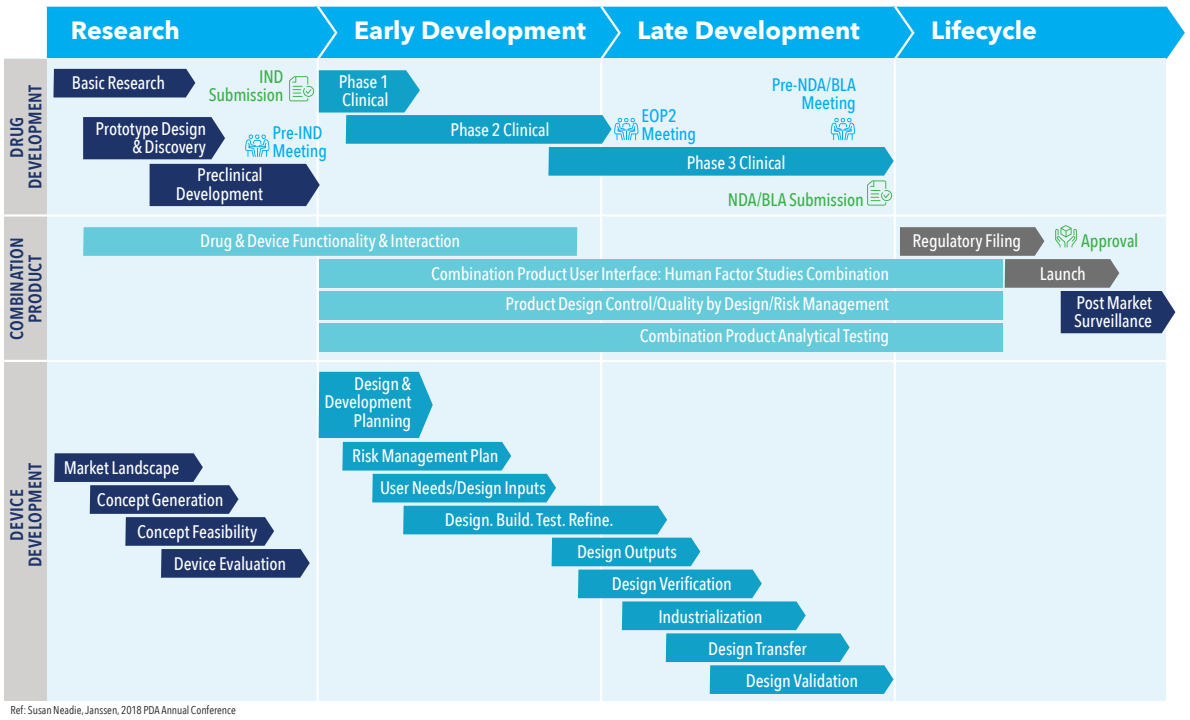

Ref: Susan Neadie, Janssen, 2018 PDA Annual Conference

Figure 1: The drug development process and device development process come together as early as possible.

> "For combination products, such as a wearable injector, the drug development process and the device development process must come together at the earliest stages to help guide the overall product strategy and to meet FDA expectations from a compliance standpoint."

focuses on the drug, leaving product and device considerations to later phases – introduces significant uncertainty and risk. For combination products, such as a wearable injector, the drug development process and the device development process must come together at the earliest stages to help guide the overall product strategy and to meet FDA expectations from a compliance standpoint. Considering the drug and device separately can introduce significant risk, even at the earliest stages of a project. Figure 1 shows what a more integrated approach might look like.

A two-pronged development process facilitates planning throughout the product life cycle and enables the sponsor team to address the following key challenges and considerations that can stand in the way of commercial success:

- Navigating the complex regulatory landscape for combination products
- Choosing the right presentation for the drug at the appropriate time
- Managing supply chain complexities.

REGULATORY CHALLENGES

Developing a device and drug in parallel requires synergies and collaboration among a number of concurrent workstreams, and they must answer a series of interconnected questions:

- What is the product's primary mode of action (PMOA)?
- Is the drug compatible with the containment system?
- Is the containment system compatible with the fill-finish process?
- Is the containment system compatible with the delivery device?
- Has the device been designed with both manufacturability and end-user needs in mind?

Making the wrong choice at any critical juncture or with any critical component can result in delays and costly reworks, but answering these questions with confidence is daunting because of the mercurial nature of the regulatory landscape. Since the final rule on current good manufacturing practice (cGMP) requirements for combination products (21 CFR Part 4) was issued in January 2013, there have been many draft guidances and other regulations introduced. It is not always easy to understand the impact of new regulations – especially when moving into different geographic regions – but failing to provide the necessary proof and documentation can result in a rejected filing, delaying the time to market.

To ensure compliance with regulatory requirements, human factors and analytical testing must be fully integrated into the development process. Human factors testing explores how end users interact with a device, and the FDA guidance focuses on three aspects: the intended users, the use environments and the user interface.[5] Regulators look for evidence of safe and effective use of a product from these three perspectives.

Analytical testing is particularly complex for combination products. Development teams must produce data to demonstrate compatibility, functionality and performance to support regulatory requirements. As ISO guidelines supporting the drug-device combination continue to evolve, however, this can be difficult. For example, the ISO 11.040 standards govern medical equipment as a category – standard 11.040.25, which provides guidance for syringes, needles and catheters, includes 73 standards alone, all or some of which may apply to a combination device.

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Additional testing requirements could also include bridging studies. These tests may include the bridging of data from combination products that employ different device components for the same drug or biologic, as well as the same device component across different drugs and biologics. Bridging study data are typically provided in addition to the foundational information included in an IND, BLA or NDA.

PATHWAYS AND PRESENTATION

Interacting with regulatory bodies presents its own unique challenges. Central to this is determining which type of premarket submission is appropriate. With the FDA, the agency taking the lead to evaluate a combination product is determined based on which constituent part of the product provides the PMOA. There are three primary regulatory pathways a product can follow: a device-led combination product, a drug-led combination product or a biologic-led combination product.

The FDA typically only requires a single application, regardless of pathway, which eliminates unnecessary duplication that may occur with multiple applications. However, there may be times when a developer decides to submit multiple applications (e.g. new drug product exclusivity, orphan status or proprietary data protection when two firms are involved). In these scenarios, the individual constituent parts of the combination product will be reviewed by applicable centres.

To determine the safety and efficacy of the whole combination product, the FDA will consider regulations for each constituent part. For a device-led product, that includes a drug constituent – the FDA will need to see data on the drug, including nonclinical and clinical pharmacology information and chemistry. This data for the non-constituent part of a combination product are not necessarily the same safety and effectiveness data required for the same part being submitted as a stand-alone drug.

Clearly, choosing the right way to present a combination product and collecting the right data is complex. Having a development roadmap from the outset of a project is critical to build a clear picture of the requirements needed throughout all phases of development. It is also important to look for partners who can supply components with technical data, which makes it far easier to provide reliable data in support of development decision-making.

SUPPLY CHAIN COMPLEXITY

The ever-changing regulatory, analytical and manufacturing needs of combination products leads to another significant challenge – supply chain complexity. Consider the scenario in which a pharmaceutical company, an expert at

"Choosing the right way to present a combination product and collecting the right data is complex. Having a development roadmap from the outset of a project is critical to build a clear picture of the requirements needed throughout all phases of development."

Figure 2: Product development teams often rely on a complex network of vendors to supplement their in-house capabilities, but a better solution is to find a single partner with extensive combination product experience.

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traditional drug development, must now think about the design of a delivery device, yet lacks in-house design expertise. The design of a device must be challenged to ensure that it does not interact with the drug. At the same time, a development team must also consider the integrity of the container closure, as well as the stability and extractables/leachable profiles.

To accommodate these design needs, a pharmaceutical company will typically outsource the work to a contractor, usually just one of many. In fact, many companies stitch together an ecosystem of multiple vendors, typically with each vendor operating independently. This can result in material shortages, inaccurate lead-times, distribution bottlenecks, quality control issues, failed inspections and lack of documentation.

Instead of this, it is preferable to work with a single partner that brings together both extensive knowledge of product design and development and the support services necessary to mitigate risk, reduce regulatory complexity and simplify the supply chain. Figure 2 shows all of the integrated solutions required to bring a combination product to the market. Clearly, having a development partner that offers some or all of these services under one roof – especially a partner with extensive combination product experience – can help to mitigate obstacles, avoid pitfalls and accelerate time to market.

CASE STUDY: WEST'S SMARTDOSE® 10 INJECTOR

West Pharmaceutical Services, a leader in the design and production of integrated containment and delivery systems for injectable medicines, has extensive real-world experience bringing combination products to the market. The company partners with the world's top pharmaceutical and biotechnology companies to bring technologically advanced, patient-centric, high-quality products to the market.

West's SmartDose® 10 Injector (Figure 3) stands as an ideal example of what these partnerships can produce. The next evolution of the SmartDose® 3.5 Injector, which was approved by the FDA in 2016 for delivery of Amgen's (CA, US) Repatha® (evolocumab) drug treatment, the SmartDose® 10 Injector delivers a dose volume of up to 10 mL, which makes it suitable for next-generation, high-viscosity drug products. Typically, such drugs would be administered in clinical settings, creating additional burden for the patient. The SmartDose® 10 Injector eliminates these issues by enabling self-administration of oncology and neuroscience therapies at the patient's home. The device is accompanied by detailed onboarding and training, and offers visual, tactile and audible feedback to boost user confidence. The result is an easy-to-use, patient-centric solution that eases patient anxiety and increases adherence.

Figure 3: West's SmartDose® 10 Injector delivers a dose volume of up to 10 mL, which makes it suitable for next-generation, high-viscosity drug products.

Because of both these benefits and West's experience with commercialising wearable injectors, the SmartDose® 10 Injector has seen increasing market acceptance. For example, in 2019, scPharmaceuticals (MA, US) announced its intent to go to market with West's SmartDose® 10 injector for FUROSCIX®, a proprietary, subcutaneously delivered furosemide solution for the treatment of worsening heart failure due to congestion. In July 2021, scPharmaceuticals announced that it is moving forwards with required bench testing and, subject to the completion of the Drug Master File by West, it is targeting the resubmission of its NDA in the fourth quarter of this year with an anticipated six-month review by the FDA.[6]

SIMPLIFY THE JOURNEY™ WITH WEST

As therapies become more complex and shift towards self-administration, pharmaceutical and biopharmaceutical manufacturers are under pressure to bring devices to market that are both more intricate and easy to use. This is particularly challenging when constantly changing regulations place more responsibility on sponsors to prove not only that their drug is reliable and safe but also that the device is fully integrated and satisfies usability requirements. Relying on a provider with both combination product and services expertise allows manufacturers to simplify their supply chain and gain compelling benefits, such as fewer partners, improved knowledge transfer and scalability across a product's life cycle, and faster root cause analysis and resolution if problems arise.

West works as a true partner with its pharma and biopharma customers, and has supported multiple development programmes through its trademarked "Simplify the Journey" process. All of this experience adds up to an impressive résumé defined by a range of capabilities.

> "As therapies become more complex and shift towards self-administration, pharmaceutical and biopharmaceutical manufacturers are under pressure to bring more intricate devices to the market that are also easy to use."

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West offers:

- Leadership in testing and verification of complex injectable drug containment, delivery systems and combination products, with the ability to support design validation testing.
- An extensive resource knowledge centre built on over 90 years of experience in developing, testing, manufacturing and commercialising containment systems and devices.
- Proven containment and device design and development history, including experience taking products from concept to commercialisation.
- A seasoned team, including human factors, regulatory and device development experts.
- A breadth of capabilities and deep expertise to support combination products from preclinical to post-market launch.
- Integrated fill-finish services ranging from small-scale fills suitable for the clinic to commercial-scale production volumes.
- Over 50 years of contract manufacturing experience, including drug delivery devices, diagnostics and medical devices.
- A platform approach to shorten time to market.

West leverages these capabilities every day on behalf of the world's top pharmaceutical and biotechnology companies, and can help development teams navigate the challenges and mitigate the risks encountered on the path to commercialisation. West offers a full portfolio of vial container closure system solutions, as well as self-injection platforms, such as the SmartDose® drug delivery system, that can help accelerate product development. West supplements this offering with a suite of analytical services, contract manufacturing capabilities, regulatory guidance and a cadre of professionals dedicated to de-risking the transition to combination product – and developing patient-centric solutions that improve the health and quality of life of patients.

ABOUT THE COMPANY

West Pharmaceutical Services is a leading provider of innovative, high-quality injectable solutions and services. As a trusted partner to established and emerging drug developers, West helps ensure the safe, effective containment and delivery of life-saving and life-enhancing medicines for patients. With almost 10,000 team members across 50 sites worldwide, West helps support its customers by delivering over 40 billion components and devices each year.

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Simplify the Journey™ is a trademark of West Pharmaceutical Services, Inc.
Repatha® is a registered trademarks of Amgen Inc.
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ABOUT THE AUTHOR

Atul Patel joined West Pharmaceutical Services as Vice-President, Devices & Delivery Systems, in 2021, and he leads the portfolio strategy for drug delivery products such as wearable injectors, handheld injectors, needle safety devices, CZ syringes and hospital and home administration systems.Prior to West, Mr Patel led the Global Medical Device team at Biogen (MA, US), and was responsible for alignment of drug pipeline and device platform strategy, which included handheld injectors, wearable injectors andimplants, by leading an end-to-end device team, including tech exploration, product development, human factors & usability, device launch and CMO tech services. Before that, as the Worldwide R&D Director of Self-Administration & Injectable systems at BD, Mr Patel was responsible for development strategy and execution of drug delivery devices for various pharma and biotech customers.

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OPTIONS FOR ACTIVATION OF BATTERY-OPERATED MEDICAL DEVICES

Here, Tim Resker, Global Business Development Manager at Coto Technology, looks at new technologies for powering on battery-operated drug delivery devices while considering battery drain, ingress protection and user-friendliness.

Battery-operated, wirelessly connected devices are becoming increasingly pervasive in today's society. Driven forward by advancements in wireless and battery technologies, coupled with increasingly miniaturised electronic components that consume less power and cloud-based services ready to collect, analyse and disseminate data, these devices commonly instantiate themselves as handheld, wearable or implantable medical devices, such as those used for drug delivery.

Whether the device is a drug delivery device or vital sign monitor, whether it is handheld, wearable, ingestible or implantable, all share a set of common requirements: small size, long life, reliability and ease of use. One of the key design aspects of these products is how to power the device on when needed.

Powering on a medical device only when it is needed (or keeping it powered down when not in use) is vitally important because designers want to use the smallest, lowest cost battery possible. For this reason, extending battery life is always a design goal; battery drain must be minimised during use as well as before it has been powered on.

One popular example is continuous glucose monitors (CGMs), which are prescribed to help patients manage their diabetes. These devices adhere to the patient's body, continuously monitoring glucose levels. The resulting data is wirelessly transmitted to the patient, doctor and/or insulin pump. CGMs must be very small, waterproof, easy to attach and have a reasonably long life before they run out of battery power.

There are three basic options for powering on these devices at the point of use or deployment. For each of these options, essential variables for consideration are battery current drain, size, ingress protection and user-friendliness (Figure 1).

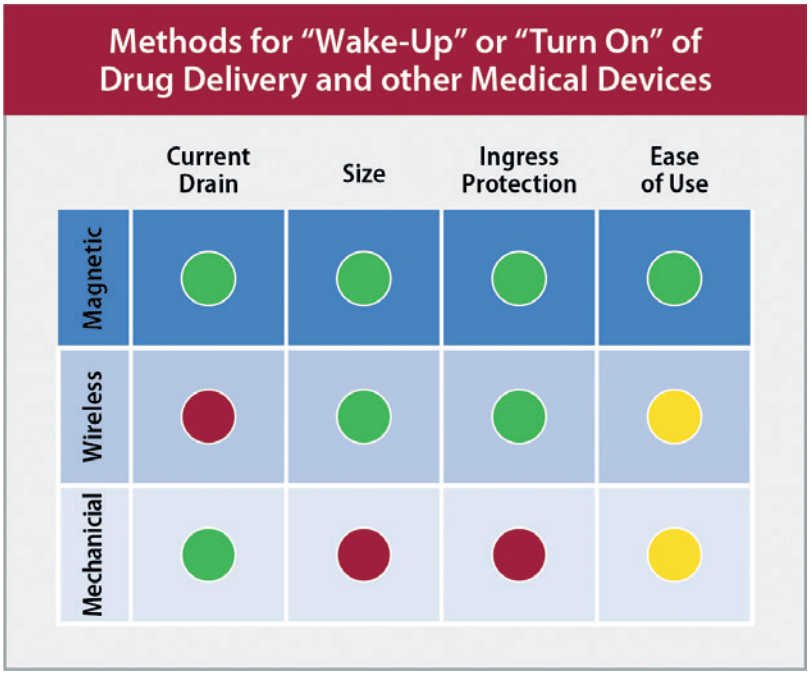

Figure 1: The TMR magnetic sensor offers almost zero power consumption in an ultra-miniature package size, and its contactless "power on" capability promotes ease of use.

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"There are three basic options for powering on these devices at the point of use or deployment. For each of these options, essential variables for consideration are battery current drain, size, ingress protection and user-friendliness."

ELECTROMECHANICAL

The first "power on" option is electromechanical – the common "switch". This option is the means for powering on most battery-operated electronic devices, such as laptops and phones. Although switches come in many forms, (e.g. push-button, slider or toggle) they operate on the same principle of opening and closing a mechanical contact to allow current to flow (when closed) or completely prevent it from flowing (when open). Regarding current drain, the electromechanical switch is highly efficient because it is a passive device that consumes no power. However, in terms of size, mechanical switches are a poor option, especially given the size constraints of many wearable, ingestible and implantable medical devices and other small Internet of Things devices. In terms of ingress protection (or the need to have a device that is impermeable to water and humidity), mechanical switches are not the best option because designing a switch that can be mechanically moved by the user into on/off positions while maintaining impermeability is challenging. Lastly, the consideration of user-friendliness, or ease of use, rates poorly with mechanical switches for two reasons. Firstly, there is a clear conflict between the requirement for a patient to manually activate a switch themselves and the design goal of the device having "out-of-the-box turn-on" – one demands manual activation, the other automatic. Secondly, a very small mechanical switch, necessitated by a very small device, could pose a problem for users' ability to actually move the switch between the on and off positions, thereby reducing usability. In summary, mechanical switches score highly in terms of current consumption but very low relative to ingress protection, size and ease of use.

"...mechanical switches score highly in terms of current consumption but very low relative to ingress protection, size and ease of use."

WIRELESS

Wireless power on is the second option to analyse. Because the devices already have wireless capabilities for data transmission, designers could technically use that same wireless capability to power on a device from a mobile phone app. From an ingress protection standpoint, powering on wirelessly is rated very highly, as well as from a size standpoint, as no additional components need to be added to the device for this functionality. However, from a current drain standpoint, wireless power on scores extremely low because a wireless receiver inside the device must be powered on to receive a signal to power on. For this reason alone, wireless power on is rarely used for devices that have stringent battery life requirements.

MAGNETIC

The third option is the use of a magnetic sensor inside the device to initiate the power on function. In this case, a magnetic field is applied to the sensor to trigger the power on. The magnetic

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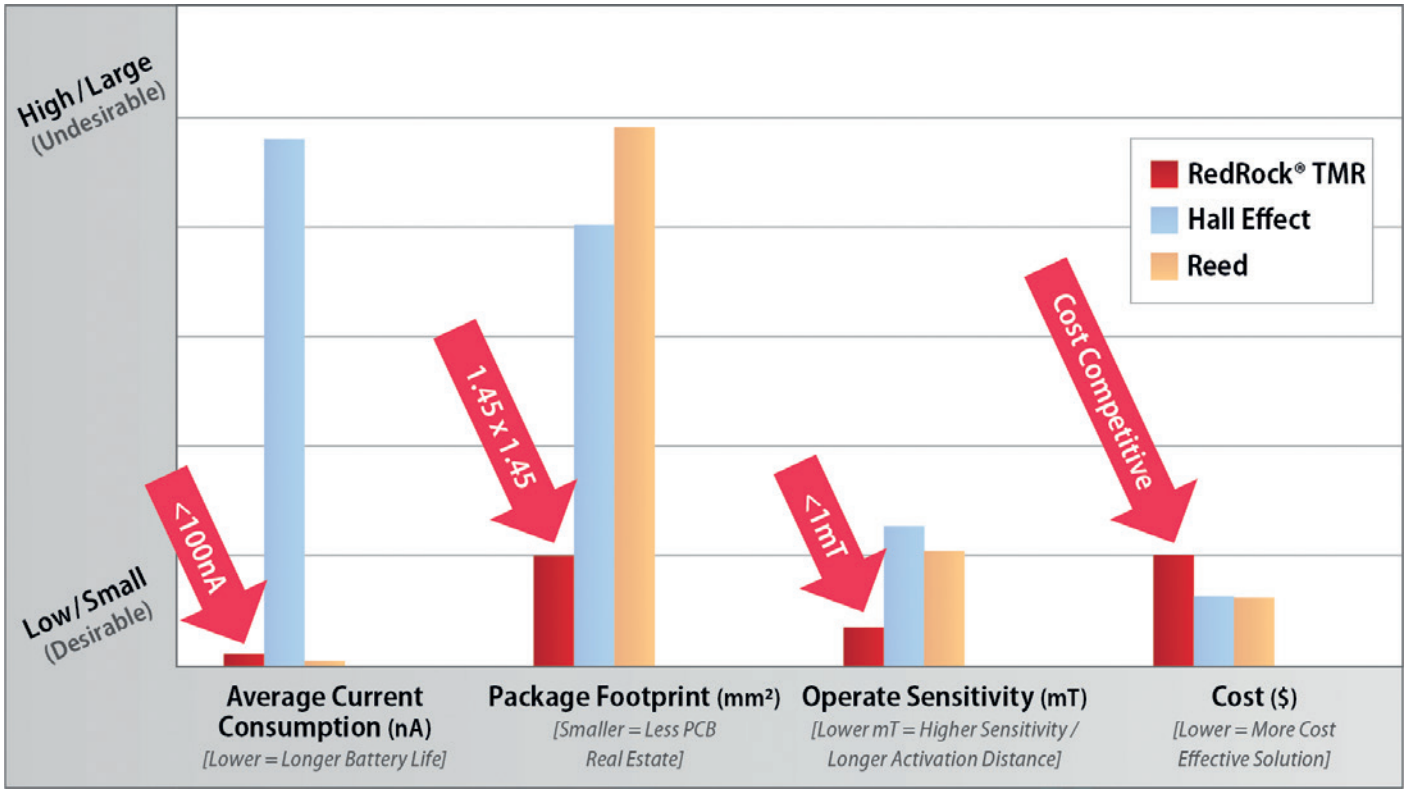

Figure 2: Magnetic sensing technology comparison.

> "Many new devices are designed with new tunneling magnetoresistive (TMR) sensing technology, which offers both very small size (as small as an LGA-4) and extremely low power consumption, similar to the reed switch."

field is typically produced by a magnet located within the product's packaging or in an auxiliary component to the device, such as an applicator for a CGM. The magnetic field can also be applied by the user swiping across the device with a handheld magnet. Magnetic sensing scores very highly for ingress protection because it is a "contactless" method. Magnetic sensing also scores very highly in ease of use – especially when the magnet can be embedded in the device packaging, enabling "out-of-the-box power on", or in an auxiliary component to the device, such as an applicator. Sometimes the device itself is designed as two components that must be connected at the time of deployment. In terms of current drain and size, the desirability of magnetic sensing depends entirely on the magnetic sensing technology in question (Figure 2). Older, more traditional magnetic sensing technology types were either small in size but high in power consumption (Hall effect) or large in size with zero power consumption (reed switches). However, many new devices are designed with new tunneling magnetoresistive (TMR) sensing technology, which offers both very small size (as small as an LGA-4) and extremely low power consumption, similar to the reed switch. In effect, TMR sensors offer the "best of both worlds".

CONCLUSION

With the current onslaught of new devices designed to be easier, safer, contactless and/or remotely operable, electronic designers are having to adopt new technologies to keep up with the evolving requirements of battery-operated medical and drug delivery devices. In terms of best capabilities relative to small size, low power consumption, ingress protection and ease of use, magnetic sensors – and TMR sensor technology in particular – are solving the problem of how to power on or activate battery-operated drug delivery devices.

ABOUT THE COMPANY

Established in 1917, Coto Technology is a worldwide market leader in the design and manufacture of advanced, high-reliability switching and magnetic sensing solutions sold into the medical, automotive, data acquisition, instrumentation, process control, telecommunications, automatic test equipment and security markets.

ABOUT THE AUTHOR

Tim Resker is the Global Business Development Manager for Coto Technology and works closely with solution providers in industrial, consumer, medical and commercial industries to address their magnetic sensing needs. Mr Resker has also worked for Analog Devices (MA, US) and other embedded technology suppliers in product marketing and business development roles.

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USING SIMULATION AND MODELLING VERSUS PROTOTYPING FOR MEDICAL RADIO FREQUENCY DESIGN

In this article, Enrico Denna, Hardware Engineering Manager at Flex, looks at the advantages of a simulation and modelling approach over prototyping for the design of medical products.

The growth of technology and end-user expectations are ever more important factors in many application areas, and medical devices are at the forefront of this innovation process. The requirements of an increasingly connected world have had a significant impact on electronic design and specifically on the area of radio frequency (RF), which, by its very nature, represents a major design challenge. Modelling and simulation are valid instruments to assist in meeting this challenge because electromagnetic design performance cannot be easily predicted in advance by relying solely on the designer's experience.

> "Several medical devices are becoming even smarter and more connected, storing big data, using apps and enabling functionality that substantially benefits users."

The world is becoming increasingly "smart". Less than 10 years ago, the smartphone was unknown, while, today, smart devices, connectivity, apps and data connection are ubiquitous parts of our vocabulary and our lives. Medical devices have naturally followed this trend and have adopted connectivity as a must-have feature to align with market demand. Several medical devices are becoming even smarter and more connected, storing big data, using apps and enabling functionality that substantially benefits users.

The design of these new features presents several challenges – one of the most critical aspects being the creation of a stable and reliable connection within a user-centric usage model. Here, we are talking about wearable models where devices are powered by smaller, sometimes non-rechargeable or non-replaceable batteries; devices that are typically either handled by, or are directly in touch with, the human body, such as insulin pens or drug delivery patch plasters; and devices that are used or stored in varying environmental conditions, not only at room temperature at home but also in the mountains, inside a car or kept in a refrigerator.

These new design requirements have spurred the creation of simulation tools to help designers refine their projects while saving time and costs during development, which, until now, has always been undertaken using trial-and-error. HFSS by ANSYS 3D electromagnetic simulation software is one of the most powerful tools available to assist designers with their projects.

> "These new design requirements have spurred the creation of simulation tools to help designers refine their projects while saving time and costs during development, which, until now, has always been undertaken using trial-and-error."

THE BENEFITS AND ADVANTAGES OF SIMULATION

A comparison of process flows reveals that, in a trial-and-error approach (Figure 1), the number of design phase iterations (n) to fine-tune and adjust the design results in an equivalent number of prototypes and

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tests, which must be conducted in an external lab with the RF instrumentation and accreditation to issue a formal certification. The cost of this process (C) is calculated from the costs of the prototyping and external laboratory testing, while the time to mass production (T) is derived from the time it takes to construct the prototypes, book the external labs, conduct the tests and issue the test reports. All these steps must be multiplied by n.

In the simulation approach (Figure 2), n only affects the number of simulations that may take a time (t) of some hours or days depending on the complexity – this time is obviously significantly shorter than the weeks necessary to realise and test a prototype. Furthermore, the only person involved in a simulation is the designer, while any prototyping test involves several experts (layout engineer, purchasing office, test operator, local prototype producer and financial office).

Another disadvantage of prototyping is linked to the time needed to take delivery of the prototype, during which the designer is unable to work on this project. Taking all this into consideration, it is clear that the prototyping process is inefficient and easily justifies the investment in a simulation tool, which can be amortised in just a few years of design activity.

The improvement realised by the introduction of simulation is clearly evident in some design examples. Figure 3 shows the modelling of the coupling of an RF identification (RFID) tag and reader the simulator enables the engineer to replicate the coils of both the tag and the reader (Figure 3A) and then to examine the magnetic field coupling between the two elements according to the spatial distance (Figure 3B).

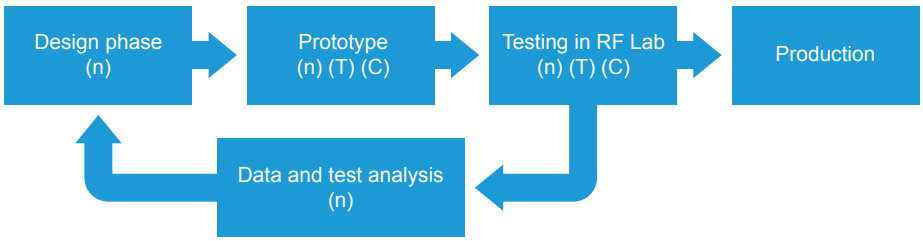


Figure 1: Standard trial-and-error approach. Final cost of the process is calculated according to the (T)ime and (C)ost of prototyping multiplied by the number of prototyping iterations (n).

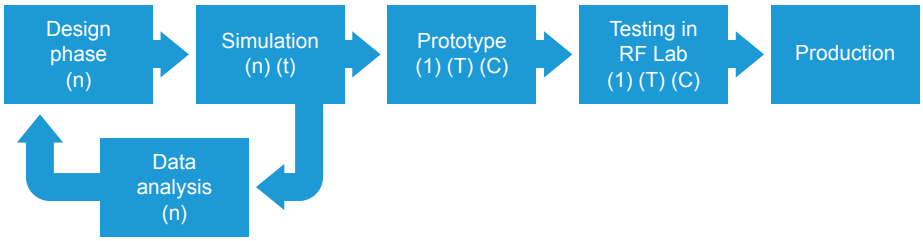
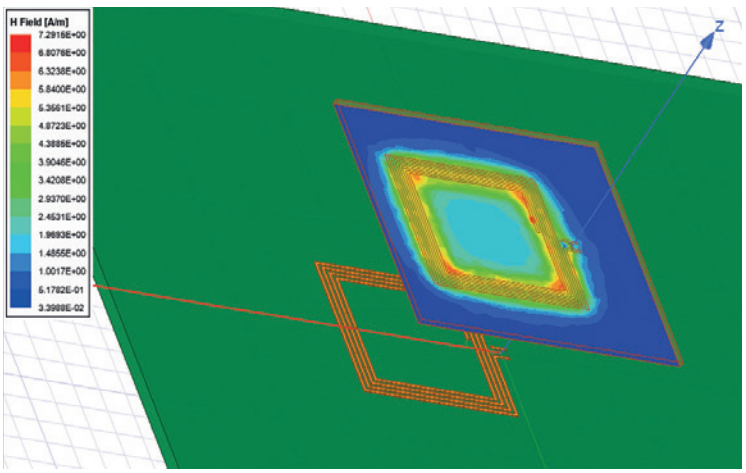


Figure 2: Simulation approach. Final cost of the process is calculated according to the (t)ime of simulation multiplied by the number of simulation iterations (n). It is evident that the cost of the trial-and-error approach (n*T*C) will invariably be higher than that of the simulation approach (n*t + 1*T*C).

Electrical designers typically begin by focusing on the printed circuit board assembly (PCBA) and Bluetooth antenna design, applying their experience and RF knowledge to implement the application notes and guidelines of the RF module and the integrated or chip antenna selected. This leads to a PCBA design that respects the ground planes and transmission lines and has controlled impedances, which then guides the layout engineer to design the microwave traces with the appropriate thickness and dimensions (Figure 4).

However, this approach may be inadequate – the mechanical parts of the device, particularly where there are multiple boards assembled together, and the metallic parts, such as the battery body, motor engine or display holder, can significantly affect the electromagnetic field. These side effects are difficult to predict in the trial-and-error approach, resulting in an increase in n. The simulator makes it possible to import complete mechanical and electrical files (such as STEP and BRD files, for instance) to obtain a complete model of the device in which it is possible to assign a material to any component using the simulator's internal library.

(A)



(B)

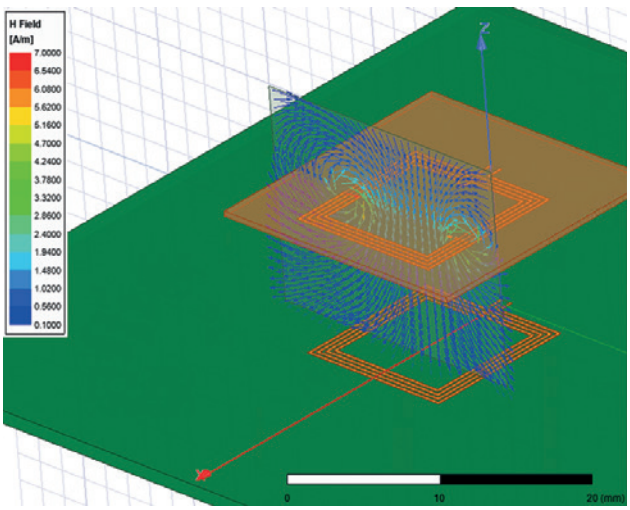


Figure 3: Modelling and simulation of an RFID tag with its reader.

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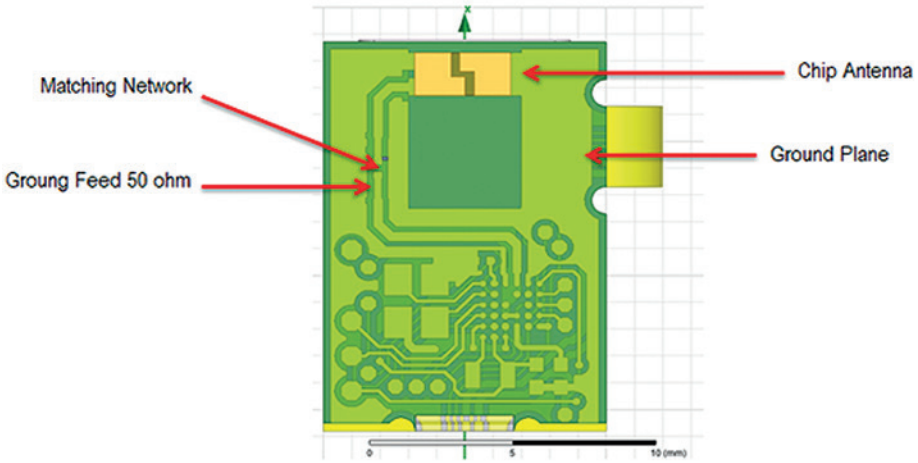

Figure 4: Example of PCBA with a chip antenna.

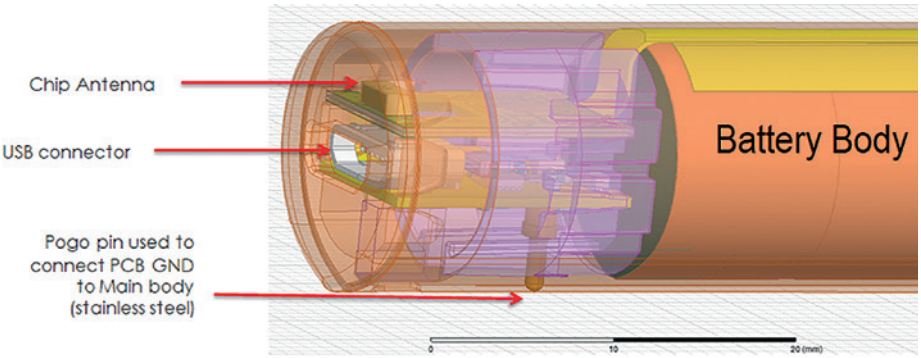

Figure 5: A 3D design of the final device including electronic PCBA and mechanical parts.

Figure 5 shows part of a pen-shaped device into which the PCBA illustrated in Figure 4 has been introduced and connected to a micro-USB connector. The device housing is made of steel with a rechargeable battery on the back of the electronic location. The PCBA is connected to the housing via a pogo pin that grants a ground connection.

This set-up and similar systems can dramatically affect both the RF transmission and the Bluetooth antenna. Once assembled, as shown in Figure 5, this system has a completely different radiation pattern compared with the initial configuration visible in Figure 4.

Figure 6 illustrates the 3D radiation pattern generated by the simulator, which immediately informs the designer that the best direction for radiation is on the back, as opposed to on the body of the battery. This could be due to internal

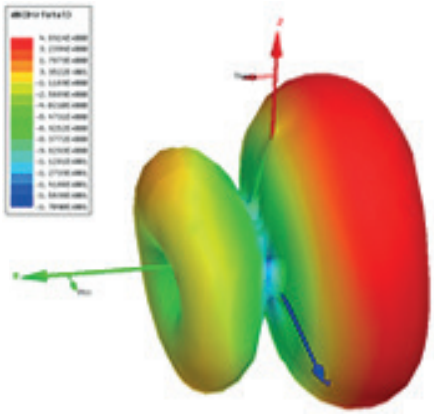

Figure 6: 3D radiation lobe.

reflection caused by metallic parts or to the mechanical portions of the opening, both of which are compatible with this wavelength.

This result is very unusual, and therefore difficult to predict. The simulation result has therefore avoided a prototype round because, previously, the only way to have discovered this behaviour would have been to test a prototype and then to rework the device to increase the performance in the forward direction; the simulation allows this behaviour to be addressed in advance.

The simulator makes several pieces of data available both graphically and numerically: 3D radiation lobes, animations of 3D phase radiation (Figure 7) and impedance and Smith charts suitable for S11 tuning and power transmission (Figure 8).

Simulation makes another major contribution during the design of a PCB antenna. In the trial-and-error approach, the application note or reference design are often only indicative (and sometimes ideal). This generally increases the number of iterations required because it is not always possible to rework the antenna,

"Simulation plays another fundamental role here by providing a model of the human body complete with skin, bones and internal organs into which it is possible to introduce the device to study its behaviour and the effect on the radiation patterns."

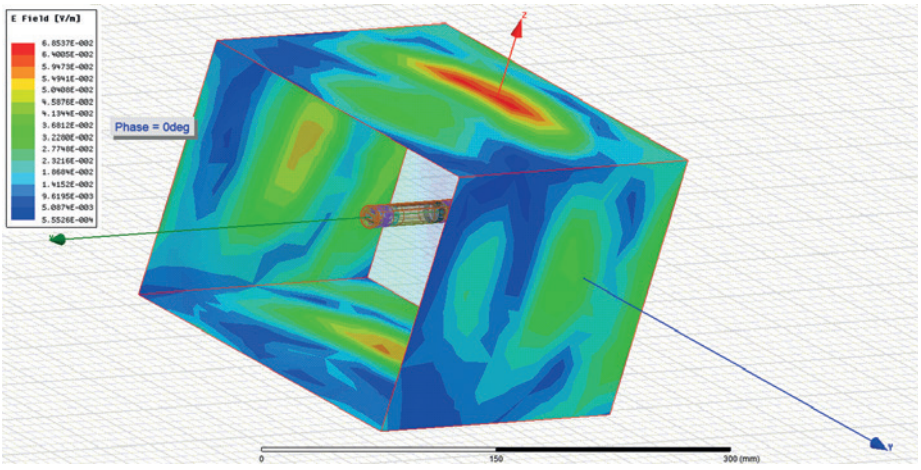

Figure 7: Animation of 3D phase radiation.

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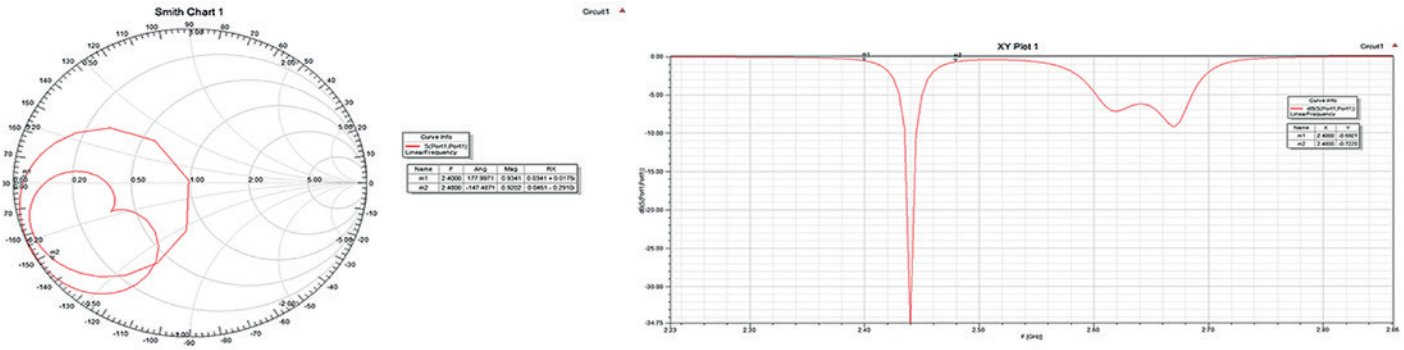

Figure 8: The simulator provides substantial engineering data. Here, you can see the Smith Chart and the S11 parameter suitable for antenna tuning and Q factor definition.

particularly for high radio frequencies where some tenths of a millimetre in the track dimensions can make a difference. An innovative solution could be accomplished using an antenna derived from the metallic parts already present in the mechanical device (Figure 9). Such a design would be easier to simulate several times before moving on to creating a prototype device once the engineer is closer to achieving the final solution.

In medical and wearable devices, the effect of the human body is not negligible – microwaves generated by Bluetooth or Wi-Fi connections are absorbed by human tissue. Simulation plays another fundamental role here by providing a model of the human body complete with skin, bones and internal organs into which it is possible to introduce the device to study its behaviour and the effect on the radiation patterns.

Figure 10 shows the simulation of a Bluetooth device attached to the shoulder of a patient. The field strength is measured at the level of the trouser pocket, which is where a smartphone would usually reside while receiving the data. This simulation allows the designer to better understand the result and the

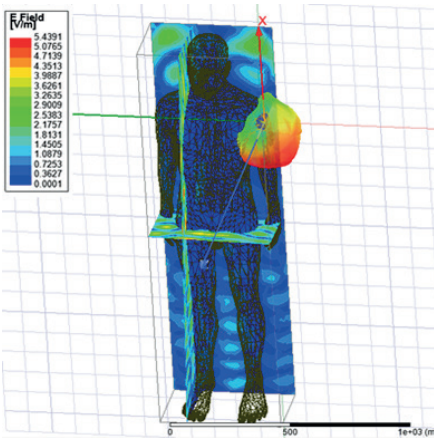

Figure 10: Human body model available in the simulation tool.

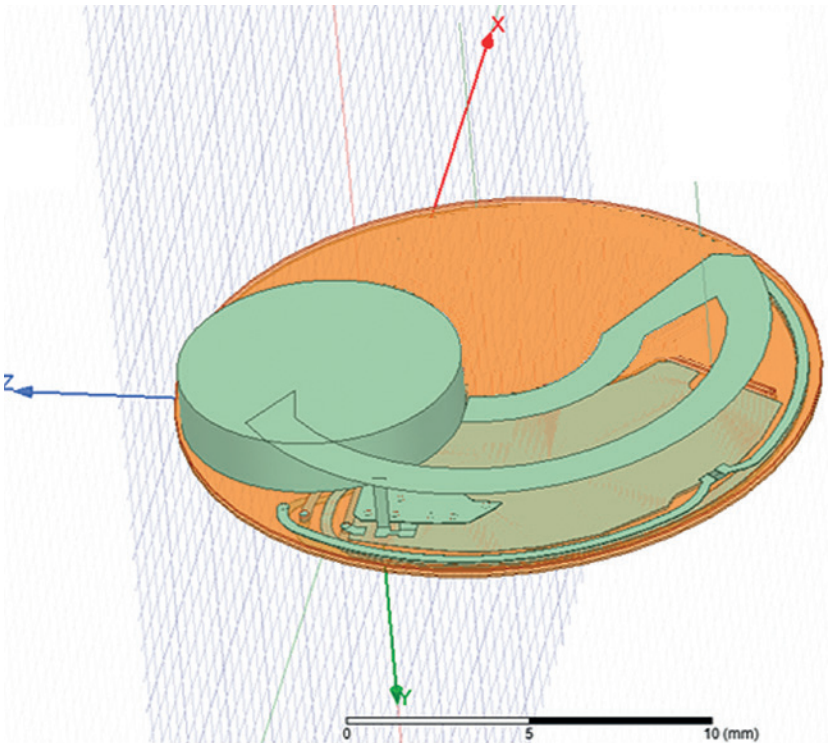

Figure 9: Metallic antenna derived from the battery clip.

reference direction of the radiation in the presence of a human body, making it possible to tune the design and also gain useful information for the usage model. It also provides an indication of other safety parameters, such as the specific absorption rate.

To optimise the confidence of the simulation result, the model can be validated during the first prototyping round. In this case, the results of tests carried out in an anechoic chamber using RF instrumentation and possible human dummy material (Figures 11 and 12) can be compared with the results obtained with the simulation, allowing the simulation model to be fine-tuned by adjusting some of the parameters or corrective coefficients in its configuration. After this final step, the designer has a powerful model that truly represents the functioning of the device inside its usage environment and that can be easily used to evaluate modifications, or as a reference for similar new devices.

"The clear advantages of the simulation approach are motivating more companies to consider investing in these tools to improve their design processes."

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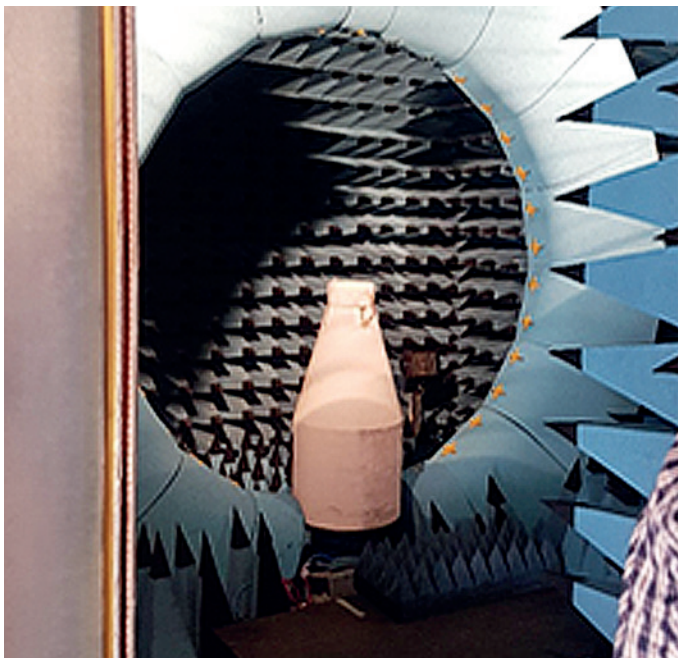

Figure 11: Measurement of a device in an anechoic chamber using a biological dummy.

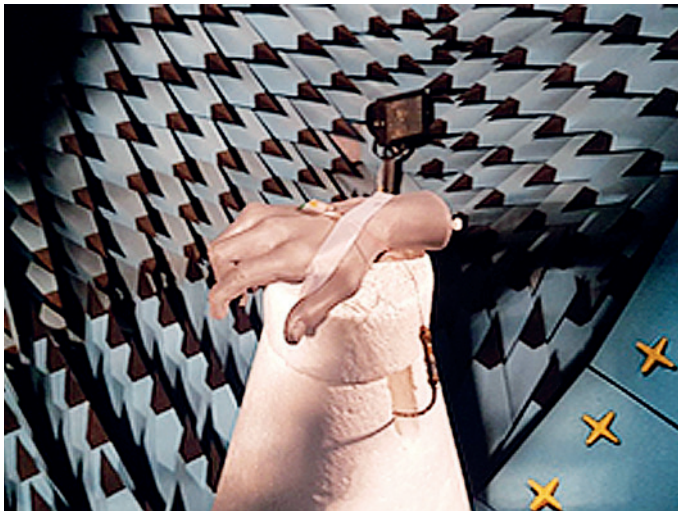

Figure 12: 3D radiation pattern measurement in anechoic chamber.

The power of this tool can be supported by other subtools, such as Optimetrics, which enables a parameter to be optimised or the optimal coefficient of the design to be found using automatic and iterative simulations. Other tools and add-ins can also be introduced to support thermal or impedance simulations.

The clear advantages of the simulation approach are motivating more companies to consider investing in these tools to improve their design processes. There are several benefits: the cost and time savings during production, the improvement of the designers' know-how and competence because of the ability to experiment (and thereby increase their knowledge and motivation in a field that is not always intuitive or easy to master) and, last but not least, simulation provides a structure to the design process that will inevitably be recognised by customers who will appreciate a more professional approach.

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ABOUT THE COMPANY

Flex provides sketch-to-scale solutions, delivering innovative design, engineering, manufacturing, real-time supply chain insight and logistics services to a wide range of industries. Flex Health Solutions is a global leader in the design and manufacture of medical products for pharmaceutical and medtech companies. This includes the design and commercialisation of more than 75 regulated medical devices, from pens and auto injectors to pumps and inhalers. The company's approach is supported by FDA-registered and ISO 13485-compliant facilities and a world-class quality system.

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