WEARABLE INJECTORS

ON drugDELIVERY
CELEBRATING OUR 100TH ISSUE

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WEARABLE INJECTORS

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

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Front cover image from Emergo by UL's article, "A Quick Guide to Usability for Wearable Injectors (see this issue, Page 49). Reproduced with kind permission.

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KEY CHALLENGES IN SUCCESSFUL WEARABLE DRUG DELIVERY & PATIENT SELF-ADMINISTRATION

In this article, Matthew Huddleston, Executive Vice-President and Chief Technology Officer, Andrew Eibling, Vice-President, Business Development and Alliance Management, and Jennifer King, Marketing Manager – all of Enable Injections – look at the key challenges involved in successful wearable drug delivery technology and patient self-administration.

Cutting-edge biologic therapies often require patients to receive treatment through frequent intravenous (IV) infusions at a hospital or infusion clinic. But what would happen if those same biologics could be given by the patient via a simple through-the-skin infusion at home? Why has there not been a greater push for wearable technology that allows people to self-administer infused medicines at home?

Armed with game-changing technology which makes this a possibility, Enable Injections' goal is to reduce the treatment burden on people living with a wide range of conditions and put control back into the hands of the patient.

> "There exists the need for a cost-effective, simple-to-use, large-volume, subcutaneous, self-administration infusion system which creates real value for both pharmaceutical companies and patients."

The world is ready for the possibility. US Healthcare costs are increasing at a rate of 3-4% per year.[1] Evidence shows a reduction in the overall cost when therapy is administered in the home compared with a doctor's office or clinic.[2] Patients are ready for it too. Evidence shows improved compliance and adherence to medications when patients can complete the therapy at home compared with administering infusion in the physician's office or clinic.[3]

Up to this point, technology has been the limiting factor. Biologic therapies often start with IV infusion and require large volumes for efficacy. Transition to subcutaneous delivery may even require higher volumes due to bioavailability. These large volumes are not suitable for administration via autoinjectors and prefilled syringes. Large infusion pumps are available for subcutaneous delivery in the home but they are complex and often require in-home infusion services for administration.

There exists the need for a cost-effective, simple-to-use, large-volume, subcutaneous, self-administration infusion system which creates real value for both pharmaceutical companies and patients. With the right technology, the market environment is primed to transition.

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PHARMA CHALLENGES

Cost

Patient-centric delivery devices must provide value and simplicity for the patient, whilst minimising development costs and maximising speed to market for the pharma company. The technologies being developed for the on-body infusor market are varied and introduce different development and manufacturing costs.

Container

Therapeutics start their lives in liquid or freeze-dried (lyophilised) form within standard vials. The challenge for large-volume, wearable delivery devices is that the standard container closures are not designed to be a component of a wearable delivery device. Autoinjectors (pens) and pumps have proven to be exceptionally valued for relatively small volumes (insulin) but the wearability of large volumes required for therapeutic dosing for biologics and biosimilars is a challenge.

To accommodate the challenge, large-volume infusor developers incorporate custom container cartridges into the delivery device design. The transition from a standard vial to a custom container introduces a host of other risks for pharma and biopharma companies, including extended stability testing, sterility issues, and packaging and transport challenges.

Delivery Challenges

Small- and large-molecule therapeutics present unique delivery challenges for drug delivery devices. Small volumes of these therapeutics have been traditionally delivered by autoinjectors with success, up to volumes of 2.5 mL. For doses larger than 2.5 mL, traditional electromechanical infusion pumps with accompanying infusion sets have been developed but are complex and not conducive to self-administration at home. Eight of the 10 most established companies developing on-body infusors have stuck with existing electromechanical or spring-driven pump technology and simply incorporated the extension set and needle within the device. These technologies are challenged by higher volume and viscosity deliveries, as they rely on a container for the drug coupled to a power source. These systems can become problematic to wear with volumes above 10 mL. The enFuse device (see Box 1) uses a sequential elastomeric toroid pump, which does not require batteries to drive the pump or lights for function indicators. The container is the power source, making the enFuse efficient and small for its delivery volume.

Molecular Integrity

Whatever method is used to deliver the drug, the delivery device cannot impact the integrity of the molecule being delivered. Care must be taken to ensure that whatever source it uses to deliver the drug, the function does not harm the drug substance.

Accuracy

The delivery device must also be accurate, delivering the prescribed dose as intended – no more, no less. This presents challenges for residual volume that may be left in the cartridge, container or reservoir after

BOX 1: THE ENFUSE ON-BODY INFUSOR

The enFuse™ platform of delivery devices is designed to enable patients to self-administer treatments at home. Moving treatment from a hospital setting to the home may potentially provide easier, more cost-effective treatments.

The enFuse is designed to deliver large volumes (up to 50 mL) of small-molecule and biologic therapeutics by the patient at home. General use on-body infusion devices able to deliver large volumes are not currently commercially available and other standard, general-use infusion pumps may require assistance from a medical professional to receive therapy at home. The enFuse technology is one of the market leaders in delivering larger volumes in a lightweight, easy-to-use device.

We believe that enabling at-home self-administration with the right wearable infusion technology can help patients can get their lives back.

"A platform technology that can be deployed across a wide range of drug products provides incredible value to the pharma company as they don't have to invest in developing and commercialising several different delivery solutions."

"It stands to reason that reducing complexity leads to a reduction in the potential for use errors and higher acceptance of the technology."

delivery. The delivery technology must account for every drop of the medication as well as ensure proper delivery into the correct anatomical space.

To accommodate for potential residual left in the device, pharma companies can overfill containers based on excess overfill guidance for viscous fluids.[5] However, this overfill can be costly. The more accurate and complete the delivery, the greater the cost saving for pharma companies providing expensive therapeutics.

Asset Value

The ease of use and patient friendliness of the delivery technology has the potential to have a significant impact on the asset for each pharma company. If a patient population is more apt to adhere to their prescribed regimen, that regimen has a greater chance of being successful – leading to a better outcome for the patient. Additionally, for pharma companies that enter highly competitive markets or those that anticipate generic competition, an on-body infusor with high patient acceptance and adherence will differentiate its therapeutic from the competition. Lastly, a platform technology that can be deployed across a range of drug products with widely varying characteristics (e.g. delivered volume, viscosity, flow rate) provides incredible value to the pharma companies as they don't have to invest in developing and commercialising several different delivery solutions. These true platform technologies allow pharma companies developing combination product therapeutics in conjunction with a delivery device to get to market faster with less investment and risk.

Manufacturability

The intricacy of a device, along with its manufacturability, impacts the overall price of the on-body infusor, as well as its ability to scale to market. For example, prefilled, preloaded drug delivery devices typically require aseptic assembly techniques which make manufacturing the combination product more challenging. Drug delivery device companies need to demonstrate investment in high-volume manufacturing from an early stage of development in order to benefit pharma partnerships in the long term.

Safety

Safety factors are an essential for delivery systems. As with any device, on-body infusors must operate precisely as they are engineered to function. The device and packaging need to perform as designed, and all the essential parts of the device must be sterile upon delivery to the patient.

Engineering verification, clinical studies and human factor validation studies establish the device's safety during development. A mature quality management programme with proper document and device tracking helps to guide the development and launch of delivery devices and respond to potential issues post-market.

PATIENT CHALLENGES

Living with a medical condition is difficult and travelling to a healthcare facility for IV infusions makes life even more challenging. But with the promise of self-administration treatments at home, a patient can get part of their life back.

Size

One prohibitive factor for patients is the size of the device itself. For patients to use an on-body infusor, the device must be comfortable and easy to handle, especially for those who have dexterity and mobility challenges.

The size of a device grows quickly when pumps, batteries and traditional vials or cartridges have to be incorporated. The larger the device, the heavier it becomes, and the more difficult it can be to ensure it remains adhered to a patient's skin at the intended location for the duration of the infusion. A lighter, less bulky infusor allows the patient to have a more comfortable experience. In addition, a more discreet delivery device permits the user to go about their normal activities as they wear the infusor.

Steps

It stands to reason that reducing complexity leads to a reduction in the potential for use errors and higher acceptance of the technology. Device designers must take into account the number of steps a patient must execute in order to administer their treatment. Human factors testing helps to elucidate potential failure modes and ensure the overall design and instructions for use are adequate. However, the number of steps required may not be sufficient in assessing the overall risk of error; the complexity of those steps must also be assessed.

Most on-body infusors in development have defaulted to using prefilled cartridges which are often already preloaded into the infusion device for the patient. Using these devices requires multiple steps by the user that may not be obvious. Often this begins by removing the device from cold storage and allowing it to warm to room temperature which could take up to an hour.[6] Notwithstanding the injection tolerability of a cold drug, some of these devices will not perform properly due to the high viscosity of the cold drug. While a patient-filled and loaded device requires an additional step to load the device, this may be preferred to waiting to start the infusion, especially if it could be used immediately after loading. The challenge for designers is to ensure loading the device is as simple as possible.

To aid the patient in self-administration, companies like Enable Injections are developing training devices. In addition, Bluetooth connectivity options can assist the patient in steps required for administration, as well as prompt convenient reminders for date and time for administration.

Digital

With Bluetooth connectivity built into an on-body infusor, caregivers and other

"While a patient-filled and loaded device requires an additional step to load the device, this may be preferred to waiting to start the infusion, especially if it could be used immediately after loading."

people involved in a patient's care can remotely monitor a patient's infusion. Real-time data can be transmitted in a low-energy signal and can often offer proof that the infusion was performed, as well as provide other meaningful data. With appropriate permissions given, digital data transmitted by Bluetooth connectivity can provide information to healthcare providers and payers – and could provide a means of confirming adherence.

Cost

Decreased healthcare deductibles could provide extra incentive for patients to perform their infusions at home via on-body infusors. By administering at home, patients can decrease their healthcare expenses and administration costs, as well as eliminate travel to and from a healthcare facility for infusions and the disruptions to normal life routines including school and work missed due to IV infusion.

Safety

Many patients experience a psychological burden of undergoing treatment involving any type of needle, including IV needles, autoinjector needles and prefilled syringes. An exposed needle any time during the administration can be an intimidating factor for many patients. With a well-designed on-body infusor, the patient does not need to be exposed to the needle at any time before, during or after the infusion, which may alleviate the psychological burden and enable them to adhere to treatment.

Patient Value

By reducing travel, the risk of acquiring an infection in a clinic and the cost of healthcare administration of IV therapeutics for many disease states, on-body infusors have the potential to provide value and improve quality of life for the patient.

THE IMPACT OF WEARABLE TECHNOLOGY

Currently, delivery of large-volume biologic and small-molecule therapeutics is inconvenient, expensive and difficult. However, new technology developments with on-body infusors which can deliver large volumes safely and conveniently in the home can change the treatment paradigm and create an improved patient experience.

> "New technology developments with on-body infusors which can deliver large volumes safely and conveniently in the home can change the treatment paradigm and create an improved patient experience."

Patients will benefit, and pharma companies will be able to differentiate products through a patient-preferred, on-body infusor platform.

Enable Injections is one such company developing and manufacturing large-volume on-body infusors, with the goal of moving patients out of the clinic, reducing the cost of healthcare and improving patient quality of life.

ABOUT THE COMPANY

Enable Injections is an investigational-stage company developing and manufacturing on-body subcutaneous infusion delivery systems designed to help improve patient quality of life. Enable's body-worn enFuse drug delivery platform uses standard container closure systems to deliver large-volume, high-viscosity pharma and biopharmaceutical therapeutics.

REFERENCES

1. *Kamal R et al, "How much is health spending expected to grow?". Peterson-Kaiser Health System Tracker, 2019.*
2. *Schmidt B, "Home Infusion Therapy: Safety, Efficacy, and Cost-Savings". PSQH, 2012.*
3. *Beijer S, "Treatment adherence and patients' acceptance of home infusions with adenosine 5'-triphosphate (ATP) in palliative home care". Support Cancer Care, 2008, Vol 16(12), pp 1419-1424.*
4. *"Subcutaneous Biologics, Technologies and Drug Delivery Systems 2018-2030 (2nd Edition)". Research Report, Roots Analysis, 2018, pp 243.*
5. *"Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products". US FDA, 2015.*
6. *Prescribing Information for Repatha (evolocumab) injection, Amgen. February 2019.*

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MITIGATING RISK TO DELIVER SUCCESS IN HIGH-VOLUME WEARABLE DEVICES

As wearable injectors rapidly emerge onto the market, the scale, volume and sophistication of manufacturing must increase quickly to meet demand whilst reducing or eliminating risk. Here, Catherine Thacker, Director, Pre-Automation Solutions, and Bill Jaworski, Director, Life Sciences Business Development, both of ATS Automation, discuss risk management strategies, including an example where autonomous intelligent vehicles and ATS's real-time industrial internet of things manufacturing intelligence system, Illuminate®, were employed as risk reduction solutions in the manufacturing architecture for a wearable injection device.

Looking out over the production floor, you see many machines, each apparently advancing the efforts of the previous – but there are no connecting conveyors. You do not see anyone moving parts between machines. Then you notice small carts transferring trays of parts from machine to machine but you do not see any tracks or guides in the floor. A fleet of autonomous vehicles (Figure 1) is moving through a production space in an elaborate dance, moving parts and continuing a complex manufacturing process. It all happens so smoothly and efficiently – no collisions, no near misses. Film scene or reality?

> "A fleet of autonomous vehicles is moving through a production space in an elaborate dance... it all happens so smoothly and efficiently - no collisions, no near misses."

COMPLEX PROGRAMMES POSITIONED TO DEAL WITH INHERENT RISK

Every project has risk associated with it – to assume otherwise or to execute a project without anticipating and planning for unique challenges would be naïve. Yet people continue to do so, always hoping that this will be the one time that risk does not derail a project or that the challenges will be manageable. It appears to be expeditious and the reward more immediate if we boldly leap out of the gate and start the race. But not if we trip over the starting block and lose valuable seconds righting ourselves before continuing or, worst case, starting all over. Risk management allows us to view the current environment and think through each of the phases and steps to ensure not only a solid start but also a sustained pace that helps ensure success.

There are many articles, blogs and textbooks about risk categories, types and management. Some general risk categories include: schedule, costs, quality, performance, scope, resources, customer satisfaction, technical, budget and operational (Figure 2). It is not the intent of this article to expound on these. Rather, through real-life examples, we will demonstrate some of the ways that ATS has helped customers to navigate their project risks successfully.

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Figure 1: Autonomous intelligent vehicles providing a lower-risk solution.

- Schedule
- Costs
- Quality
- Performance
- Scope
- Resources
- Customer satisfaction
- Technical
- Budget
- Operational

Figure 2: Some examples of risk categories.

ATS Automation has been in business for more than 40 years, supplying bespoke systems to some of the world's largest manufacturers. With over 30,000 systems deployed around the globe, ATS has a proven track record of delivering to customer specifications and expectations. The life sciences division has collaborated with many Fortune 100 life sciences companies to deliver compliant assembly solutions at all phases of a product's development lifecycle – product design, clinical trials, launch, ramp, maturity, and "new and approved" product relaunch or product extension launch.

The sheer variety of projects has meant that ATS has a vast knowledge library of what works and, conversely, what will be challenging based on thousands of data points. As a result, ATS is the partner that medical device, pharmaceutical and diagnostic companies turn to over and over again to minimise or mitigate risk and to ensure best-in-class delivery.

RISK IDENTIFICATION

Helping to ensure success for our clients starts with identifying the potential areas of challenge or risk. We believe that leveraging the basic framework of people, process and technology is key to helping us identify risk (Figure 3).

People

At ATS, we have continued to evolve how we best engage with the customer and develop a strong symbiotic relationship that positions both organisations for success. This evolution has moved from a transactional, single point of contact to an interwoven, multimodal relationship that ensures that various levels of our client's organisation are communicating with various levels and individuals within ATS. This multi-layer interaction, when paired with active listening, helps surface the real needs and a more complete understanding of the programme. It also provides a rich platform to collaborate on potential solutions and get agreement on success factors.

A network of individuals all providing inputs to help ensure success could be its own risk without a firm understanding and management of roles and responsibilities. Our global organisation and depth of expertise allows us to welcome the right mix of people and experiences into the fold as well as ensure that the project team is not biased with too many project managers, too few operational people, a disproportionate representation of product developers or an inappropriate number of engineers.

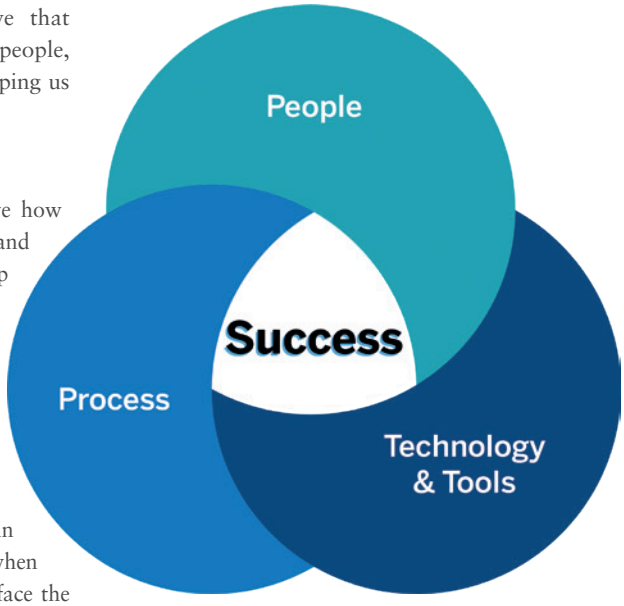
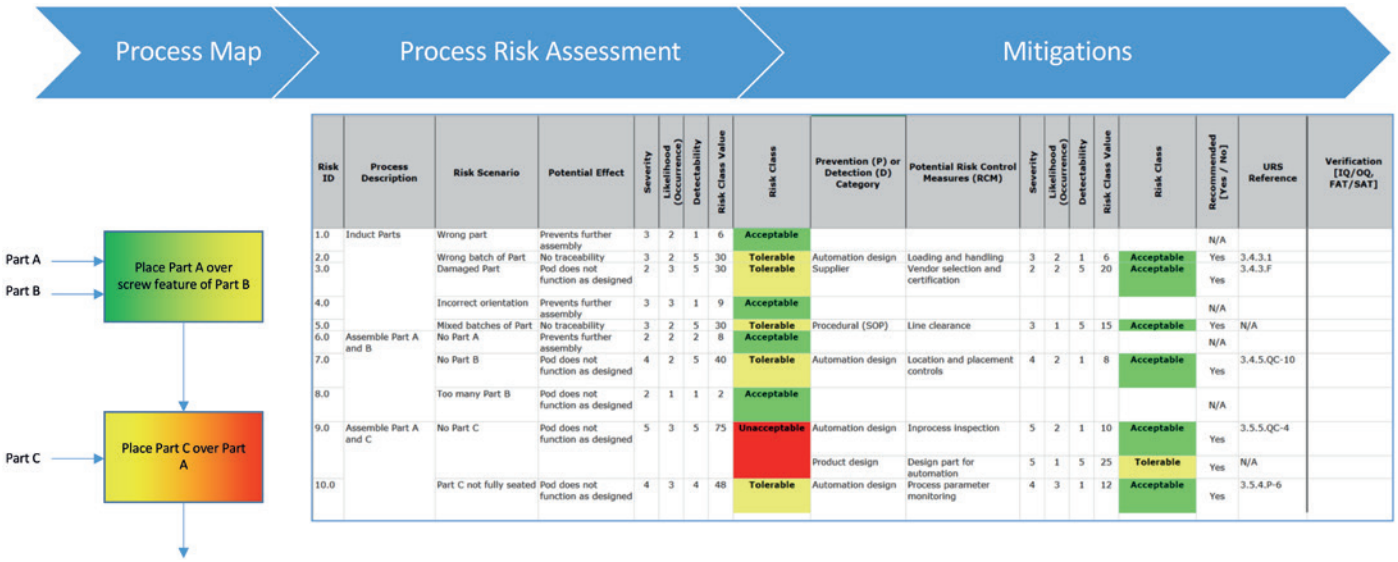


Figure 3: Identification and mitigation of program risk at ATS.



Risk ID	Process Description	Risk Scenario	Potential Effect	Severity	Likelihood (Occurrence)	Detectability	Risk Class Value	Risk Class	Prevention (P) or Detection (D) Category	Potential Risk Control Measures (RCM)	Severity	Likelihood (Occurrence)	Detectability	Risk Class Value	Risk Class	Recommended [Yes / No]	URS Reference	Verification [IQ/OQ, FAT/SAT]
1.0	Induct Parts	Wrong part	Prevents further assembly	3	2	1	6	Acceptable								N/A		
2.0		Wrong batch of Part	No traceability	3	2	5	30	Tolerable	Automation design	Loading and handling	3	2	1	6	Acceptable	Yes	3.4.3.1	
3.0		Damaged Part	Pod does not function as designed	2	3	5	30	Tolerable	Supplier	Vendor selection and certification	2	2	5	20	Acceptable	Yes	3.4.3.F	
4.0		Incorrect orientation	Prevents further assembly	3	3	1	9	Acceptable								N/A		
5.0		Mixed batches of Part	No traceability	3	2	5	30	Tolerable	Procedural (SOP)	Line clearance	3	1	5	15	Acceptable	Yes	N/A	
6.0	Assemble Part A and B	No Part A	Prevents further assembly	2	2	2	8	Acceptable								N/A		
7.0		No Part B	Pod does not function as designed	4	2	5	40	Tolerable	Automation design	Location and placement controls	4	2	1	8	Acceptable	Yes	3.4.5.QC-10	
8.0		Too many Part B	Pod does not function as designed	2	1	1	2	Acceptable								N/A		
9.0	Assemble Part A and C	No Part C	Pod does not function as designed	5	3	5	75	Unacceptable	Automation design	Inprocess inspection	5	2	1	10	Acceptable	Yes	3.5.5.QC-4	
									Product design	Design part for automation	5	1	5	25	Tolerable	Yes	N/A	
10.0		Part C not fully seated	Pod does not function as designed	4	3	4	48	Tolerable	Automation design	Process parameter monitoring	4	3	1	12	Acceptable	Yes	3.5.4.P-6	

Figure 4: Example of a risk heat map.

Process

ATS's project management process and techniques closely follow from the PMBOK Guide and PMI global standards. It is our project management discipline that allows our organisation to not only manage the layered customer engagement spoken about above but also ensure that the long-term goals are top of mind, success factors are being met and overall programme progress is being made. There has to be someone who keeps the team on track and meeting the programme deliverables. In many respects, it is rigour behind tracking scope, budget and schedules, and the communication to key stakeholders, that drives success more so than the unique, out-of-the box, engineered solution.

Technology & Tools

Tools are enablers. Developed correctly, tools act as efficient procedural reminders and checklists. Used appropriately, tools document findings, decisions and supporting justifications, and inform future choices. Through the lifecycle of a complex project, ATS regularly employs tools such as product design for manufacturability and assembly, product/process/equipment failure mode and effects analysis, total cost of ownership modelling, requirements trace matrix and simulation.

> "Developed correctly, tools act as efficient procedural reminders and checklists. Used appropriately, tools document findings, decisions and supporting justifications, and inform future choices."

One of the primary tools we deploy is a risk heat map (Figure 4). As product and process risks are identified, this tool helps the programme team categorise, visualise, prioritise and communicate those risks. From this prioritised list it is then possible to explore means to mitigate the most pressing risks identified.

The prioritised list of risks is then worked through with a cross-functional team to fully define the risk and develop plans to de-risk or lower the risk profile of the challenge. Where innovation, unique technologies or a new process may be required, technology experiments or proof of principle (PoP) tests may be conducted. These technology studies are designed with specific identified objectives and then representative systems or experiments are built to demonstrate that the solution adequately reduces the risks (performance, capability, feasibility, reliability, safety, etc).

Another way technology can be deployed is via simulation modelling. Digital and animated representation of the processes and procedures allows systems designers to analyse flow assumptions, review different designs concepts and predict overall equipment efficiency (OEE). Modelling and simulation can be used in many cases to prove out a solution but without some of the costs associated with developing a physical technology experiment or PoP.

It is through this deployment of people, process and technology that ATS provides low-risk solutions related to complex systems for our life science customers. In the next sections, this article will use an on-body drug delivery system to exemplify this approach.

NOVEL MANUFACTURING SOLUTIONS MITIGATE RISK

A leading medical device manufacturer recently approached ATS about repatriotising the manufacturing of its wearable injection device. The product was being manufacturing in China by a contract manufacturer and required a significant number of production associates to complete. The medical device manufacturer's senior leadership team felt that, for reasons of supply consistency, proximity to target markets and product quality reliability, it required a US-based factory.

To establish a viable North American supply base, a dramatic reduction of production associates would be required, along with an increased level of sophistication for automated assembly and test. The product was already quite complex in that it required the step-wise build up of more than 40 unique components to produce one personal on-body injector.

The ATS team, in concert with the client, began using people, process and technology methodology to identify various challenges associated with the programme. Some of the technical and performance challenges or risks that were identified are described below:

- **Component handling** – many of the components had unique geometries and sizes. Production associates had the

ability to view and manipulate parts due to a person's innate ability to assess, judge and react. Deploying automation to mimic this type of human behaviour can be difficult.

- **Process complexity** – many processes had documentation but in the form of work instructions for production associates. Process parameters and process ranges were not readily available for translation into automation designs and technologies.
- **Sequence of operations and interdependencies** – the order in which the various components were assembled necessitated parallel and sequential processing. This introduced a line-balancing complexity which was compounded by the number of processing steps. The challenge was that delays in one process would have a ripple effect throughout production and could significantly impact output.
- **Confidence in automation** – as the wearable injection device was already commercially available, it was critical that any new manufacturing methodology should result in a product with no apparent, functional or behavioural differences. The device produced from automation had to show equivalency in performance, reliability, consistency and quality.
- **Material handling** – in addition to introducing parts to the assembly process, there was the challenge of offloading completed sub-assemblies and transferring them for introduction into subsequent processes and assembly cells. All of this had to be managed while maintaining product control and traceability as well as a steady production flow.

These challenges were prioritised on a risk heat map of the kind shown in Figure 4. Various actions were taken to lower the risk profile for each, including the use of technology experiments or PoPs. However, the material handling challenge was particularly intricate. Table 1 shows the various risk reduction concepts with respective pros and cons.

Together, ATS and the client decided that one of the better means to reduce the risk would be a solution that would deploy autonomous intelligent vehicles (AIVs) and tray handlers. The advantages seemed to outweigh the disadvantages although there were still reservations about reliability and performance.

In order to prove out this concept, ATS researched AIV suppliers before selecting Aethon, Inc (Pittsburg, PA, US), a part of ST Engineering (Singapore). Aethon is the developer and supplier of TUG, an autonomous mobile robot (AMR). With its market-specific designs, high payload, wireless guidance system, and flexibility, the TUG was ideally suited for the logistics complexity associated with manufacturing the wearable device. Aethon was also extremely interested in partnering with ATS to solve the material handling problem.

ATS and Aethon developed a unique PoP – setting aside a section of factory floor to create a mock-up of the final production line.

The AMRs were programmed and set into the "sand box" to operate and mimic typical production with the associated interactions. ATS and Aethon collaborated on the design of appropriate tray platforms and then stressed the resultant AIV systems under different loads and with various obstacles introduced. Hours of simulated production data was collected and reviewed to develop confidence in the AIV technology and system design, thereby mitigating the perceived risk. In addition, tray loaders were designed and built and set into their own sandbox to test interactions with the AMRs – optimising the docking design.

A particularly exciting development in this solution was the incorporation of ATS's Illuminate® product as part of the solution. Illuminate® is a real-time industrial internet of things (IoT) manufacturing intelligence system which collects and maintains attribute data, performance data and status data for automated manufacturing. In this instance, its function

Concept	Advantages	Disadvantages
Conveyors with buffers	• Known technology • Few machine operators • No need to offload / introduce subassemblies • Components and subassemblies consumed as they are processed • Subassemblies "controlled" / traceability	• Physical barriers when trying to move around the equipment • Sizeable length of conveyors to provide adequate buffering • Pucks, nests or other intermediate transport platform required to maintain position or orientation for next machine
Machine operators with tray handlers	• Little investment in material handling	• Ongoing labour expense • Potential for system starved conditions for downstream cells • Potential for Lot mix-ups • Potential for WIP build-up • Trays or other intermediate transport platform to facilitate transfer to next machine
Automated guided vehicles (AGVs) with tray handlers	• Known technology • No physical barriers or obstructions to equipment • No operators • Subassemblies "controlled" / traceability	• Guidance systems in plant floor – limits future flexibility • Larger capital investment • Require docking station design and logistics • Trays or other intermediate transport platform to facilitate transfer to next machine
Autonomous intelligent vehicles (AIVs) with tray handlers	• No operators • No physical barriers or obstructions to equipment • Subassemblies "controlled" / traceability • Maximum routing flexibility – self-teaching to learn alternative routes to avoid obstacles	• Larger capital investment • Limited experience with technology • Require docking station design and logistics • Trays or other intermediate transport platform to facilitate transfer to next machine

Table 1: Comparison of various material handling solutions.

was combined with the AMRs. Illuminate® was able to manage date and time-stamp information for every tray of components and subassemblies, maintaining traceability of parts and confirming that the correct trays had arrived at the correct machine before being introduced. The AIV data, and the millions of production data points and quality attribute photos, combine to create a comprehensive device history record for each medical device produced. As a result, the device manufacturer has complete traceability on the manufacturing of each individual wearable injection device.

PARTNERS IN SUCCESS

When building programme teams, careful consideration and deliberation before final selection can mean the difference between success and failure.

Customers approach and select ATS because of a reputation for not only delivering superior equipment but because of a demonstrated ability to identify and mitigate risk. We recognise that our life science customers require low-risk, turnkey, compliant and, often, complex manufacturing systems but at the same time we must remain open to new technologies and new innovations as possible solutions to complex problems. ATS's approach to risk mitigation helps deliver on that low-risk need.

Our extensive network of equipment and automation suppliers and years of integration experience enable our turnkey offering. Our global install base of life sciences systems attests to our understanding and delivery of compliant solutions.

Autonomous robots and the IoT are no longer science fiction or things that dreams are made of. They are elegant solutions designed to reduce risk in a complex manufacturing system.

ABOUT THE COMPANY

ATS is an automation solutions provider to the life sciences, chemicals, consumer products, electronics, food, beverage, transportation, energy, and oil and gas industries. Its offering includes custom automation, repeat automation, 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.

ATS provides life science customers with low-risk, turnkey, compliant, manufacturing systems for medical devices, pharmaceuticals and diagnostic companies. ATS understands that quality of product, assurance of supply and sustainable manufacturing is of particular interest to drug delivery companies. Clients trust ATS with the development of systems for autoinjectors, transdermal devices, syringes, inhalers, electronic meters and devices, IV catheters, tube sets, specialised infusion kits, high-accuracy dispense and placement, filling and packing.

ATS employs approximately 4,400 people at 23 manufacturing facilities and more than 50 offices in North America, Europe, Southeast Asia and China. ATS Automation Tooling Systems, Inc, is publicly owned, and its shares are traded on the Toronto Stock Exchange (TSX: ATA).

ABOUT THE AUTHORS

Catherine Thacker, PEng, is the Director of Pre-Automation Solutions for ATS Automation. She has provided pre-automation services for ATS since 2006. Prior to ATS, Ms Thacker held various positions with several major life sciences manufacturers, building her expertise in project management, construction, organisational design, production planning and management, facility and maintenance operations, technical transfer, product launches and validation.

William (Bill) Jaworski has held a variety of strategic roles at the intersection of healthcare and technology. This includes Product Manager, Segment Marketing Manager, Global Marketing Director with GE Healthcare and Business Development Director at ATS – Life Science.

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Stevanato Group

CAN WEARABLE DEVICES BRIDGE THE GAP BETWEEN PEN INJECTOR AND PUMP?

In this article, Steven Kaufman, Vice-President of Drug Delivery Systems, and Paolo Golfetto, Drug Delivery Systems Business Development Director, both of Stevanato Group, explore the potential for wearable injectors to be disruptive technologies in the drug delivery market.

As we consider the drug delivery market today, there is a convergence of trends pointing towards a demand for innovative device solutions that can administer medicine reliably, monitor compliance and improve patient quality of life. This is providing fertile ground for disruptive technologies to emerge that offer new levels of functionality and usability – even in a therapeutic area such as diabetes, that helped to pioneer the use of self-injection systems.

> "A new category of wearable products is emerging, bridging the gap between functionality and cost, while introducing improvements to patient safety and quality of life."

DIABETES GROWTH RATES

According to the International Diabetes Federation (IDF) Diabetes Atlas 2018, the global diabetic population is expected to grow by 48% per year between 2017 and 2045. Global trends show how diabetes incidence will rise much more in low- and middle-income countries than in high-income countries: India is predicted to have the highest growth in absolute values (+70 million diabetic people), moving from second in 2017 to first in 2045 in terms of diabetic population, while the North Africa region will almost double with a 106% increase, and China will move to having 119 million people with diabetes.

DEVICE LANDSCAPE

The landscape of devices used to deliver insulin has traditionally been divided into two categories: pen injectors and vials/syringes on one side, and insulin pumps on the other. Each category offers different levels of functionality and usability at a very different therapy cost.

At present, for patients who inject insulin, approximately 95% of those receiving treatment for Types 1 and 2 diabetes use a syringe or pen injector. Patients on multiple daily injection (MDI) therapies for Type 1 and Type 2 typically require 3–5 injections of insulin a day. Administration requires several, non-discreet preparation steps that can lead to patients delaying therapy to avoid injecting in public.

The frequency of injections can also be difficult to track, leading to missed doses or even double doses. Monitoring patient compliance is difficult for doctors, making it hard to make effective adjustments to treatment. These challenges are compounded when administering injections to children.

Compared with pen or syringe systems that only dispense discrete doses of insulin, pumps are intended to deliver insulin continuously at an adjustable flow rate, are therefore better suited for complex therapy

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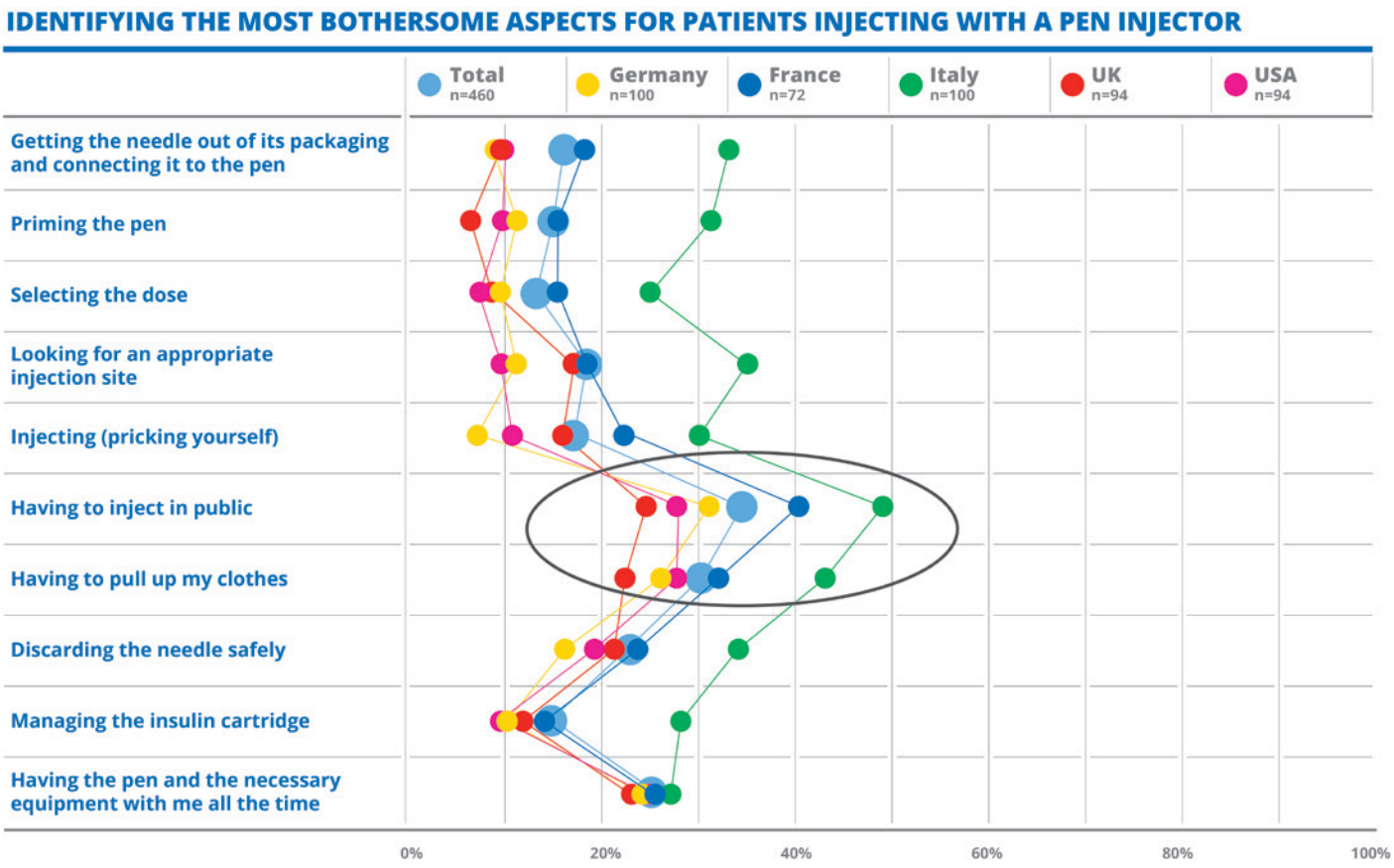

Table 1: A quantitative survey by Curth & Roth performed in 2017 for Medirio, a Stevanato Group company, shows diabetic patients using pen injectors objected most to having to inject in public and having to pull up their clothes.

regimens, and are typically adopted for Type 1 diabetes. The electronics and software architecture of the device gives patients and healthcare professionals better monitoring capabilities – and the ability to conceal the device is preferable for patient quality of life and compliance.

However, preparing the pump for use requires a more complex handling process, including programming the device correctly and transferring the drug to an internal reservoir. Ensuring the pump delivers a small and precise dose brings an increase in the device development and manufacturing costs. With an annual cost of therapy that is more than double that of a pen injector, many countries will only reimburse a pump system for Type 1 diabetes.

THE PATIENT EXPERIENCE

A quantitative internal survey was conducted in 2017 by the agency Curth & Roth for Medirio, a Stevanato Group company, involving a sample of 960 participants aged from 20 to 65. The survey was conducted in Germany, Italy, France, UK and the US – and included 460 diabetic patients and 500 professionals including nurses/educators, internists, diabetologists and endocrinologists.

The survey (Table 1) showed that insulin-dependent people who used pen injectors objected most to:

1. Having to inject in public
2. Having to pull up their clothes.

Besides discretion, other concerns included the fear of needles and of painful injections, which was reported mostly by new insulin users. Many patients expressed shock at the lifestyle changes required, continually having to carry medical supplies and ensuring that insulin doses were accurate and never missed. The feedback provided an insight into the desire of patients to be able to live with regular medicinal treatment while still having an active and social lifestyle.

WEARABLES – BRIDGING THE GAP

A new category of wearable products is emerging, bridging the gap between functionality and cost, while introducing improvements to patient safety and quality of life. One example is the cartridge-based wearable device currently under development by Stevanato Group, which received Best Innovation in Drug Delivery Device award at this year's Pharmapack event in Paris (Figure 1). The product comprises a disposable, wearable pod and an intelligent, reusable handheld controller that serves as the user interface and control unit for the pod (Figure 2).

Figure 1: Stevanato Group's cartridge-based wearable device received the Best Innovation in Drug Delivery Device award at this year's Pharmapack event in Paris.

Figure 2: The reusable handheld controller activates the disposable pod, bridging the gap between the functionality of pump technologies and the cost of pen-injector technologies.

"The ability to track and share injection data can help to improve patient adherence and therapy outcomes."

By separating the drug delivery system's mechanical components into a disposable pod, and the electronic components for dose selection and verification into a reusable handheld controller, this new self-injection device can bridge the gap between the functionality of pump technologies and the cost of pen-injector technologies. The system has several features that have been carefully considered from an end-user perspective (Table 2).

PRODUCT HANDLING

In terms of handling the product, the user – or the healthcare provider, if used for other non-insulin therapies – first inserts the factory-sealed, sterile cartridge into the pod (Figure 3). This is designed to be intuitive, easy to use and quick. The patient then removes the backing to an adhesive sticker and places the pod on the body. This can be done earlier than required and then activated later during the day.

Once attached to the body, the user triggers the cannula insertion with the controller and the system is ready to begin injection. Then, for each dose required, the user selects the dose using the handheld controller. The user then places the controller in proximity above the pod to mechanically activate the injection. The pod unlocks and receives energy to begin the drug delivery. Injection durations can last up to 10 seconds and the pod remains attached to the skin for up to 72 hours.

ADVANCING THE INDUSTRY

Thanks to its innovative yet simple technology, this system provides new levels of comfort, convenience and discreetness that can improve patient quality of life in therapeutic areas (TAs) other than diabetes. The handheld controller uses magnetic coupling to manage the interaction with the pod and, thanks to Bluetooth connectivity, it allows injection data to be exchanged.

The ability to track and share injection data can help to improve patient adherence and therapy outcomes. Stevanato Group is currently evaluating how additional features and customisations could be integrated for different TAs, such as:

- Hormone therapy
- Pain relief
- Alzheimer's disease
- Rare/orphan drugs.

Since these TAs may require a different user interface or different ways for doctors or pharmacists to prescribe the device to

PATIENT BENEFITS OF THE STEVANATO GROUP CARTRIDGE-BASED WEARABLE DEVICE

Features		Patient Benefits
POD	Pre-filled glass cartridge	No drug transfer
	Highly tolerant adhesive	Comfortable to wear for extended periods (for a maximum of 3 days), increased wearable stability
	Light-weight	Increased comfort during travel and physical activity
	Integrated, flexible, soft canula	Minimized number of handling steps for canula insertion, minimized pain of injection and removal of needle-stick injury risk
	Flat profile, small dimensions	Discreet and easy to conceal
	Disposable	No maintenance, minimal waste of components
CONTROLLER	Activates pod through clothing	Increased discretion and convenience
	Logs injection data	Ability to track and manage therapy
	Dose selection verification	Avoid over-dose, double-injections or missed injections

Table 2: Patient benefits of the Stevanato Group cartridge-based wearable device.

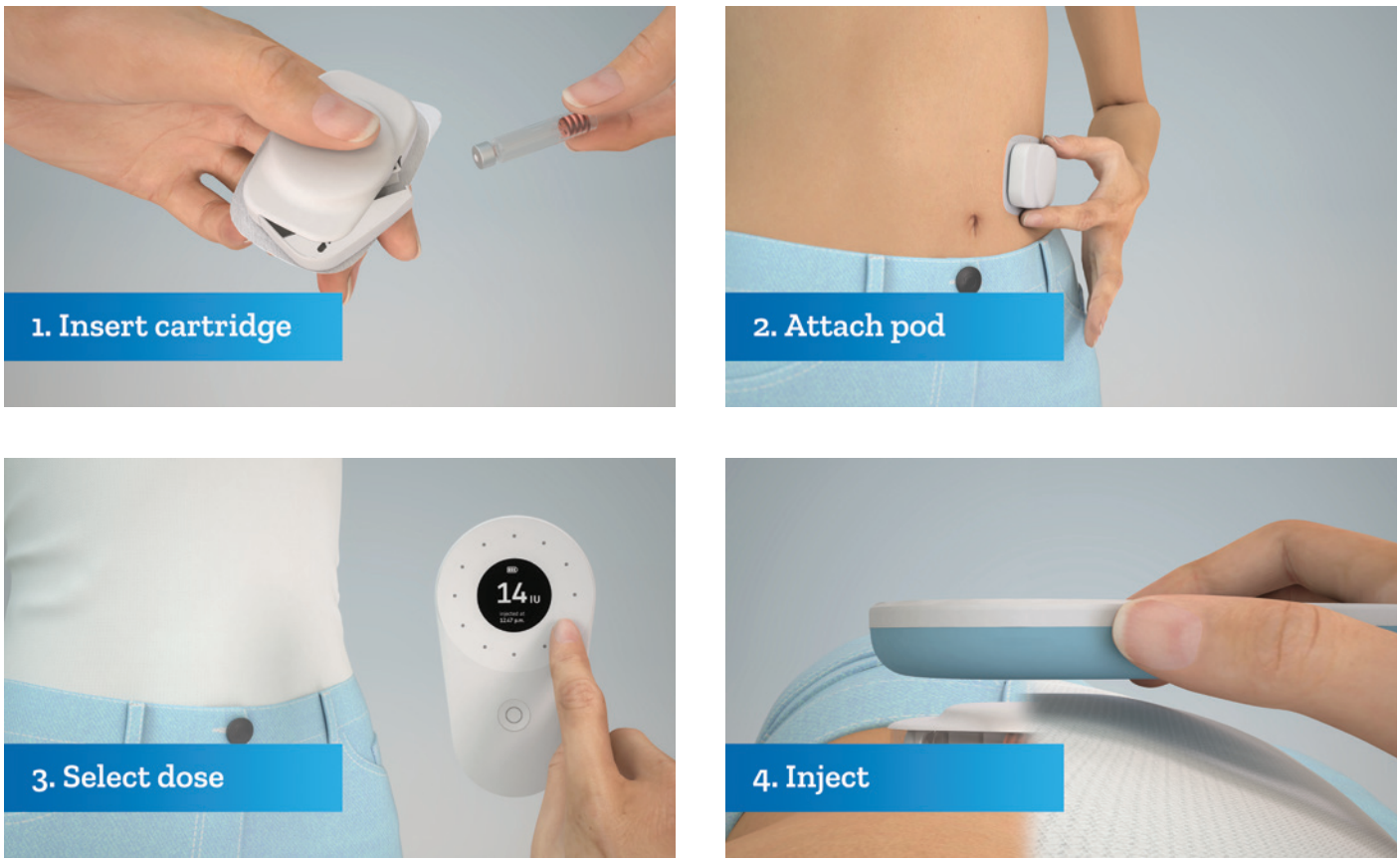

Figure 3: Steps to activate the self-injection cartridge-based wearable device by Stevanato Group.

patients, a thorough case study needs to be developed around the device, according to each different area, in co-operation with biopharma partners. Thanks to its integrated capabilities, Stevanato Group can manage the product development up to industrialisation as well as having the ability to add customisation.

DEVICE MANUFACTURING PARTNER READINESS

Bringing a device to market is complex. Biopharma companies are required to work with a range of specialty service providers in manufacturing, primary container, equipment and so on. Having one partner that can offer the required capabilities and services under one roof – from the container closure system to the assembly technology – is a key advantage to help ensure manufacturing readiness and reduced time to market.

Stevanato Group provides a range of flexible, scalable capabilities to handle device projects such as safety systems, pen injectors (Figure 4), autoinjectors, wearables and inhaler systems – whether it's done with proprietary IP developed by Stevanato Group or when Stevanato Group is acting as a contract manufacturer to produce the devices of biopharma companies.

Services range from designing, producing, testing and controlling a glass container's integrity to the integration of ready-to-use prefillable syringes and cartridges into the ever-increasing number and range of drug delivery devices. Stevanato Group provides precision injection moulding and tooling, and product development services, within an ISO13485 quality system at US FDA-audited facilities.

Flexible, modular sub-assembly and final assembly and packaging of medical devices is carried out, with inline quality control to ensure final product quality. Stevanato Group is well positioned to optimise performance of the entire system, with one point of contact and responsibility for the customer.

Figure 4: Flexible and modular assembly line developed and produced at Stevanato Group for pen injectors.

Since the 1990s, Stevanato Group's high-performance glass primary containers – whether they're syringes, cartridges or special formats – have been used effectively in a number of devices on the market today. With the acquisition of further knowledge in injection moulding and tooling – as well as the incorporation of inspection, assembly and packaging capabilities – the company is now looking forward to bringing its wearable device and other self-injection devices to market to support the needs of biopharma customers, in co-operation with its partners.

ABOUT THE COMPANY

Established in 1949, Stevanato Group is the world's largest privately owned designer and producer of glass parenteral packaging for the pharmaceutical industry. From its outset, the group has developed its own glass converting technology to ensure the highest standards of quality throughout the production process. It comprises a wide set of capabilities dedicated to serving the biopharmaceutical and diagnostic industries: from glass primary packaging with its historical brand Ompi, to high-precision plastic moulding equipment, to engineering machines and lines related to glass converting, visual inspection, assembly and packaging. The group also benefits from the SG Lab that provides technical and analytical services to study container-drug interactions and guarantee drug integrity.

ABOUT THE AUTHORS

Steven Kaufman is Vice-President of Drug Delivery Systems at Stevanato Group. He is responsible for managing the business development, proposal management and project management as well as the strategic initiatives of the drug delivery systems business. He has been active in the drug delivery device field for more than 15 years, working with leading multinational biopharmaceutical companies to provide pen injectors, autoinjectors and wearable injection systems, as well as test equipment, assembly equipment and final device assembly services. Mr Kaufman has a Master of Business Administration with an emphasis on marketing and international business.

Paolo Golfetto is the Director of Business Development, Drug Delivery Systems at Stevanato Group. In his position, he leads the development and execution of the business strategy in the drug delivery system field, supports the external technical communication of the global product platforms and manages project acquisition and transfer to the internal development structures, securing the integration of the different capabilities of the group.Before taking this position, Mr Golfetto was the Primary Packaging Development & Customer Care Director, leading new glass packaging introduction and technical support to the group's biopharmaceutical clients. Mr Golfetto is a PDA member and lecturer.

Stevanato Group

Our Device Portfolio:

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YOUR INTEGRATED SOLUTION PROVIDER

Assembly & Packaging Equipment

SG SVM

Specialty Plastics

SG Balda

Glass Primary Packaging & Analytical Services

SG Ompi | SG Lab

WEARABLE INJECTORS: CHOOSING AND TESTING ADHESIVES FOR OPTIMAL PERFORMANCE

Neal Carty, PhD, Global Director, Research and Development, and Deepak Prakash, Senior Director, Global Marketing, both of Vancive Medical Technologies, highlight the importance of choosing and testing adhesives for optimal wearable drug delivery device performance.

Wearable drug delivery devices are a compelling area of medical device and pharmaceutical industry development. Innovations already on the market are enhancing patients' quality of life, and many developments in the pipeline have the potential to deliver increasing levels of comfort, convenience and lowered healthcare costs.

These devices have diverse applications, from closed-loop continuous glucose monitoring (CGM)/insulin delivery systems to wearable large-volume injectors (LVIs) for delivery of a growing number of biologics and other drugs.

LVIs, in particular, are gaining attention for enabling patients to self-administer novel medications for chronic diseases in the home. More than 50% of the global population suffers from a chronic disease, according to a Roots Analysis report citing data from the University of Michigan's Center for Managing Chronic Disease. A prevalent way to administer many newer biologic drugs for chronic diseases is through intravenous (IV) injection or infusion in the hospital or other clinical setting – but this has drawbacks.

"The majority of the available treatment options require parenteral administration, frequent dosing, involve repeated hospital visits and are associated with multiple other concerns, such as dosing and medication errors, risk of microbial contamination and needlestick injuries. These challenges represent a substantial threat to medication adherence and, thereby, are likely to significantly impact therapeutic outcomes," said Roots Analysis in the overview to its December 2018 report.[1]

"Over the past few years, a number of companies have developed advanced therapeutic delivery solutions to alleviate the pressing concerns associated with the administration of both conventional and novel drug / therapy molecules," according to Roots Analysis. "Amongst modern drug delivery practices, the concept of self-injection has facilitated advanced medications to be administered beyond the clinical setting. This has also served to reduce healthcare costs, improve therapy adherence and optimise the utilisation of healthcare resources per treatment."

Michael Hooven, President and Chief Executive Officer of Enable Injections, noted that there are more than 2,700 biologics in development, including new treatments for cancer, autoimmune disease, neurologic disease and other diseases. And that researchers have found that their economic value may depend on their cost of administration.[2]

Prescient & Strategic Intelligence (P&S) has estimated the wearable injector market will grow from US$2.16 billion (£1.78 billion) in 2015 to $13 billion in 2024. P&S has predicted cancer treatments will become the largest application area. Other application areas expected to experience growth include treatments for autoimmune, infectious and cardiovascular diseases, and blood disorders. "Growing need for advanced drug delivery is one of the major factors driving the growth of the global wearable injectors market. Increasing demand for homecare and advanced drug delivery requiring minimal expertise and lesser hospitalisation of patients is expected

> "Wearable devices have wide-ranging wear time requirements and performance specifications, so there is no "one size fits all" when it comes to adhesive selection."

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to drive the demand for wearable injectors, globally," P&S said in an October 2017 blog post.[3] "Also, many biopharmaceutical companies have been looking for a better mode of drug delivery for their portfolio of biologic drugs, for which wearable injectors are an appropriate solution."

In many of the same ways that LVIs are making life easier for patients with various chronic diseases, integrated CGM solutions have been game changers in the daily quality of life for patients with diabetes. Patients using closed-loop CGM systems no longer have to check their blood glucose levels multiple times per day. Instead, the CGM solution automatically monitors glucose levels in their interstitial tissue just below their skin surface and adjusts their insulin flow accordingly.

Abbott, maker of the FreeStyle Libre CGM system, discussed during its second quarter 2019 earnings call[4] that the Libre technology has "enormous potential" beyond monitoring glucose. It remains to be seen how this type of continuous monitoring solution, integrated with drug delivery devices, will evolve into other disease categories but the potential is exciting.

Many of the latest CGM and LVI solutions offer connectivity to smartphone apps so that patients and, if desired, their support networks can stay apprised of their medication status, make sure doses have been delivered successfully and receive reminders.

"Connectivity between sensors and devices is enabling healthcare organisations to streamline their clinical operations and workflow management, and improve patient care, even from remote locations," said the Deloitte Centre for Health Solutions in a 2018 report.[5] "Provided medtech companies can convince clinicians and patients of the value and benefits of connected medical devices, the pace and scale of healthcare transformation will be exponential."

ADHESIVE SELECTION CONSIDERATIONS

The "wearable" in wearable drug delivery devices is often enabled by adhering the device directly to the body with a medical-grade pressure-sensitive adhesive (PSA) material (Figure 1). Wearable devices have wide-ranging wear time requirements and performance specifications, so there is no "one size fits all" when it comes to adhesive selection. For example, the body-worn portion of an integrated CGM system may consist of a half-inch diameter patch that needs to stay on for 15-30 days. On the other hand, there are much larger LVI devices designed to deliver anywhere from 2-50 mL of medication, and they may need to remain on the body for 15-30 minutes or a few days.

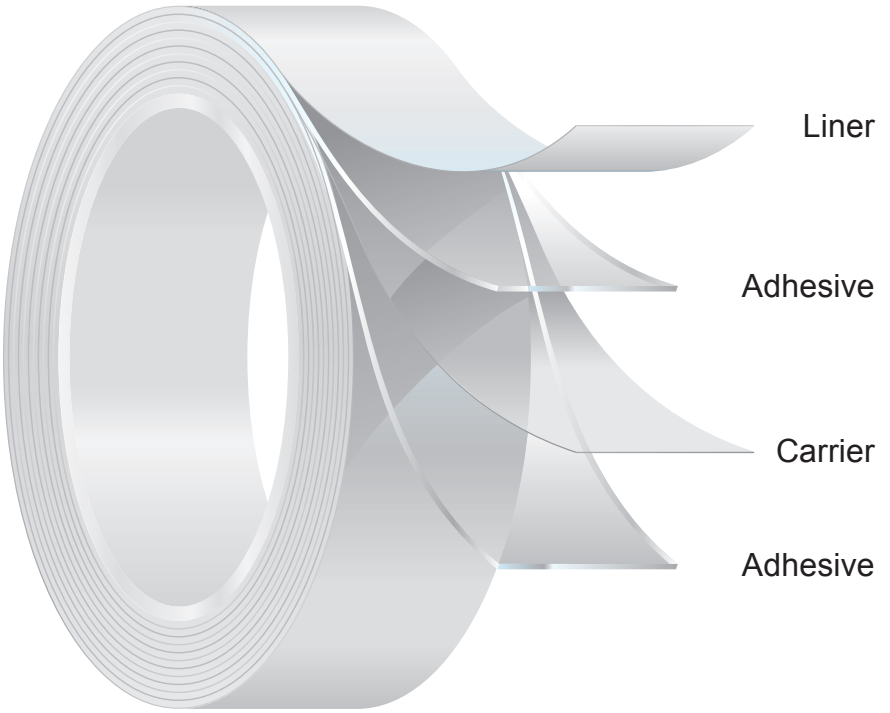

Figure 1: The construction of a double-coated PSA medical tape. This type of tape is commonly used in wearable medical devices.

Regardless of the wear time duration, the devices generally need to withstand a patient's normal daily life activities and movements. For extended wear devices, this often includes showering and exercise. The PSA material should also allow for easy fixation of the device to the body and atraumatic removal. With these goals in mind, the following are some adhesive factors to consider.

Moisture Management

Moisture management and patient comfort go hand in hand. A wearable device's skin-contact layer adhesive and any construction-layer adhesives should offer an effective means of removing perspiration and moisture that inevitably will present on the patient's skin. The two primary methods of moisture management are fluid absorption (being absorbed and contained in the material) and vapour transmission (being evaporated through pores in the material).

Related questions to consider:

- What is the average perspiration rate for the body location where the device will be worn during different levels of physical activity?
- Will the patient be exposing the device to moisture through bathing, exercising or other daily life activities?

Static Shear

The static shear, or cohesion, of an adhesive is its ability to hold in position through shearing forces, such as stretching, bending and twisting of the body.

Related questions to consider:

- How long will the device be worn and what activities will the patient likely perform during this time?
- Is the body location for the device one that experiences frequent twisting, stretching or bending?

Peel

The peel, or peel adherence, of an adhesive is its ability to resist removal by peeling. Some peel adhesion tests measure how much force is required to peel the adhesive from a certain substrate.

Related questions to consider:

- Will the typical device end user have delicate, fragile skin?
- How large and heavy is the device, and how long must it be worn? How strong does the peel adherence need to be?

Tack

An adhesive's tack determines how quickly it sticks, or adheres. A high tack level may

"Before locking in an adhesive material choice or freezing the device design, wear testing of early concepts can help with decisions about what materials and features to carry forward into product development."

mean that the adhesive adheres almost instantly. Others may need to be held under light pressure for a little while to be secured.

Related questions to consider:

- Is it likely the drug delivery device end user will need to be able to reposition the device if he or she misses the desired application position on the first attempt?
- Will the device be applied to the body in a location that allows the patient to easily hold it in place for several seconds with gentle pressure for proper securement?

Biocompatibility

Adhesive materials that are highly biocompatible are less likely to cause irritation or allergic reaction when adhered to the patient's skin. At a minimum, these adhesives have passed the ISO 10993 standard tests for cytotoxicity, irritation and sensitivity.

Related questions to consider:

- In addition to ISO 10993, have the adhesive materials been engineered to meet localised biocompatibility requirements for different geographic markets?
- Can the supplier address specific allergen concerns relative to the device application?

EARLY CONCEPT WEAR TESTING

Each of the adhesive characteristics described above can and should be tested in a laboratory using industry-recognised, standardised testing methods, and these tests and their results are very important. However, laboratory testing can only tell a device developer so much about how a human being will respond to a body-worn product. Before locking in an adhesive material choice or freezing the device design, wear testing of early concepts can help with decisions about what materials and features to carry forward into product development.

Wear tests conducted early in the product development cycle can provide an opportunity to discover important end user reactions and perhaps dispel some erroneous assumptions. Concept drawings frequently take a naïve view of how a wearable device may fit on an idealised human form. But through user testing on real human subjects we can discover how well a device actually works with a diversity of different body types.

For example, women may find a wearable device to be far more uncomfortable or impractical than male subjects for a reason as simple as a difference in how undergarments or a purse strap rub the device in an irritating way. Human bodies come in an incredibly diverse set of shapes and sizes, and that diversity's impact on product performance should not be underestimated. Wear testing can reveal how a wearable product concept really looks and feels on a variety of people of different ages and with different body masses, skin types and behaviours.

Often, these early concept wear tests can be performed and results analysed within a relatively quick timeframe, so device developers do not need to worry about losing months of cycle time for such testing. By investing time early on for wear testing, the device maker might avoid time-consuming setbacks later in product development and regulatory review.

CONCLUSIONS

Wearable drug delivery devices represent a fast-growing segment of the healthcare industry. Innovations in this space provide a key link in a future focused on more connected, accessible and economical healthcare solutions. While the pharmaceutical drug inside these devices is unquestionably the most valuable aspect of the system, it's crucial for every material and component to play its supporting role perfectly, otherwise patients may not realise the full benefit of their therapy.

Often the primary point of contact between the device and the patient's body, advanced medical PSA, is instrumental in device securement and patient comfort. Device construction, moisture management and wear location can affect manufacturability, wear time and the patient experience.

"It's crucial for every material and component to play its supporting role perfectly, otherwise patients may not realise the full benefit of their therapy."

ABOUT THE COMPANY

Vancive Medical Technologies, an Avery Dennison business, is a medical technology company with more than three decades of expertise in adhesive chemistries and material technologies for medical applications using pressure-sensitive adhesives. The company's applications and technologies are an integral part of products that are in daily use in medical facilities throughout the world. Through long-term relationships with original equipment manufacturers, industry-specific converters and leading universities, Vancive Medical Technologies continually finds new ways to develop products that can improve patient care.

REFERENCES

1. *Roots Analysis, "Large Volume Wearable Injectors Market (4th Edition), 2018-2030". 2018.*
2. *Hooven S, "Large-Volume Wearable Injectors: A New Delivery Approach Could Change the Game". BioProcess International, 2018, Vol 16(5).*
3. *Prescient & Strategic (P&S) Intelligence Private Ltd, "Bolus Injectors Contribute Largest Revenue to Global Wearable Injector Market". P&S blog, 2017.*
4. *Muoio D, "Abbott ramping up FreeStyle Libre production following bountiful Q2". MobiHealth News, 2019.*
5. *Ronte H, Taylor K, Haughey J, "Medtech and the Internet of Medical Things: How connected medical devices are transforming health care". Deloitte website, 2018.*

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Neal Carty, PhD, is Global Director, Research and Development, for Vancive Medical Technologies. Dr Carty specialises in polymer science, having worked for Avery Dennison, Vancive's parent company, for 11 years. He received his doctorate in Chemical Engineering from the California Institute of Technology (Pasadena, CA, US), his MBA from Case Western Reserve University (Cleveland, OH, US) and his BSc degree in Chemical Engineering from the University of Kentucky (KY, US).

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SCALABLE ASSEMBLY SOLUTIONS – FULLY INTEGRATED AND TRULY GLOBAL

With the demand for more stringent standards, greater variety, smaller volumes and ever-shorter product lifecycles, the requirements for automation solutions have risen sharply in manufacturing industries. Here, Rolf Rihs, President, and Jean-François Bauer, Head of Marketing & Business Development, both of Mikron Automation, look at how – to meet customer needs – Mikron has specialised in flexible, modular assembly solutions that are easy to evolve during the different stages of a product lifecycle: from the development phase through to fully automated, maximum-performance production.

Demands on manufacturers in industries such as medical, pharmaceutical, automotive, consumer goods and electronics are especially high. In an extremely competitive market, pressure on costs is rising and the lead time for new products is getting ever shorter. An assembly solution often has to be ready before all the details of the new product are even known. In many cases, assembly solutions also need to be frequently switched to another variant.

It's no wonder then that demand for innovative, cost-optimised solutions has risen dramatically over the past few years. The future belongs to flexible automation systems that can be expanded and enhanced easily and cost effectively – from the development phase through to fully automatic production.

FIRST PROTOTYPES TO FULLY AUTOMATIC PRODUCTION LINES

Providers of automation solutions should be involved from the very beginning of product development. As a fully integrated project partner, we often learn all about the process at the same time as our customer. We always have a sound grasp of the risks involved and, through constant communication, we are able to anticipate future changes

Figure 1: High-performance automatic assembly and test systems.

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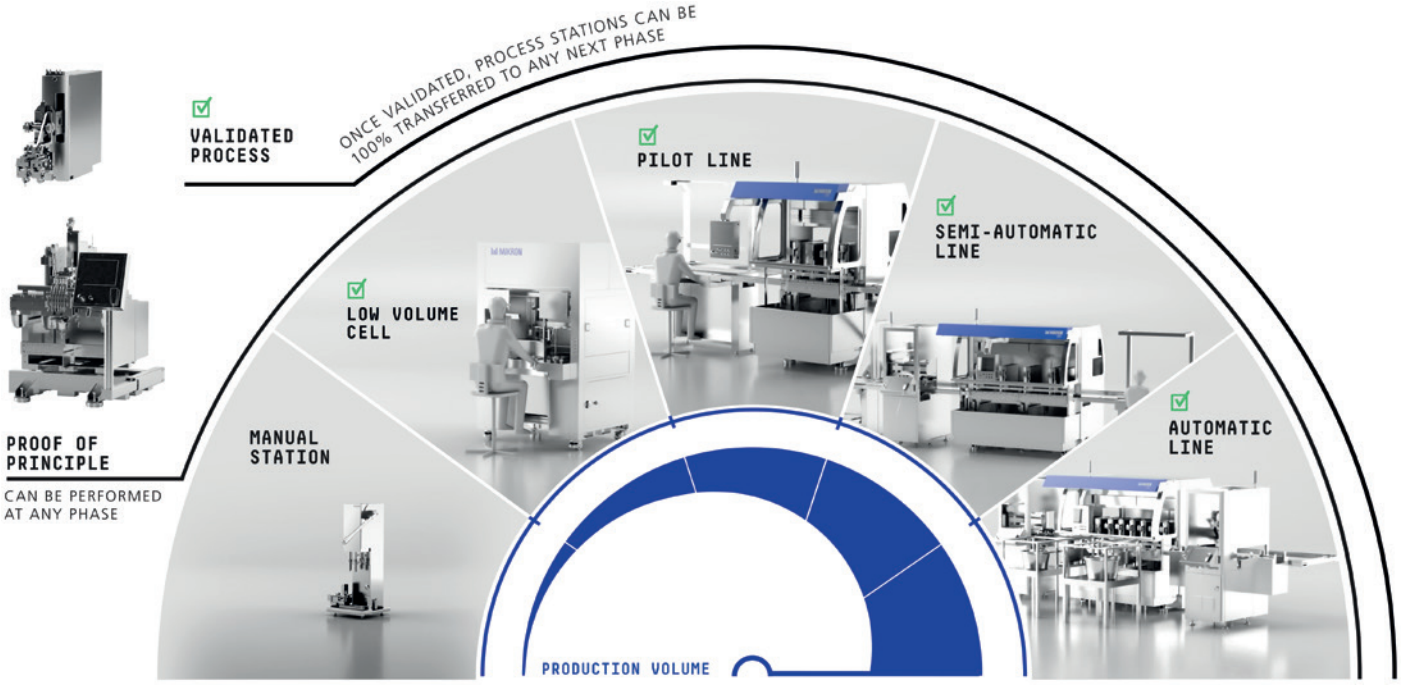

Figure 2: Mikron's scalable solution from the first idea to the highest performance solutions.

"A close partnership with our customers enables us to understand their needs and react immediately."

– from design for assembly to proof of principle, and from the validation process through to the pilot line and high-performance production (Figure 1).

A close partnership with our customers enables us to understand their needs and react immediately. That's why the flexibility of our automation systems is so important. As a global company, Mikron is ready to go to its customers wherever they are. This means the customer can start their production in very small batches anywhere in Europe, for example, and finish it in very high volumes somewhere in America or in Asia. Thanks to the multi-cell configurations of our automation systems and the integration of manual workplaces, we offer almost unlimited layout options. Throughout the whole process, it is easy to redeploy and reconfigure whenever necessary. This considerably increases cost efficiency and greatly shortens delivery times. What's more, process validation can be transferred from one automation level to the next.

"The key word in the brave new world of flexible automation systems is 'scalability'."

MINIMUM RISK WITH FLEXIBLE PRODUCTION STARTS

The key word in the brave new world of flexible automation systems is "scalability" (see Figure 2). For our customers, the new approach means minimum risk and a faster, more flexible production start – in several stages, if required. For many years, Mikron Automation has enjoyed an international reputation as a partner for high-performance automation solutions in the large-scale manufacture of precision products. For many, however, the fact that Mikron Automation is also one of the leading providers of scalable and flexible automation systems is a huge bonus. This strengthens our position as a first-choice, long-term partner.

ABOUT THE COMPANY

To date, Mikron Automation has installed more than 3,500 assembly and testing systems worldwide. Its international customers operate in the following markets: pharmaceutical, medtech, automotive, electrical/electronics, consumer goods and construction/building. Mikron Automation employs around 680 people and is headquartered in Boudry (Switzerland), a region that is regarded as the heart of the Swiss watchmaking industry. It also has sites in Berlin (Germany), Denver (CO, US), Singapore, and Shanghai (China).

ABOUT THE AUTHORS

Rolf Rihs, Dipl Ing ETH, took over as head of the Mikron Automation business segment in mid-2002, prior to which he worked for the Sulzer Group for eight years in various regions and functions. He was previously a consultant at Helbling Management Consulting working on numerous projects for well known Swiss companies. Mr Rihs is a member of the Swissmem specialist group "Assembly and factory automation".

Jean-François Bauer is Head of Marketing & Business Development for Mikron Automation. He has been working for Mikron Automation for 21 years. As of today, he has 35 years of industrial experience with 25 years in precision machinery. Mr Bauer has occupied several management functions from production to purchasing, and from after sales to product management.

PRIMARY PACKAGING FOR WEARABLE INJECTION DEVICES

In this article, Dominique Bauert, Head of Business Development Sterile Solutions Cartridges & Wearables, and Anil Kumar Busimi, Senior Global Product Manager SCHOTT iQ® Platform, both of Schott, provide an overview of existing wearable injector solutions and new requirements, with a focus on the role of the primary packaging inside the devices.

Patients have used pen and autoinjectors at home to treat chronic conditions like diabetes and rheumatoid arthritis for quite some time. Home administration of novel biological drugs presents many challenges. Subcutaneous injection of viscous biologic drugs is possible if injected in high volumes or over a longer duration. To achieve this, a new class of drug delivery platform, wearable injectors, has gained wide attention in the industry.

Undergoing medical treatment is a time of intense stress for patients. In addition to the illness itself, patients sometimes endure multiple trips to doctors' offices. Self-injection gives patients the ability to avoid these trips and maintain a sense of normality and autonomy. And it's exactly this requirement for patient acceptability, for comfort and convenience, that has become a major priority for drug makers.

Biologics now comprise a substantial portion of the pharmaceutical industry's development pipeline yet designing corresponding self-injection scenarios is still a challenge. The first reason lies within the drug formulation itself. Their high doses, particular storage requirements, and high viscosity mean that many biopharmaceuticals need to be administered intravenously (IV). Patients receiving such biologics have to travel to a hospital or doctor's office for treatments. To create the necessary conditions for biologics to be self-administered, pharma companies have devised formulations that are capable of being injected subcutaneously (SC) or intramuscularly (IM). Either this happens through pen injectors or prefilled syringes, the latter often supplemented by auto injection or safety devices.

However, SC self-administration faces some challenges when applied to biologics; again often due to their large volume, high viscosity, or both. While many biologic formulations require volumes of up to 10 mL, most pen injectors and prefilled syringes are currently designed to deliver a maximum of 2.5 mL per injection. The strategy to increase the concentration of the formulation might reduce the volume yet leads to an increase in viscosity and subsequently the requirement for a higher injection force. Either way, the injection of large volumes and viscous liquids mostly involves more discomfort for the patient. In addition, there tends to be an upper limit of the time a patient can hold an injection device in place during administration, which amounts to approximately 15 seconds.

Because of these constraints, there has been a consistent focus within the industry on the design of wearable large-volume injectors (LVI) to administer biological drugs that require longer injection times due to higher volumes and/or higher viscosity.

LARGE-VOLUME WEARABLES FOR BIOLOGICS – AN OVERVIEW

Wearable injectors adhere to the body and administer highly viscous medicines at high volume. There are already several examples on the market, including devices from West Pharmaceutical Services, Ypsomed, Enable Injections, Sonceboz, Sorrel Medical, Subcuject, Weibel CDS (all featured elsewhere in this issue).

> "At the heart of any wearable injection device sits the primary packaging. It is a crucial component because it is the main point of contact between the drug and the device, yet its importance is often overlooked."

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Figure 1: A selection of the companies currently developing wearable LVIs (images courtesy of the mentioned companies).

To make them more patient-centric, many of the wearable LVIs currently in development (see Figure 1) are capable of delivering volumes of 20 mL and more over scheduled intervals.

For example, Amgen's Neulasta® Onpro® kit combines the biological medicine that gives a boost to the immune system with a wearable injector that adheres to the patient's body (Source: Letter to Shareholders, Amgen, 2017, p 8). The device is affixed to the patient, and medicine is delivered over a period of 45 minutes, approximately 27 hours after chemotherapy treatment, allowing patients to avoid a return to the hospital.

Additionally, medical device designers can incorporate a wide array of features and components into a device. Figure 2 provides an overview of device features and design considerations in available wearables.

At the heart of any wearable injection device sits the primary packaging. It is a crucial component because it is the main point of contact between the drug and the device, yet its importance is often overlooked.

PRIMARY PACKAGING – WHAT IS NEEDED?

Wearable injectors rely on multiple primary packaging systems. Some use flexible bladders or bags, others use rigid glass or polymer containers such as syringes or cartridges. Whilst some injectors are filled at the point of use, the trend in wearable LVI injectors has leaned toward prefilled doses as they reduce the risk of medication error. Irrespective of the material, each of these prefilled containers must fulfil specific requirements.

Drug Stability

The term primary packaging refers to the fact that the container comes in direct contact with the drug, including stoppers or closures, plungers, and lubricants such as silicone oil. The complex molecular structure of long-chain biologics increases risk of the drug interacting with the components of the container, which can lead to interactions and may reduce its efficacy. For drug developers, these interactions are impossible to predict, which is why extensive risk analyses and stability tests are required before regulatory approval. They can minimise the number of variables by relying on high quality containers that exhibit a reduced extractables and leachables (E&L) profile from the start. More often, such containers are made from high-quality

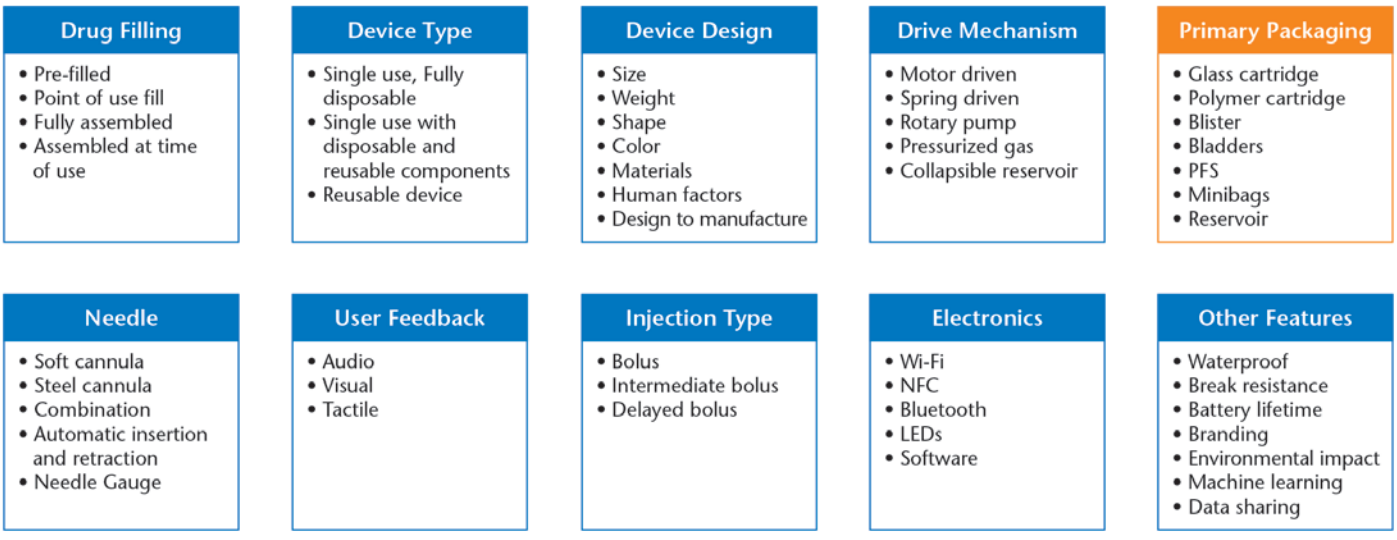


Figure 2: Overview of device features and design considerations in available wearable injectors.

> "New cocreation approaches enable the pharma company and the design manufacturer to adjust the container design to the device, creating ever smaller and more discreet applications, instead of building the wearable around an existing type of primary packaging."

borosilicate glass, or high tech polymers like COC or COP, feature reduced, baked-on, or cross-linked silicone, and incorporate specialised elastomer components that come with a reduced E&L risk.

Functionality

Container functionality comprises numerous aspects that again contribute to the stability of the drug. For example, container closure integrity (CCI) has become an area of concern, as appropriate test methods for verification of the sterility of polymer bags or bladders are currently not in place.

Proper function also contributes to a convenient administration – which is the ultimate goal of any wearable injector. Here, the geometrical precision of rigid containers like cartridges or syringes already supports dosage accuracy and ease of use thanks to reduced break-loose and gliding forces.

Whether glass or polymer offers the better functionality depends on the individual application. Both materials have their advantages. Borosilicate glass is still the gold standard to package biologics due to its high chemical stability and proven track record. Polymer, in turn, can offer more design freedom. New cocreation approaches enable the pharma company and the design manufacturer to adjust the container design to the device, creating ever smaller and more discreet applications, instead of building the wearable around an existing type of primary packaging.

In any case, drug makers should investigate the best possible material route together with a packaging manufacturer who offers a complete portfolio of both glass and polymer solutions.

Economics in Fill & Finish

The narrow patient population for biologics has had a downstream effect on filling operations, which naturally also effects the primary packaging for biologics to be used within a wearable device. Most biologics are produced in smaller batches, and pharma manufacturers have been working on ways to fill these small quantities cost-effectively. The industry has thus seen a trend towards ready-to-use (RTU) containers that rely on the same industry standard nest-and-tub format for each container type. This allows the same filling line to be used for multiple container formats with minimised changeover time in between. In addition, RTU packaging arrives sterile at the manufacturing line, allowing for fully aseptic manufacturing.

While extensive experience with rigid RTU containers such as syringes, vials, and increasingly RTU cartridges is available in the industry, comparable small volume (<100 mL) scenarios with flexible polymer containers still lag behind.

FINALLY - IS THERE AN IDEAL PRIMARY PACKAGING FOR WEARABLES FOR BIOLOGICS?

The cartridge has emerged as the primary packaging container that fulfils the diverse requirements of wearables for biologics. With cartridges, designers have wide latitude to choose container length, volume, diameter, neck and flange design, and the stopper and plunger material. Another benefit of cartridges is that many of their functional parameters, particularly glide force, have been tested to full extent according to ISO standards. Finally, this type of primary packaging container is available in different materials, delivered in bulk and recently also as an RTU variant in industry standard tub and nest configuration.

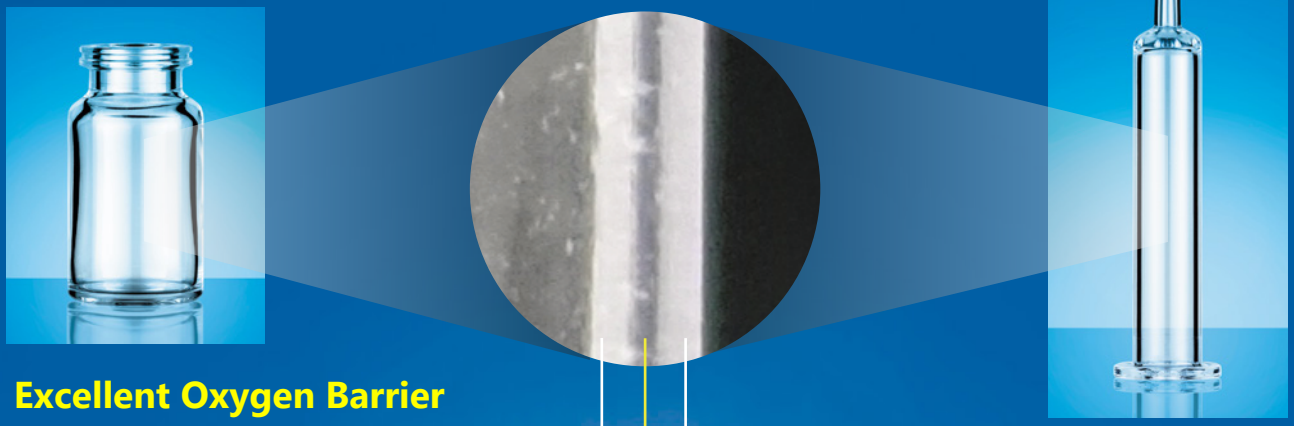
This article draws from an earlier work of Busimi & Bauert, published in Pharmind 2019.

ABOUT THE COMPANY

Schott Pharmaceutical Systems is a supplier of primary pharma packaging and analytical lab services. Its portfolio includes ampoules, syringes, cartridges and vials as well as various polymer solutions. Its lab analytics experts offer a wide variety of lab services for pharmaceutical packaging to customers in order to find solutions to their most challenging packaging requirements. Production facilities and products comply with the highest international pharmaceutical standards.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

Excellent Oxygen Barrier

High Water Vapor Barrier

Very Low Extractables

Low Protein Adsorption

Excellent Ultraviolet Barrier

High Break Resistance

High pH Stability

Silicone Oil Free Barrel

Pre-sterilized Vial & Syringe

Customizable

Suitable for Biologics

MITSUBISHI GAS CHEMICAL

Mitsubishi Gas Chemical Company,Inc.

https://www.mgc.co.jp/eng/products/abd/oxycapt.html

Mitsubishi Gas Chemical America, Inc.

http://www.mgc-a.com

E-mail: nb3.pharmapackage@mgc.co.jp

MITSUBISHI GAS CHEMICAL

ADVANCES IN MULTILAYER TECHNOLOGY FOR WEARABLE INJECTOR PRIMARY PACKAGING

Here, Hiroki Hasegawa, Researcher, and Tomohiro Suzuki, Associate General Manager, both of Mitsubishi Gas Chemical's Advanced Business Development Division, discuss how multilayer technology used in the drinks bottle industry can be used to create syringes and vials for biologics, avoiding problems such as oxidation and absorption that occur with other materials.

Improving the quality of plastic vials and syringes is an important aspect of ensuring that wearable devices deliver biologic drugs in the best possible condition to patients. This includes preventing oxidation of the drugs and absorption of unwanted particles.

Mitsubishi Gas Chemical (MGC), one of the Mitsubishi companies, is a leading company in the field of oxygen barrier and absorbing technologies. It has created an innovative polymer, Nylon-MXD6, which has been used for the middle layer of multilayer beverage bottles for many years to prevent oxidation and evaporation of carbon dioxide from drinks. The company also developed an oxygen absorber, AGELESS®, that has been used for IV solutions and prefilled syringes to prevent oxidation of injectable drugs for more than 30 years.

Based on these technologies and experiences, we have successfully developed multilayer plastic vials and a syringe called OXYCAPT™ (Figure 1).

OXYCAPT™ consists of three layers; the drug contact layer and the outer layer are made of cyclo olefin polymer (COP), and the oxygen barrier layer is made of our novel polyester (Figure 2).

BENEFICIAL FEATURES OF OXYCAPT™

The OXYCAPT™ Multilayer Plastic Vial & Syringe can offer a range of benefits including:

- An excellent oxygen barrier
- A high water vapour barrier
- An excellent ultraviolet ray barrier

Figure 1: OXYCAPT™ Vial & Syringe.

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- Very low extractables
- High pH stability
- Low protein adsorption and aggregation
- A silicone-oil free barrel
- High transparency
- High break resistance
- Easier disposability
- Lighter weight.

OXYCAPT™ also has excellent UV barrier properties. Specifically, whereas about 70% UV light of 300 nm transmits through glass and COP, only 1.7% transmits through OXYCAPT™ (Figure 3). This feature also contributes to the stability of biologics.

PRODUCT DETAILS

There are two types of OXYCAPT™, OXYCAPT™-A and OXYCAPT™-P. OXYCAPT™-A is suitable for drugs that are especially oxygen sensitive as it has a glass-like oxygen barrier (Figure 4) and an oxygen-absorbing function. According to some internal studies, this function gives OXYCAPT™-A a lower oxygen concentration in headspace than Type 1 glass. OXYCAPT™-P is recommended for all drugs as, although there is no oxygen-absorbing function, the oxygen barrier of OXYCAPT™-P Vial is about 20 times better than that of COP monolayer vial.

In terms of the water vapour barrier, OXYCAPT™ is not equal to the performance of glass. However, it is similar to COP, which has been used for injectable drugs for a long time, and easily meets the requirements of a water vapour barrier for the ICH guideline.

OXYCAPT™ Syringe consists of a tip cap, barrel, PTFE-laminated stopper and a plunger rod. Although a very small amount of silicone oil is sprayed on the stoppers of the syringe, no silicone oil is baked on the barrel. According to our internal studies using existing antibody, we have found this feature leads to much less protein aggregations compared to existing type 1 glass syringes.

OXYCAPT™ Vial & Syringe are produced by co-injection moulding technology. Although this technology has been applied to beverage bottles for many years, we are the first company that has succeeded in using it to develop multilayer plastic syringes. We have also developed inspection methods for the oxygen barrier layer. All of the containers are 100% inspected by state-of-the-art inspection machinery.

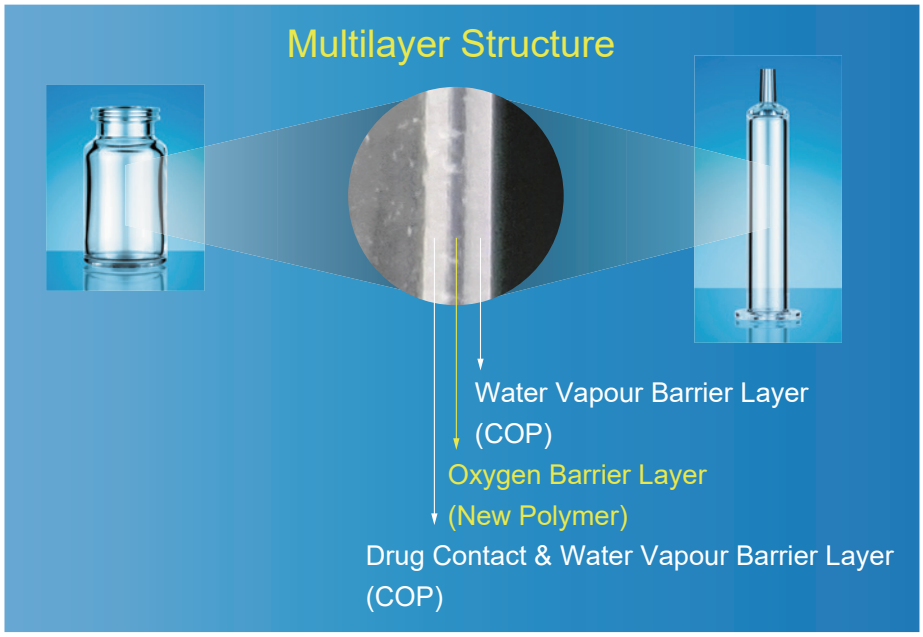


Figure 2: The multilayer structure of OXYCAPT™.

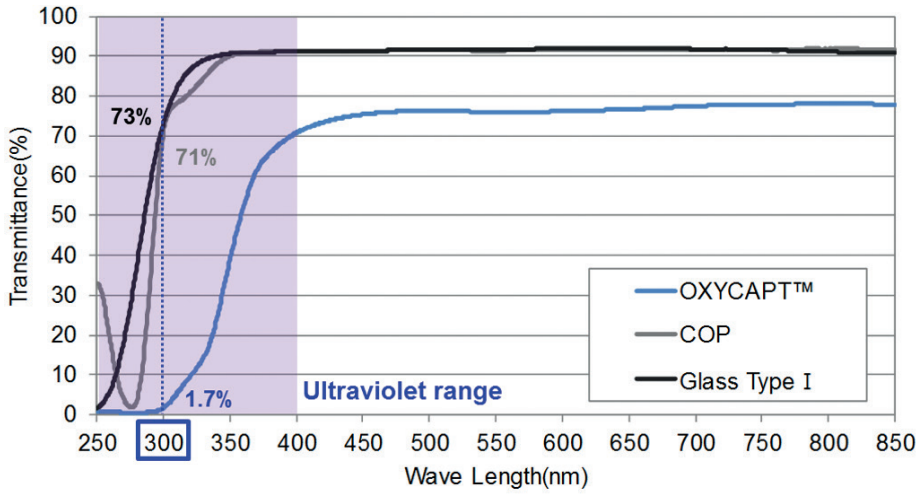


Figure 3: Percentage of light transmitted through the UV barrier.

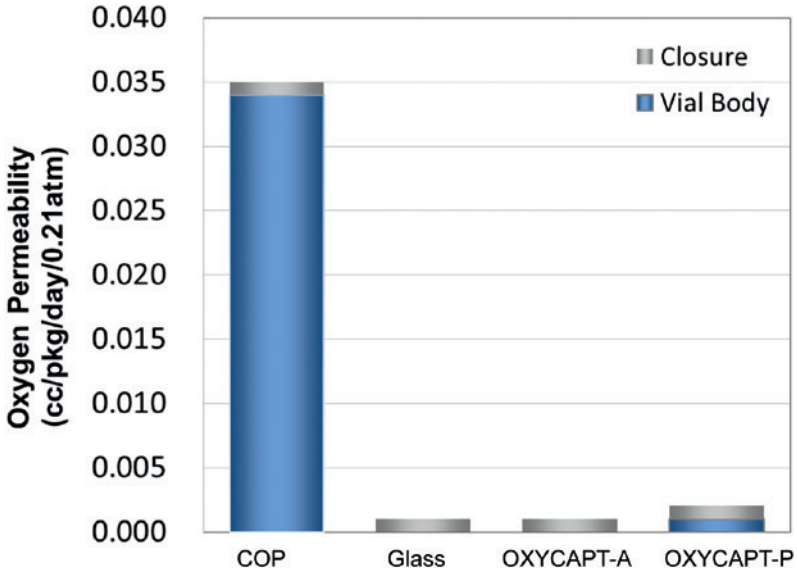


Figure 4: Oxygen permeability of the types of OXYCAPT™.

Figure 5: The nest and tub format for vials.

Figure 6: The nest and tub format for syringes.

"The levels of extractables were similar to those from COP, which is well known as an extremely pure polymer, and less than Type 1 glass."

MGC can offer bulk vials, ready to use (RTU) vials and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-based nest and tub formats (Figures 5 & 6). The nests and tubs are usually sterilised by gamma ray. There are 2 mL, 6 mL, 10 mL and 20 mL options for the vials, and 1 mL "long" and 2.25 mL for syringes. We are happy to provide some samples for initial testing, free of charge.

Each polymer meets the requirements of USP661, USP87, USP88, EP, and has been filed in the US FDA's Drug Master File (DMF). The syringes are produced and controlled in accordance with ISO 13485.

RESEARCH EVIDENCE

Studies have shown extremely low extractables with OXYCAPT™. One study was conducted to confirm volatile, semi-volatile and non-volatile impurities from OXYCAPT™. Water and four solutions (50% ethanol, NaCl, NaOH and H_3PO_4) were used and impurities were measured by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with control, no impurities were detected in any of the OXYCAPT™ containers.

The second study was conducted to confirm inorganic extractables from

pH Stability

· pH level of water in glass vial increases with time.
· pH level of water in OXYCAPT™ vial doesn't change.

<Test method>
- Filled with 10mL Water
- 23℃ · 50%RH
- Analysis; pH meter

OXYCAPT™
10mL Vial

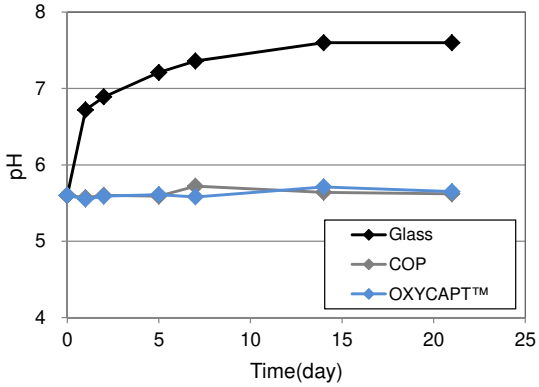
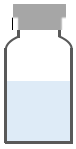


Figure 7: The pH stability of OXYCAPT™ versus water.

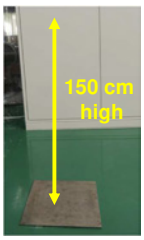
Resistance to breakage at Cryogenic Temperature

OXYCAPT™ Vial retains its contents after dropped from 150 cm high at Cryogenic Temperature .

<Test Samples and Method>



- Number of vial: 20 (OXYCAPT™-A 10mL Vial)
- Closure: Brominated butyl rubber (Aluminum seal)
- Filled with 10mL distilled water
- Stored: approximately -180° C(liquid nitrogen gas phase)
- Samples were dropped to a steel plate from 150 cm high.



<Test Results>

Number of breakage	
OXYCAPT™-A Vial	COP Vial made by another company
0/20	8/20

COP vial

Figure 8: Suitability of OXYCAPT™ to cold storage.

OXYCAPT™. The levels of extractables were similar to those from COP, which is well known as an extremely pure polymer, and less than Type 1 glass. The smaller amount of inorganic extractables contributes to the stability of the pH in drugs (Figure 7).

Recently, we also investigated the ability of OXYCAPT™ to withstand cold storage. OXYCAPT™ vials and a competitor's COP monolayer vials were stored at approximately -180˚C, using liquid nitrogen, and all the vials were dropped from a height of 150 cm. Although some COP monolayer vials were then broken, no breakage was observed in OXYCAPT™ vials (Figure 8). As liquid nitrogen storage has gradually become more popular thanks to the spread of regenerative medicine, it is expected that OXYCAPT™ could benefit from this development.

CONCLUSION

OXYCAPT™ has been developed to solve some of the problems facing the pharmaceutical industry in creating syringes and vials suitable for wearable devices. In addition to special features of COP such as a high water vapour barrier, high break resistance, very low extractables and low protein absorption, OXYCAPT™ can offer a high oxygen and UV barrier. We believe OXYCAPT™ definitely brings a lot of benefits which could contribute to improving patients' lives.

ABOUT THE COMPANY

Mitsubishi Gas Chemical (MGC) operates in a wide range of fields, from basic chemicals to fine chemicals and functional materials. MGC established the Advanced Business Development Division in 2012 as a centre to create new businesses, and developed OXYCAPT™ Plastic Vial & Syringe as an alternative to glass containers.

ABOUT THE AUTHORS

Hiroki Hasegawa is a researcher in the Advanced Business Development Division of Mitsubishi Gas Chemical, in charge of macromolecular science, especially in the composition development of thermosetting resin. He's worked for the company since April 2015 and, since 2018, he has been part of the team developing multilayer plastic vials and syringes for biologics. Mr Hasegawa gained a Diploma in Science in 2013 and a Master Degree of Science in 2015 from Osaka University, Japan.

Tomohiro Suzuki joined Mitsubishi Gas Chemical in 1998. He worked in the Oxygen Absorbers Division until 2011, and was then transferred to the Advanced Business Development Division in 2012 to join the OXYCAPT™ development team. Since then, he has been in charge of the marketing of the OXYCAPT™ Plastic Vial & Syringe. His current position is associate general manager.

SHARING IS CARING: POLYMER SUPPLIERS AS MEDICAL DEVICE DEVELOPMENT PARTNERS

Manuel Scherer, Business Development Manager, Europe in the healthcare segment of SABIC's Specialties business looks at whether the advent of wearable injectors calls for a more collaborative approach between polymer suppliers and medical device developers.

The advent of biologic drugs and wearable injectors for drug delivery presents new opportunities for plastic materials in the medical devices sector. A look at a few of the most significant trends influencing drug device development for high-viscosity injectable drugs provides insights into how the polymers industry is addressing such challenges. This article highlights the complex landscape of patient, converter and original equipment manufacturer (OEM) needs as well as considerations for polymer manufacturers in the development of new material formulations.

> "For many decades, the use of polymer resins in the medical device industry has brought significant value for the medical sector and enabled life-preserving treatments to the patients it serves."

Designing a novel medical device to meet the high-end requirements of the evolving pharmaceutical drug delivery market requires the involvement of material specialists at an early stage to help identify materials that can maximise device performance and manufacturability whilst also addressing the important element of patient safety. Based on material engineering data, material specialists can identify potential device failure modes and provide design and material recommendations to support the development of high-performance medical devices.

POLYMERS: A STRONG TRADITION IN MEDICAL DEVICES

For many decades, the use of polymer resins (commonly referred to as plastics) in the medical device industry has brought significant value for the medical sector and enabled life-preserving treatments for the patients it serves.

Several major milestones indicate just how important developments in this area have been to modern patient care. Boehringer Mannheim revolutionised blood sugar measurement with its Reflolux® devices – the first series of blood glucose meter that enabled patients to measure their blood glucose level at home for the first time. In the early 1980s, Fresenius Medical Care launched the dialyser to treat kidney disease that featured plastic housing, end cap and polymer membrane. In the field of drug delivery, Novo Nordisk's NovoLet® pen was amongst the first commercially available single-use injector pens to treat diabetes. What all of these examples have in common is that polymers enabled efficient large-scale production, mainly using injection moulding processing technology.

KNOWLEDGE INSPIRES UPTAKE AND INNOVATION

Over time, knowledge of plastics, conversion technologies, secondary operations and predictive engineering capabilities has dramatically increased. This has allowed the device industry to enhance the user friendliness of their devices, integrating additional functionalities into subsequent device generations.[1] Products have become smaller, easier to use, safer, and visually and haptically more appealing. The healthcare industry is risk averse, meaning that advances in healthcare devices have come largely using polymer materials that have been in use for many years in other industries with faster innovation cycles in place.

We are now entering a new era in care with a growing role for biopharmaceuticals, whereby modern-day techniques have made this class of protein-based drugs a more viable

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treatment option. Biologics are medicines that are made or derived from a biological source and, as such, are complex macromolecules.

As they easily degrade in the digestive tract, biologics must be delivered by injection in one of three ways: subcutaneous, intravenous (IV) or intramuscular (IM). Their macromolecular nature causes their solutions to have a higher viscosity than those from small-molecule pharmaceuticals. When diluted down to practical viscosity levels, the required volume to be delivered calls for wearable devices that can do so in a controlled manner. Such devices typically contain more complex mechanical parts than, for example, an injector pen. This requires proper material selection, device design and an optimal industrialisation strategy in the early stages of new device development.

THE IMPLICATIONS OF THE SHIFT

What implications does the paradigm shift towards biologics have on device development and consequently on the plastic materials selected? Consider that biological drugs are large-volume molecules with significantly higher viscosities than small-molecule drugs.[2,3] At the same time, the device industry is challenged to enable self-administration by the patient. This shifting in the point of care from the hospital environment to the home is driven in part by the need for authorities to reduce healthcare-related costs. These elements have consequences for device design, specifically in relation to push force and dosage accuracy.

$$\Delta P = \frac{8\mu L Q}{\pi R^4}$$

where:

ΔP is the pressure difference between the two ends,
L is the length of pipe,
μ is the dynamic viscosity,
Q is the volumetric flow rate,
R is the pipe radius.

Figure 1: Hagen-Poiseuille equation.

COUNTERING AN ECOSYSTEM IMBALANCE

As one can derive from the Hagen-Poiseuille equation (Figure 1), the main parameters influencing the push force that must be applied to perform the injection mechanism are viscosity, flow, needle diameter and length. One of the key targets in any new device development is to ensure that overall push force remains stable (or ideally decreases further) to make the injection as convenient as possible for the patient. The rise of biologics initially moves the ecosystem for push force out of balance.

Counteracting the increased viscosity of biological drugs with needle diameter or flow rate is not a recommended option because it results in increased pain and can trigger other negative side effects for the patient. Hence, other options should be considered during the design process to be able to cope with either the higher push force or the longer delivery time of a larger volume of liquid.

Integrating a mechanically loaded spring system into pen injectors has been a solution for more than a decade. Such a system reduces the activation or push force for a patient to unleash the injection mechanism. The higher viscosity of biologics has created a new challenge in this space, however, whereby significant plastic deformation can emerge from the higher spring loads. When coupled with prolonged storage times, this can lead to device failure.

OVERCOMING PLASTIC DEFORMATION

Typically, in autoinjectors and pen devices, spring loads are applied to the dosing mechanism to minimise the push forces for the patient. In the case of wearables where injections are performed over a longer time, mechanical gears and pump systems also

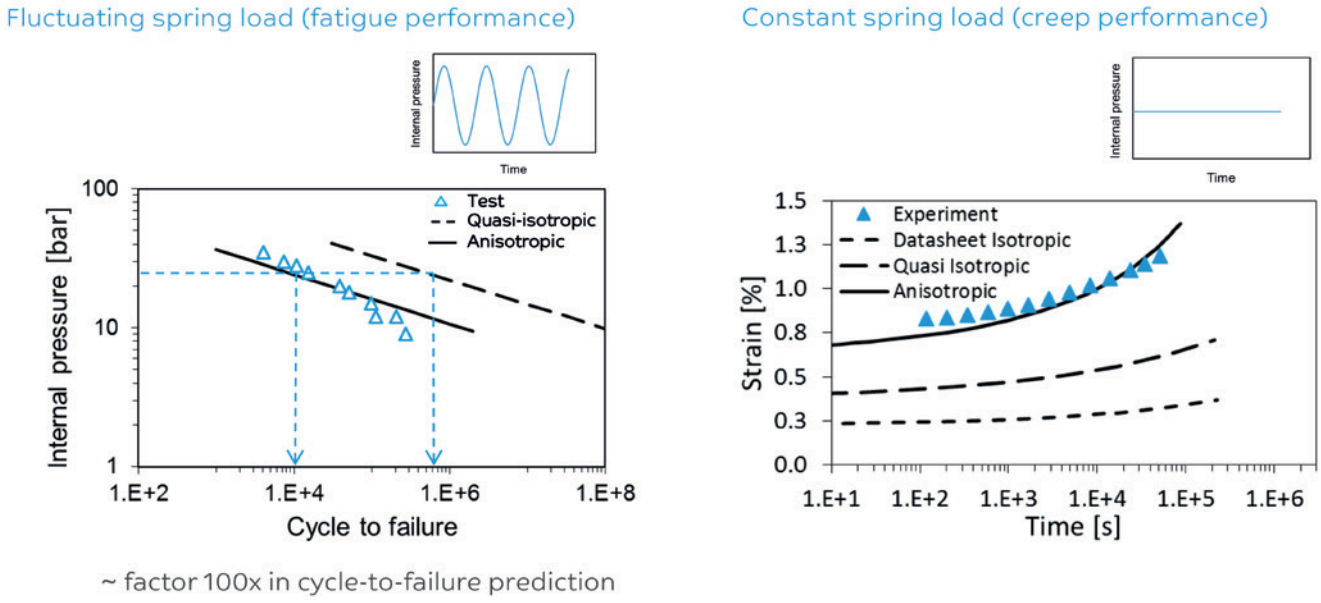

Figure 2: Creep and fatigue failure prediction models.

come into play. This inherently brings static and dynamic loads on the materials used in the device over its lifetime, potentially resulting in plastic deformation, which may cause inaccurate dosage and/or fluctuating push forces.

Hence, materials with a proper impact/stiffness balance and, more importantly, creep and fatigue behaviour should be considered during the design phase to reduce the chances of failure. In this regard, different polymer families show different inherent properties. Specifically in relation to filled resins and irrespective of polymer type, anisotropic data is required for a predictable performance (Figure 2).[4]

Besides increased mechanical loads, components involved in the drive mechanism will also be subject to movements. These movements should be smooth and accurate so as not to compromise dosage accuracy and push force. Internally lubricated high-performance materials with low co-efficients of friction, developed to overcome such specific tribological challenges, are being widely adopted by the device industry.

THE RISK OF OVERESTIMATION

Reinforced polymers are a viable option to design polymers for improved creep performance over the life of the device. However, an inherent consequence of designing devices with reinforced materials is anisotropy in the mechanical properties. Predictive engineering based on high-quality material data and computer-aided engineering (CAE) expertise is an essential step to mitigate failure modes and leverage device miniaturisation potentials.

> "Designing smaller devices is not only aligned with patient expectations but also represents another viable route to achieving carbon footprint reductions."

Figure 3 illustrates the effect of material anisotropy on the balance between tensile strength and elastic modulus. Thorough process modelling methodology – combining Moldflow® (Autodesk, San Rafael, CA, US) Digimat® (Hexagon, Luxembourg) and Abaqus® (Abaqus, Johnston, RI, US) software – is employed to establish the processing-morphology-property relation in fibre-reinforced parts and predict their anisotropic mechanical performance.

The right-hand side of the figure illustrates how fibres may be oriented in an actual part based on predictive engineering techniques. The left-hand side shows the importance of using proper data for feeding the CAE tools for actual performance prediction. The grey dots describe the actual properties measured in three directions at two different locations in the sample plaques shown.

This data enables the best performance prediction. The blue dots average out those three measuring directions (0°, 45°, 90°) for the various samples and are an isotropic simplification of the real data. Using the datasheet values indicated by the yellow dot would lead to an overprediction of part performance. Only with the right expertise and accurate data can one come to the right predictions of performance and hence select the optimum material.

Figures 2 and 3 highlight the need for anisotropic data versus datasheet values. Anisotropic data is an important element in the design stage of a device, especially with regard to predicting long term static or dynamic failure modes. Relying purely on datasheet values in the design phase can increase the chance of designing too optimistically.

MINIATURISATION: SMALLER ALSO MEANS MORE SUSTAINABLE

Designing smaller devices is not only aligned with patient expectations[5] but also represents another viable route to achieving carbon footprint reductions. However, practical considerations such as tool filling or stiffness – along with the integration of more functions (e.g. connectivity) and larger primary containers (a result of the paradigm shift of towards biologics) – represent natural limitations to the extent that downgauging can be realised.

In relation to tool filling, copolymer technologies exist which show significantly better rheological behaviour at high shear rates, despite the fact that they show identical flow per data-sheet values. This potential can be translated into wall-thickness reductions.

Consider comparing two polycarbonates of identical flow, as per their datasheet values. As Figure 4 shows, in spite of the identical flow, polycarbonate copolymer PC2 achieves either a greater flow length or

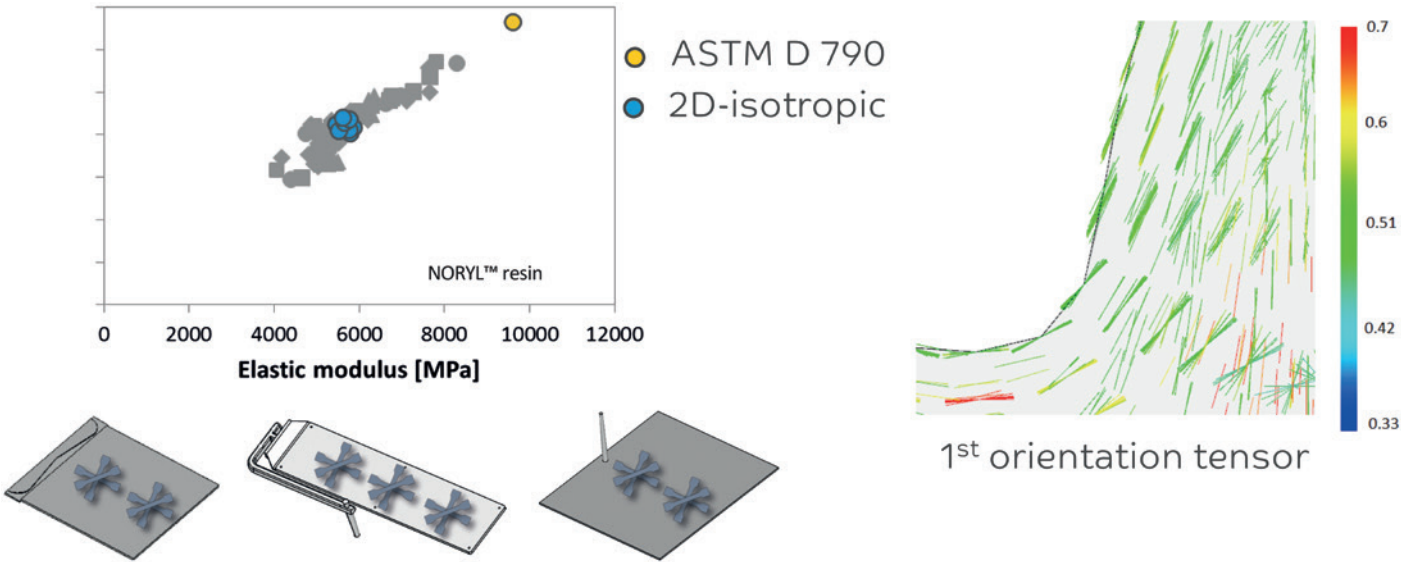

Figure 3: The effect of material anisotropy on the balance between tensile strength and elastic modulus.

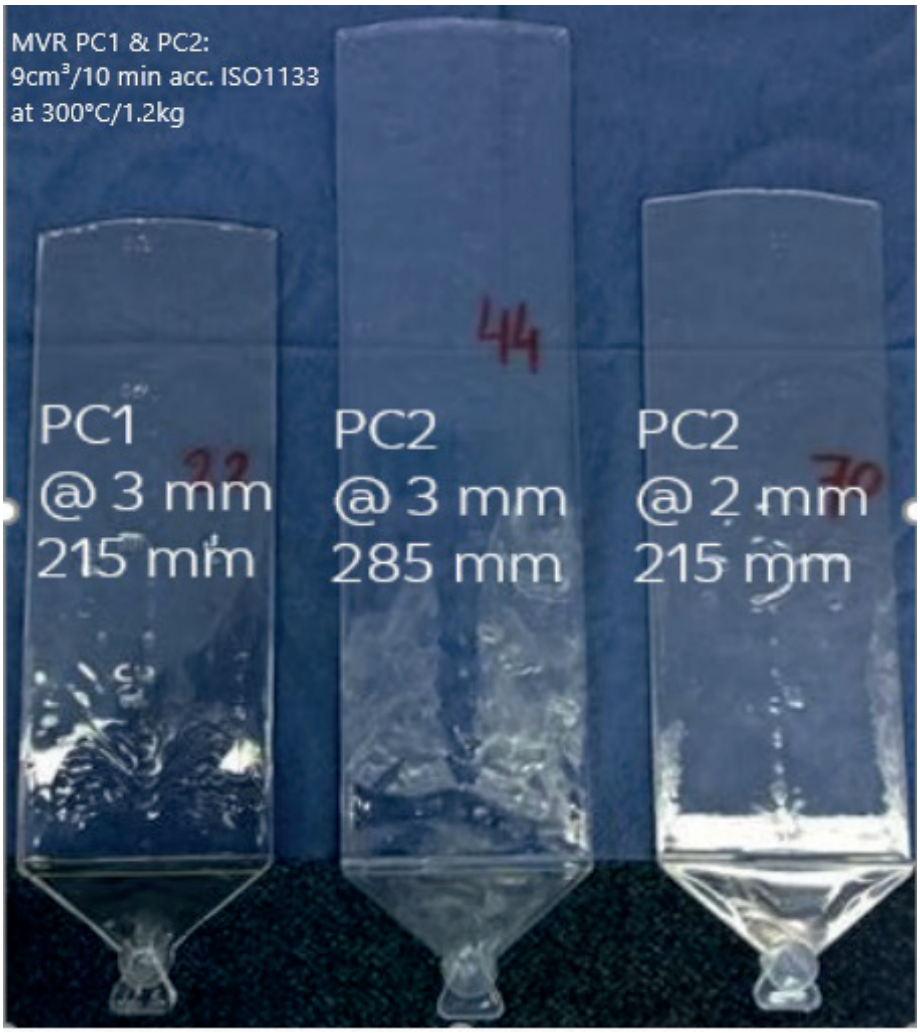

Figure 4: Materials with identical MVR on their datasheets processed at identical injection pressures show a different L/D flow behaviour.

provides a 1 mm wall thickness reduction over standard polycarbonate PC1, when processed under identical conditions. This is an implication of the molecular backbone of the material that enables increased flow length over wall thickness (L/D), specifically at the high shear rates that occur during injection moulding. This feature can be used to miniaturise or downgauge the wearable device or to leverage the potential energy reduction due to lower melt temperatures which can be translated into cycle-time reductions.

Figure 4 also highlights the need to look beyond material data sheets during the material selection stage. Teaming up with material specialists during the design phase of the project will help to optimise the design and maximise the value of the wearable.

WEARABLE DEVICES: THE NEED FOR SUPPLIER COLLABORATION

The advent of wearable injectors poses interesting and new opportunities for polymer suppliers. Product and service offerings provided by material suppliers can address this trend and contribute to a broader and faster adoption rate of wearable injectors. By diversifying and expanding its collaborations with plastic suppliers, the device development industry can leverage polymer manufacturers' knowledge of material, conversion processes, secondary operations and predictive engineering capabilities to promote a successful launch of new medical device platforms.

ABOUT THE COMPANY

SABIC is a global leader in diversified chemicals headquartered in Riyadh, Saudi Arabia. It manufactures on a global scale in the Americas, Europe, Middle East and Asia Pacific, making chemicals, commodity and high-performance plastics, agri-nutrients and metals. SABIC supports its customers by identifying and developing opportunities in key markets such as construction, medical devices, packaging, agrinutrients, electrical and electronics, transportation and clean energy. SABIC has more than 33,000 employees worldwide and operates in around 50 countries. It has 11,738 global patent filings, and significant research resources with innovation hubs in five key geographies – the US, Europe, Middle East, South Asia and North Asia.

REFERENCES

1. *"Interview: Simon Michel, Chief Executive Officer, Ypsomed". ONdrugDelivery Magazine, June 2016 (Issue 68), pp 56–59.*
2. *Adler M, "Challenges in the Development of Pre-filled Syringes for Biologics from a Formulation Scientist's Point of View". Am Pharm Rev, February 2012.*
3. *Kanai S et al, "Reversible Self-association of a Concentrated Monoclonal Antibody Solution Mediated by Fab-Fab Interaction that Impacts Solution Viscosity". J Pharm Sci, 2008, 97(10), pp 4219–4227.*
4. *Cathelin J, "Through-Process Modelling for Accurate Prediction of Long Term Anisotropic Mechanics in Fibre Reinforced Thermoplastics". 12th International Fatigue Congress, Poitier, France, 2018.*
5. *"Critical Considerations For High Viscosity/High Volume Drug Delivery Devices". Clinical Leader, July 2019.*

ABOUT THE AUTHOR

Manuel Scherer is a Business Development Manager for SABIC's Specialties healthcare segment in Europe. He leads a team of healthcare business professionals, focused on multinational healthcare OEMs, working across the value chain to drive innovations in medical device platforms. Prior to this role, he was a sales account manager at SABIC, responsible for regional and global OEMs and connected tiers, primarily in the healthcare and E&E industries. Mr Scherer holds an MBA from Heinrich-Heine University in Düsseldorf (Germany) and a Bachelor of Arts from UC Santa Barbara (CA, US). In addition, he has a Lean Six Sigma Green Belt certificate.

THE CHALLENGES OF VERIFYING A WEARABLE INFUSOR

A body worn infusor can be life changing for patients needing continuous medication but it is important to verify these devices' performance first. Team Consulting was tasked with the design and verification of one such wearable infusor. Michael Penman, Electronics and Software Engineering Consultant, Team Consulting, highlights the challenges and learnings along the way.

A wearable infusor can make a dramatic difference to patients' lives but to ensure that it is effective, it must be tested for performance and safe operation in all foreseeable environments and interactions.

Foreseeable Environments

Patients using the wearable infusor we tested were unlikely to partake in strenuous activities. With that in mind, the design aimed to avoid adding any further limitations to the daily life of such patients. This meant the wearable infusor had to be tested in all environments it might foreseeably be worn. From a cool and dry winter's day in Beijing, to a hot and humid summer's day in Hong Kong; from the high atmospheric pressure at the shores of the Dead Sea, to the low-pressure heights of La Rinconada, Peru; and so on. These examples may sound extreme, but some of these environmental changes exist in day-to-day life for most of us: from sitting in a cool and dry air-conditioned office, to having a hot and humid shower; pressure changes in the aircraft cabin during a flight, and so on.

Foreseeable Interactions

There are several predictable interactions a continuous-delivery wearable infusor may encounter whilst worn by a patient carrying on with their day-to-day routines. These range from being knocked on a piece of furniture, crushed by a portion of the patient's weight, shaken on a bumpy road, experiencing changes in back pressure when a patient transitions from lying down to standing up, etc.

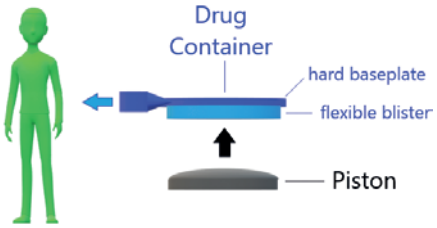

Figure 1: Drug delivery mechanism.

> "Design verification at the system level aims to assess the wearable infusor's performance and safety against all foreseeable environments and interactions."

SYSTEM LEVEL APPROACH

Design verification at the system level aims to assess the wearable infusor's performance and safety against all foreseeable environments and interactions.

Delivery Accuracy Performance

The wearable infusor was designed to deliver drug at a flow rate of 42 µL/hour with a nominal tolerance of ±6% on the total dose. Delivery is achieved by using electronics and a bespoke expanding component to displace a piston, which in turn pushes the flexible blister of a drug container (Figure 1). The rate of displacement of the piston is kept in check by a proportional derivative control system. To achieve the intended rate of delivery, the target rate of piston displacement is

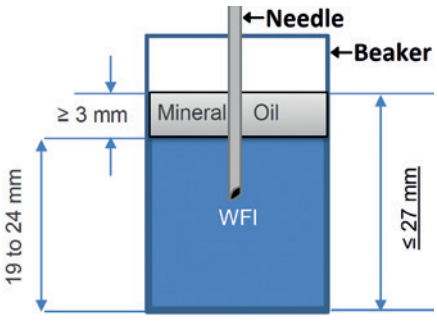

Figure 2: How the collection beaker is set up to capture mass changes used to calculate delivery accuracy.

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set to 34 µm/hour. Put in context, the pace at which the piston moves is only slightly faster than the rate at which hair grows from the human scalp.[1]

In design verification, delivery accuracy was determined by continuous logging of the mass change on a precision balance, weighing a collection beaker set up as shown in Figure 2. Note the layer of oil, needed to avoid evaporation which if allowed to occur would reduce the measured change in mass, and thus the perceived delivery accuracy by approximately 30%.

Delivery accuracy had to be assessed for a set of wide-ranging circumstances. This meant the set-up described had to be possible in all the test environments shown in Figure 3. A lot of method evaluation was necessary to optimise the test protocols for each scenario.

Additional Performance Requirements

In addition to tests assessing delivery accuracy, a separate suite of tests was conducted, assessing design features with their own performance requirements (Figure 4). For example, audible and visual indicators were required to be observable from 1 m; the skin adhesive patch had a minimum peel force; the user status button had to be robust; the enclosure had to be protected against ingress by water and solid foreign objects; etc.

CHALLENGES AND LEARNINGS

Bubbles

Initial testing revealed some periods of unexpectedly erratic delivery accuracy. Investigations into these disturbances concluded that the root cause was the presence of air bubbles in the drug container of some of the wearable infusors. The transfer of these bubbles to the collection beaker was observed to cause the erratic measurements.

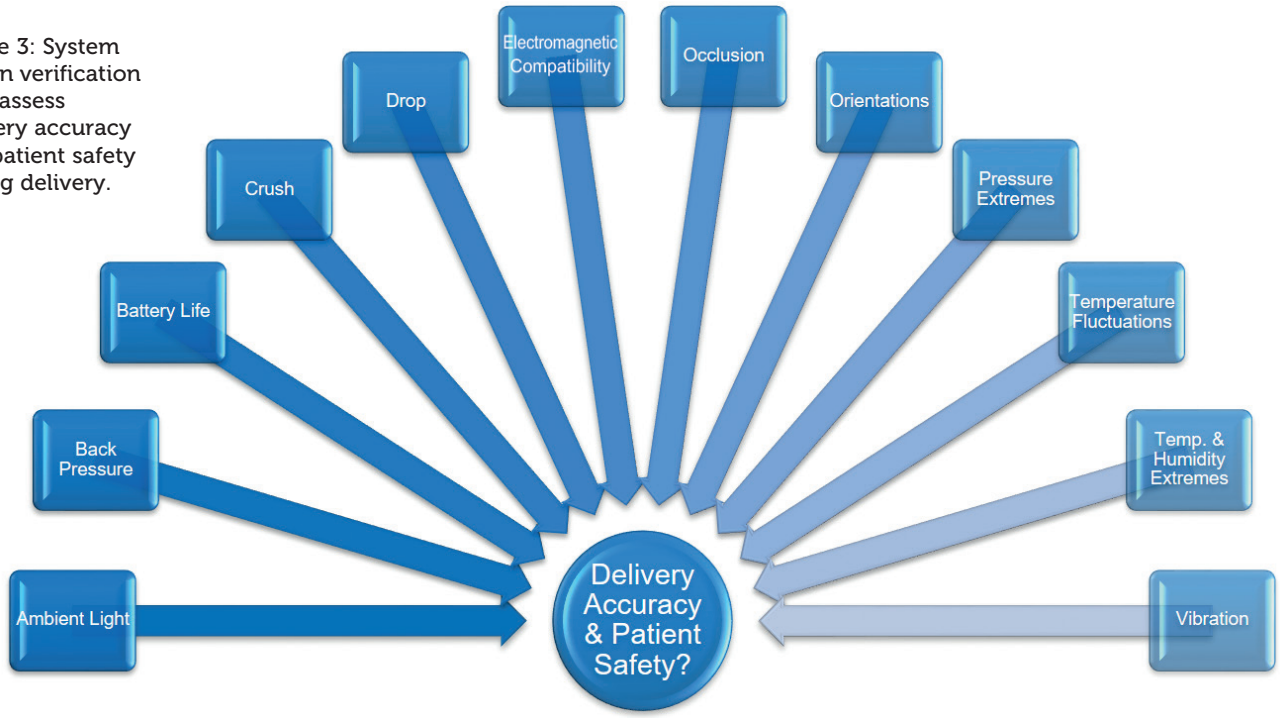

Figure 3: System design verification tests assess delivery accuracy and patient safety during delivery.

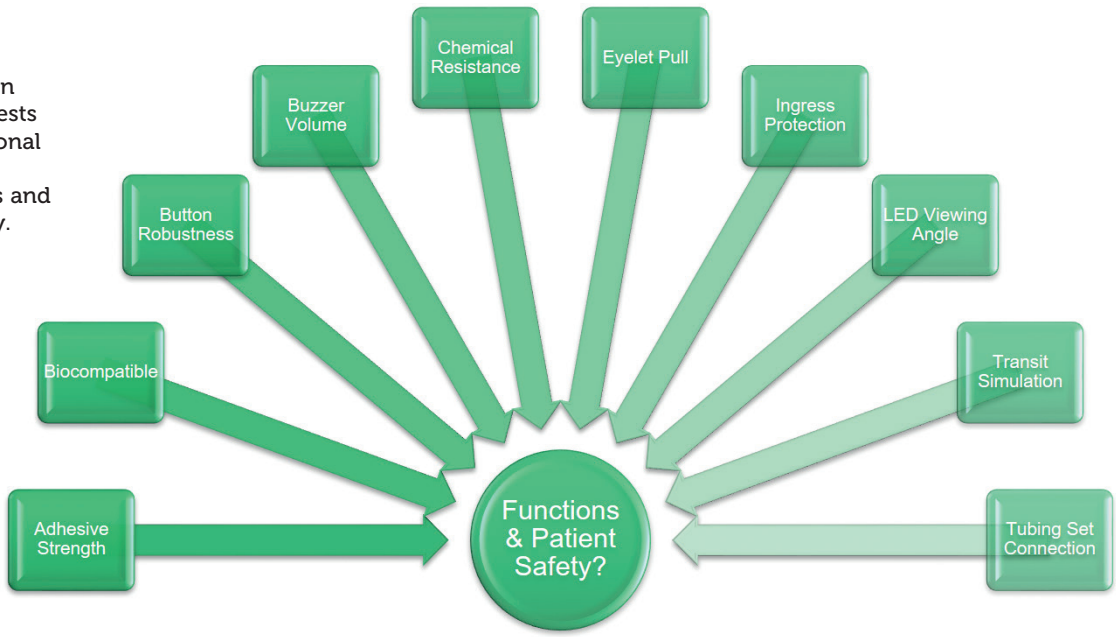

Figure 4: System design verification tests assess additional performance requirements and patient safety.

Preliminary test data (Figure 5) shows three effects on the logged mass (converted to volume in the figure) and the calculated flow rate:

1. A temporary occlusion, causing cumulative volume figures to stay constant and 15-minute-averaged flow to start to drop. This was caused by an air bubble reaching a constriction.
2. A short-term rise in flow rate, caused by the air bubble passing the constriction and the air having a viscosity around 50 times lower than fluid, allowing it to move through the wearable infusor's fine bore tubing set more quickly.
3. Step decreases in flow rate and the drops in cumulative volume, caused by bubble-release in the collection beaker. Bubbles were captured exiting the needle in the collection beaker at these points, confirming the theory.

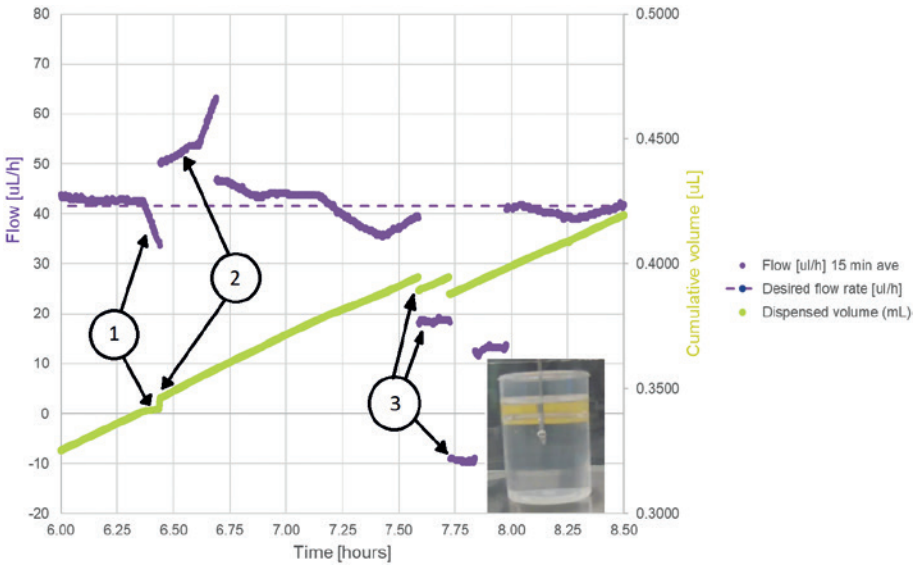

Figure 5: Test artefacts that are introduced by air bubbles.

The Effects of Accelerated Ageing

Accelerated ageing is a useful tool for testing the performance of a system at the end of its shelf life sooner than would otherwise be possible. The effect of elevating temperature to speed up the ageing process of most materials is reasonably well understood, so much so that ASTM International (formerly American Society for Testing and Materials) has a Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.[2] However, the overall effect on a complex system will contain unknowns.

Preliminary test runs on accelerated aged wearable infusors showed side effects, leading to design changes. The initial design of the wearable infusor included a battery voltage check within the first few milliseconds of start-up. Devices tested after accelerated ageing failed this check, rendering them unusable. Investigations showed that the batteries were not in fact defective and returned to acceptable start voltages within seconds of start-up (Figure 6). The low initial voltage was due to passivation, a film of lithium chloride that forms on the surface of the lithium anode giving protection against excessive self-discharge. It led to a more sophisticated battery voltage start-up check taking measurements over the first 40 seconds of operation. A simple fix, but a good reminder that a preliminary round of testing, including any ageing intended to be part of the formal test programme, is essential to avoid unwanted delays. Furthermore, it is always advisable to start a real-time ageing programme in parallel in order to differentiate between the representative and unrepresentative effects of accelerated ageing.

> "It takes a lot to design and verify a medical device that will keep patients safe whilst providing them with a therapy that improves their condition."

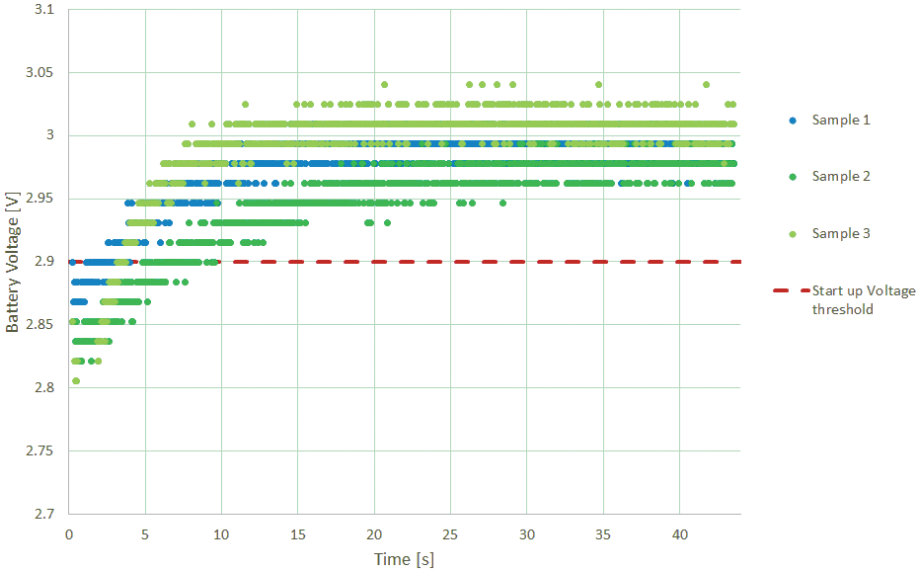

Figure 6: Battery de-passivation can occur after ageing.

Data Capture

Paper forms were used to capture test operator actions, observation, etc. in the preliminary test programme. Efforts were made to minimise the number of custom forms needed. This meant there was a lot of cross-referencing, and keeping all the forms relating to the tests performed on a device was a significant administrative burden.

This led to the development of database-driven electronic data capture forms, allowing a built-in audit trail and report generation. This simplified the data capture and reduced the administration needed. The electronic data capture form databases themselves had to be validated, which was no mean task, but once that was done, operators, reviewers and report writers found themselves in a much better position to work efficiently.

SUMMARY

It takes a lot to design and verify a medical device that will keep patients safe whilst providing them with a therapy that improves their condition. We've not touched on the lower level verification programmes needed for the wearable infusor's electronics, software or critical components in this article – rest assured each of these were equally thorough and challenging. Add the user studies needed to ensure the device is useable and will have little to no negative impact on patients' daily activities, and you have a substantial task on your hands.

The EN 60601 Medical Electrical Equipment and Systems family of standards provided by the British Standards Institute (BSI Group) is an excellent place to look for test methods to ensure a medical device like the wearable infusor will perform and be safe. Ignore them at your peril. However, they must be carefully interpreted and customised for the unique requirements of each device.

ABOUT THE AUTHOR

Michael Penman is an Electronics & Software Engineering Consultant at Team, with more than a decade of experience solving complex medical electronics engineering problems. Working principally on embedded software development, along with electronics and sensor-based projects, Michael has contributed his expertise to a variety of successful product solutions for Team's global client base.

ABOUT THE COMPANY

Team Consulting is an award-winning medical device design and development consultancy based outside Cambridge, UK. For over 30 years, we have worked closely with our clients at the world's leading pharmaceutical and device companies to develop better medical devices. As specialists in medical device development, our work covers sectors ranging from respiratory and parenteral drug delivery through to medtech, surgical and diagnostics.

Team provides all stages of device development for our clients. Our approach combines design, human factors, science and engineering from inspiration right through to industrialisation. We also deliver specific independent consulting services that support our clients' in-house device development activities. Everybody at Team is driven by the same desire – to make things better by working in collaboration with clients and each other.

REFERENCES

1. *Loussouarn G, Lozano I, Panhard S, Collaudin C, El Rawadi C, Genain G, "Diversity in human hair growth, diameter, colour and shape. An in vivo study on young adults from 24 different ethnic groups observed in the five continents". Eur J Dermatol, 2016, Vol. 26(2), pp 147–148.*
2. *ASTM F1980-16, "Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices". ASTM International,West Conshohocken, PA, 2016, www.astm.org*

2019 UNIVERSE OF PRE-FILLED SYRINGES & INJECTION DEVICES PREVIEW

Gothenburg, Sweden, October 21-25, 2019

By Falk Klar, PhD, General Manager, PDA Europe

PDA Europe is proud to present the 16th edition of its signature event The Universe of Pre-filled Syringes and Injection Devices – a must-attend conference for everyone working in the fields of parenteral drugs and device development, covering solutions to challenges regarding new developments, regulatory considerations, and industry trends.

The conference started in 2004 as a small local event, with a sole focus on prefilled syringes, which attracted about 100 attendees. Back then it was the first event of its kind to offer a platform for high-level exchange on the topic. A few years later, injection devices were added to the conference title, reflecting the expanding role of the prefilled syringe as the container of choice for this rapidly evolving market segment. After growing consistently over the years, PDA Europe is proud that in 2019 we are expecting >1,000 delegates and >100 exhibitors.

Once again, a special focus is set on the patient, as reflected in its motto: *Advancing Drug Delivery Systems to improve Patients' Lives*.

The patient perspective is also provided directly by a patient speaker, as has become a PDA tradition at this event. With all the innovations around connected health the patient will address what it actually means to be a patient in the digital age.

Speakers from the pharma industry and the payer side will discuss the growing number of drugs that are delivered in a home setting followed by a panel discussion. Fresh perspectives will be exchanged on how all stakeholders can operate and benefit from innovations in drug delivery systems.

As is customary, industry speakers will discuss technology news and highlights as well as providing regulatory highlights. Digital health keeps evolving as a hot industry topic and hence many speakers will also review this in the industry context.

The Bill & Melinda Gates Foundation will present on the unique challenges they face to bring injectable therapies to the developing world. Besides the plenary keynote speakers, there will be multiple parallel tracks with presentations across the board. Speakers will discuss topics including large-volume injection, human factors in engineering, connectivity and devices, novel therapeutics, manufacturing & processing technologies, and more – and of course there will be regulatory perspectives.

A series of multiple satellite events around the two-day conference offers attendees the chance to learn about container closure integrity testing, test methods for prefilled syringes, extractables & leachables, and innovative drug delivery systems and combination products.

A large industry exhibition will take place during the main conference. Here delegates will have the opportunity to look at innovations and recent developments around drug delivery systems. Furthermore, they can interact and network with industry peers.

For more information and to register, visit www.pda.org/EU/UPS2019. If you have questions or need more information, please contact PDA Europe. T: +49 30 436 55 08-10. E: registration-europe@pda.org.

ABOUT THE ORGANISATION

PDA is the recognised authoritative voice and leading technical organisation in the field of parenteral science and technology. Dedicated to advancing bio/pharmaceutical manufacturing science and regulation so that its members can better serve patients. PDA is guided by the vision to maximise product quality, safety, availability, and value by connecting people, science, and regulation.

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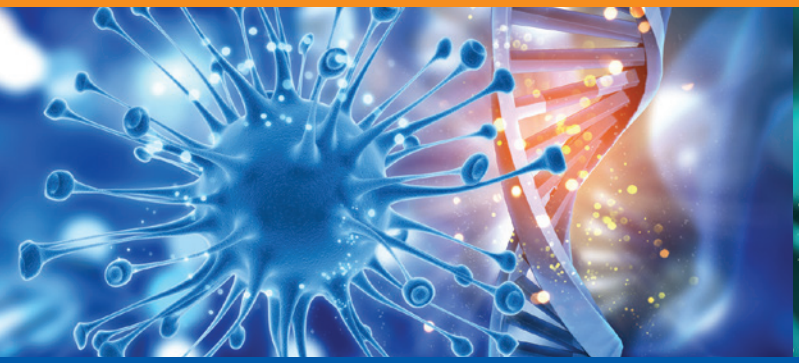

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Subcuject

DEVELOPMENT OF AN OSMOTIC LARGER VOLUME WEARABLE BOLUS INJECTOR

Here, Claus Schmidt Moeller, Chief Technology Officer & Founder, Subcuject, provides an overview of the mechanism, functionality and applications of the company's osmotic, single-use, low-cost, versatile wearable bolus injector.

As of today, only a few wearable injectors for the subcutaneous home administration of pharmaceuticals – also called large volume injectors and wearable bolus injectors – are marketed or in clinical development. They can deliver viscous drugs at about 1 mL per minute. They represent a promising class of delivery device and many pharma companies have high expectations of what wearable injectors can bring to the table for the delivery of biologics.

Subcutaneous injection of high viscosity liquids, or injection against high backpressures through thin needles, has a number of challenges and requires a high force. Therefore, most wearable injectors are based on electromechanical solutions that can control the injection and generate the needed high force, often by means of an electrical motor, a battery and a gearing mechanism. But electromechanical solutions generally become complicated and expensive, and most solutions do require more user steps than would be the case with, for example, a prefilled autoinjector. Furthermore, disposal of electronics after a single use is not preferential in an ever more environmentally conscious world, and cold storage of batteries for years represents another challenge.

> "The patented, osmotically driven Subcuject WBI creates pressure by drawing water through two semipermeable forward osmosis membranes into a pressure chamber, by means of a patented osmotic agent."

> "Disposal of electronics after a single use is not preferential in an ever more environmentally conscious world, and cold storage of batteries for years represents another challenge."

In response to these challenges, Subcuject is developing a wearable bolus injector, the Subcuject WBI, based on osmosis as the driving force. Osmosis as a power source is inexpensive, does not require an additional energy supply (such as electricity from a battery), is noiseless and can create very high forces in a smooth and controlled way. Furthermore, disposal of an osmosis-powered device has a low environmental impact due to there being no electronics or batteries.

Subcuject is currently testing a moulded functional model of the device (see Figures 1 and 2) and preliminary results of these tests – as well as earlier tests – show

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Figure 1: Functional model of the Subcuject device with a 3 mL standard cartridge.

that the osmotic actuator's function is not sensitive to higher viscosities or high back pressures. This also means that the device functions well with a range of needle gauges, even with relatively high-viscosity formulations. Specifically, injection rate is approximately 1 min/mL and it is seen that injection of water against a very high back-pressure of 69 kPa (10 psi) only takes about 30% longer than injection against a back-pressure of 21 kPa (3 psi). Injection of 50 cP sucrose solution with a G27 needle also takes about 30% longer compared with water (1 cP) with any needle gauge.

"All primary packaging materials are known and well characterised in relation to drug stability."

The patented, osmotically driven Subcuject WBI creates pressure by drawing water through two semipermeable forward osmosis (FO) membranes into a pressure chamber, by means of a patented osmotic agent. The excess water in the pressure chamber then acts as a hydraulic plunger rod, pushing the plunger in a cartridge forward.

A constant flow rate is provided by gradually increasing the membrane area that is subjected to the osmotic agent over the injection time. This compensates for dilution, while at the same time it prevents the majority of the osmotic agent from escaping with the excess water from the actuator and into the back end of the drug cartridge, pushing the plunger. This ensures a relatively constant flow up to at least 10 mL of injection (Figure 3, next page).

Furthermore, the device's function is quite independent of physical orientation (up, down etc). The use of two membranes ensures that approximately the same amount of osmotic agent is in contact with the membrane, irrespective of the orientation.

The osmotic process is initiated when the user presses the start button. This releases the dissolved osmotic agent from a non-permeable container inside the pressure chamber. As the osmotic agent cannot pass out through the forward osmosis membranes, the actuator will instead draw water into the pressure chamber from a water supply on the outside of the actuator, in an attempt to create an ionic balance.

Needle insertion and retraction is automatic and controlled mechanically. The needle is inserted into the patient when the start button is pressed and, by means

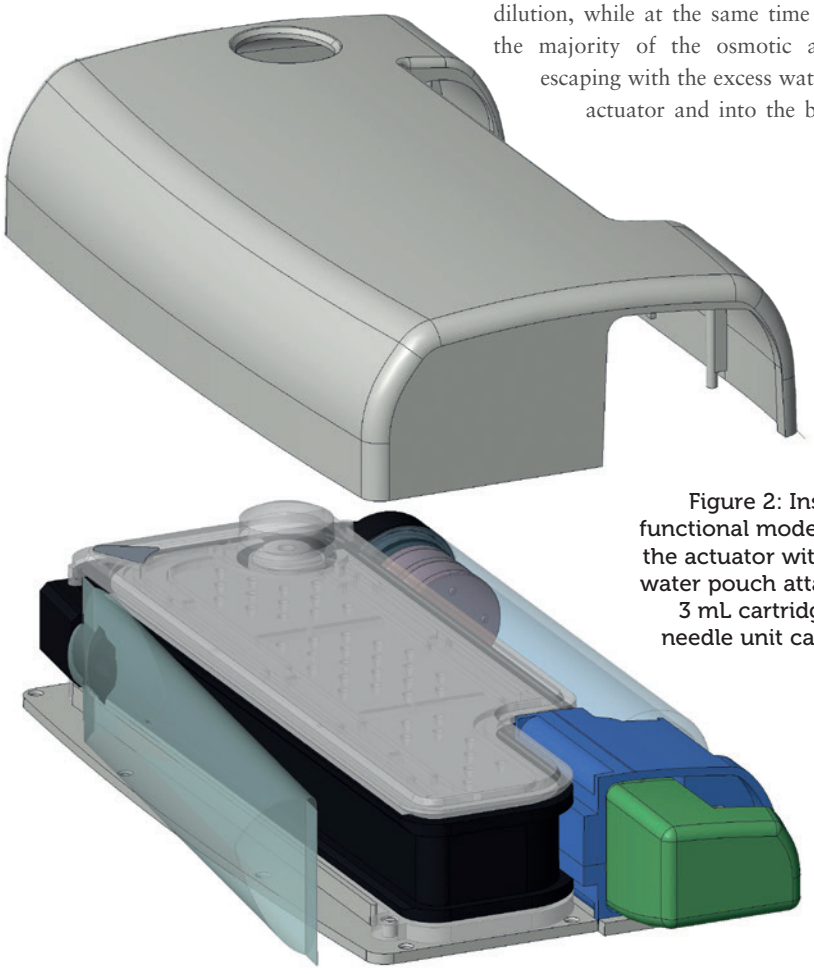

Figure 2: Inside of the functional model, wherein the actuator with the feed water pouch attached, the 3 mL cartridge and the needle unit can be seen.

"The device contains only a small number of inexpensive components and the manufacturing price is comparable with that of autoinjectors. Only the assembled and filled cartridge and the needle unit need to be sterilised, meaning no terminal sterilisation is necessary."

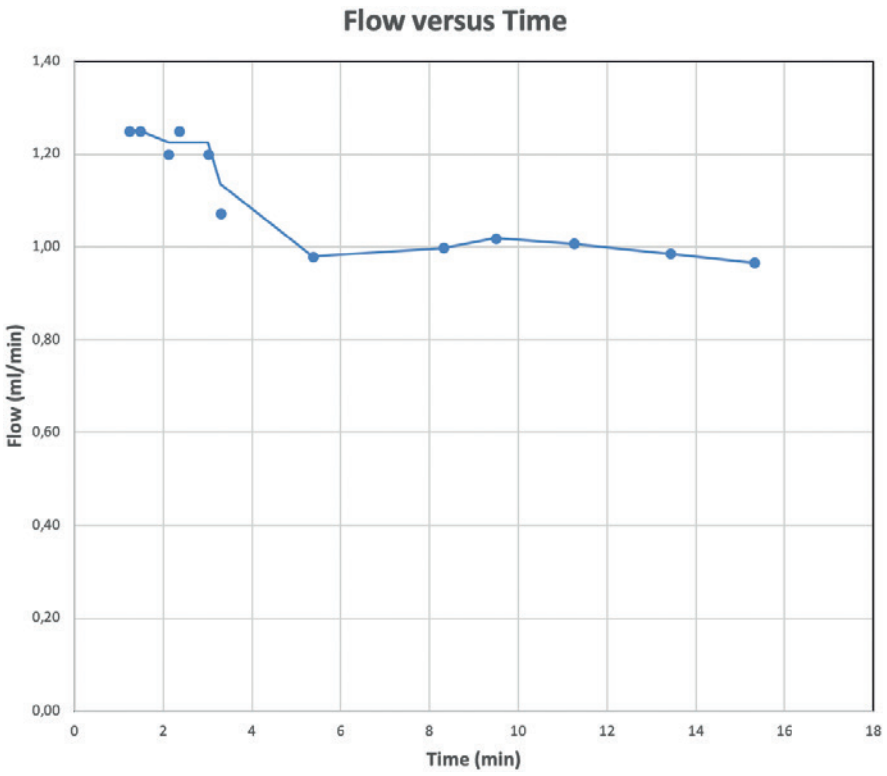

Figure 3: Graph showing results from an earlier isolated actuator test with same internal geometry as the above functional device model. Flow rate stabilises at about 1 mL/min and is stable for minimum 15 mL injection.

of a patented cartridge valve, the needle is caused to be retracted by a spring when the cartridge plunger reaches the end position.

The Subcuject device currently in development is a 3 mL version, which makes use of off-the-shelf cartridges and off-the-shelf plungers. This means that all primary packaging materials are known and well characterised in relation to drug stability. Given the osmotic actuator performance, the device can be developed for injection volumes up to 10 mL.

From a users' point of view, the Subcuject WBI is a prefilled, relatively small, noiseless device with only one button to push, and which is acceptable for disposal after single use.

From a pharma company's point of view, the device contains only a small number of inexpensive components and the manufacturing price is comparable with that of autoinjectors. Only the assembled and filled cartridge and the needle unit need to be sterilised, meaning no terminal sterilisation is necessary.

ABOUT THE COMPANY

Subcuject is developing an innovative and proprietary device platform for wearable bolus injection. It is a virtual organisation, working closely with external experts and specialist organisations. The management team and Board of Directors has decades of experience and a track record in medical devices, pharma and drug delivery. Located north of Copenhagen, Denmark, Subcuject is privately held.

ABOUT THE AUTHOR

Claus Schmidt Moeller, Founder of Subcuject and inventor of the Subcuject device concept, has 25 years' experience in innovation of drug delivery devices. He is the inventor of the mechanical concept of Novo Nordisk's Novopen 4, 5 and 6, and co-inventor of the company's Flexpen and Flextouch insulin pens. Additionally, he has developed and licensed several injection device concepts for major pharma and device companies, and is named as inventor or co-inventor on more than 60 patent families. Mr Moeller holds a BSc in Mechanical Engineering.

A QUICK GUIDE TO USABILITY FOR WEARABLE INJECTORS

Here, Cory Costantino, Director of User Interface Design, and Lauren Fennelly, Senior Human Factors Specialist, both of Emergo by UL, list some typical steps a user might take while using wearable injectors, providing tips and points to note at each step, including design tips that might pre-empt potential interaction problems, and points to consider when conducting usability testing.

INTRODUCTION

Although there are a wide variety of wearable injectors, there are also many common characteristics that impact the user's experience. Here we present a Quick Guide list of some of the trends we've observed supporting the design and usability testing of these products. For each step, we provide our insights on potential usability issues to consider when developing and testing a wearable injector's design (see Figure 1).

1. GATHER SUPPLIES

Gathering essentials such as alcohol s wabs, hand sanitiser, the device, and medication onto a clean surface might seem like an obvious and simple first step. But, there can be some critical choices to make.

- **Drug differentiation.** Users might have to select among multiple drugs for use in the device. Legible, conspicuous labelling on the medication cartridges, vials, syringes, and other accessories will help users avoid selecting the wrong medication or concentration.

> "Newer users will likely feel apprehensive as they position the device onto their skin, focusing on the startling needle stick they'll feel in just a few moments rather than the task at hand. However, device design can help account for users' misplaced focus."

- **Dose/Device differentiation.** To support easy differentiation when devices are available in different volume capacities (and prevent incorrect dosing), each device's carton and labelling on the device itself should display its capacity in large text (e.g. 14-18 pt) and different coloured labels. Better yet, the devices themselves could be different colours or sizes to make visual distinction even more emphatic.

Testing tip: Provide adequate workspace needed to accommodate supplies. Supplies on a neatly set test room table can double or triple in footprint when participants remove inner packaging, drug vials, blister packs, and unfold the IFU (see Table 1 for a summary of the testing tips).

2. PAIR DEVICE WITH CONTROLLER OR APP

Some wearable injectors feature a controller or app that enables the user to program an injection, view dose history, or adjust other device settings.

- **Simple.** Pairing and setting up connected devices can seem cumbersome and confusing, particularly to less tech-savvy users. Seek ways to simplify the process, for example separate the task of pairing the controller and device from other setup steps like creating accounts and connecting to networks.
- **In sync.** Ideally, the controller will be able to detect where the user is in the workflow, and be forgiving when users perform steps out of order (and provide support to get the user back on track).
- **Age appropriate.** Consider how young adults might be comfortable using a controller or app along with the device, whereas elderly patients might be more resistant to a screen-based paradigm.

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Figure 1: Patients can face many opportunities for interactive problems when working with wearable injectors. Numbers in the figure above correspond with the steps outlined in this article.

Testing tip: Ensure the people in your usability tests – the participant sample – reflect the age range of people who have the condition(s) the product is designed to treat.

3. WASH HANDS

For all injection devices, washing hands is a critical step to preventing infection. Although cleanliness can be subjective, manufacturers should include helpful graphics in an instructional step to help patients remember this step and establish good habits.

Ensure adequate workspace for participants
Include a representative patient sample, including a variety of ages (if applicable to condition)
Video record key steps (such as filling the device) during the session
Exercise human subjects protection practices (especially if device will be applied to skin)
Intervene before a needlestick injury occurs
Use a "cooking show" format to simulate time passing
Include scenarios with and without controller component

Table 1: Key tips for conducting usability tests of wearable injectors.

4. FILL THE DEVICE

For myriad reasons, it's not always possible to provide a prefilled device. In this case, simplifying the device filling process is the next best thing.

- **Filling tools.** Using a standard syringe to fill a device can be a difficult task. Users face challenges such as handling delicate/sharp needles, viewing small graduation lines, reading the meniscus, pushing against high-viscosity drugs or back pressure, and targeting small, inconspicuous fill ports. In general, filling accessories should aim to minimise these challenges and demands on users' dexterity. A Luer lock filling port, for example, rather than a small port that must be accessed by a needle, could be a simple improvement.
- **Fill location.** We often see users struggle to find the fill port. This can happen because the fill port closely resembles other small, neutral colour device features, including indicator lights, vents, or the plastic housing. Conspicuous graphic icons (e.g. a syringe icon printed on the adhesive liner) can help users differentiate the fill port from other device features.
- **When to fill.** Some wearable injectors require users to fill the device before interacting with other system components. In such cases, on-device labelling – such as stickers preventing the user from moving a specific component – can be an effective method to prevent filling at the wrong time.

Testing tip: Focus a tripod-mounted HD camera closely on the patient's hands during filling tasks. Analyse this footage retroactively to pinpoint filling interactions that are particularly challenging for users.

5. REMOVE ADHESIVE LINER

Adhesive liners with inadequate gripping area can result in tearing or wrinkling the adhesive, resulting in compromised contact with the patient's skin. Ensure the adhesive liner has adequately large pull tabs and separates easily from the adhesive pad – especially when designing for patients with reduced visual acuity or dexterity impairments.

6. PREPARE INJECTION SITE

Similar to handwashing, patients have a broad range of cleanliness standards. Instructional materials should include helpful graphics to help patients establish good habits.

Testing tip: Some individuals might have adhesive allergies or be uncomfortable exposing skin during the test session. If test participants must place the device on the skin (versus on simulated skin), inform potential participants during the screening and consent process.

"Ideally, devices have a small footprint and low profile with rounded edges. This helps ensure comfort in a variety of body locations, and reduces the likelihood of the device bumping into objects in the environment or getting caught in the user's clothing."

7. PLACE DEVICE ON BODY

Newer users will likely feel apprehensive as they position the device onto their skin, focusing on the startling needle stick they'll feel in just a few moments rather than the task at hand. However, device design can help account for users' misplaced focus.

- **Location**. Instructional materials should use simple anatomical graphics with enough context to help users identify suitable body locations for a wearable device.
- **Orientation**. Users might place a device in an incorrect orientation. Ideally, the device design enables the user to access critical controls and view critical indicators irrespective of orientation or location on the body. Regardless, always provide clear instructions and very conspicuous orientation markings to guide proper placement.
- **Comfortable design**. Users should feel comfortable wearing the device, and confident that the device will remain secure. Ideally, devices have a small footprint and low profile with rounded edges. This helps ensure comfort in a variety of body locations, and reduces the likelihood of the device bumping into objects in the environment or getting caught in the user's clothing.

8. ACTIVATE INJECTOR AND START INJECTION

Although the need to insert the needle and start injection is arguably the most obvious and anticipated step for the user, there are still opportunities where use error can confound their efforts.

- **Unlock**. An unlock step can provide a simple means of blocking mechanical, electrical, or chemical functions from occurring inadvertently until the time of use. If included, ensure such features are salient and simple, such as a button with "unlock" icon, a one-way twisting motion, or a coloured pull tab or cap.
- **Power on**. Users might expect to have to power-on a wearable injector that includes a screen and buttons before using it. However, if the device is relatively simple (e.g. a single-use device) users might have difficulty determining if the device first needs to be powered-on, then started, or simply started in one action. In either case, ensure that the device clearly distinguishes between "on" and "start" if both steps are needed.
- **Inadvertent activation**. Preparation steps can require varying degrees of handling, which could lead a user to press a start button inadvertently before applying the device to their body. Such a use error can waste valuable medication, breach sterility, or cause needle-stick injuries. Explore opportunities to protect the start button with a protruding rim or unlock feature.
- **Needle awareness**. Ensure that the device provides clear graphics and features indicating the needle's location so users keep their hands away from the needle's path, and position the device properly. Even if the injector includes a sensor to detect proper skin contact before allowing the needle to deploy, consider whether a user could inadvertently activate the sensor when handling the device.

Testing tip: If there is potential for needle-stick injury, inform participants before starting the test session. The moderator can intervene if they think a participant is about to get a needle stick.

9. MONITOR INJECTION

If users need to check on their injection status or if the device needs to get the user's attention (e.g. due to an occlusion), the device should clearly indicate its status in a passive or assertive manner, respectively.

- **User's perspective**. While it might seem opportune to present information (screens, LEDs, dose windows) on the device's largest flat surface, that surface is often perpendicular to the user's line of sight, given that the larger surface would have the adhesive patch. Seek opportunities to place key information on sides that are in direct line of sight, which might be the shorter, protruding side of the device.
- **Infusion duration**. Some wearable injector products might infuse drug over several minutes and only be used once a week or once every few weeks, while others might infuse drug for longer periods. Assume that devices delivering longer infusions might be subjected to more varied use environments and user activities, and those with longer durations between infusions might stretch the user's ability to remember the proper injection workflow.

"While it might seem opportune to present information (screens, LEDs, dose windows) on the device's largest flat surface, that surface is often perpendicular to the user's line of sight, given that the larger surface would have the adhesive patch. Seek opportunities to place key information on sides that are in direct line of sight, which might be the shorter, protruding side of the device."

Testing tip: Longer infusion times can pose a challenge for typical usability test durations. Consider using a "cooking show" format during testing: participants prepare and

start an injection, then, after a short period, the test moderator artificially triggers the end of infusion, and the participant resumes as they would at the end of infusion.

- **Labels**. During an injection, static labels can offer an effective gauge of infusion progress. For example, legible syringe barrel graduations against a high-contrast plunger can create a simple, effective gauge. Similar inspiration might come from an automobile fuel gauge, where a pointer moves along the scale from full to empty.
- **Signals**. While audible and vibratory signals might gain users' attention, users will likely seek visual confirmation for a device-related event. Therefore, ensure the haptic and audio feedback is intense enough to be detected and prompt inspection, but also provide intuitive visual signals to confirm the current status. Additionally, consider limiting the number of distinct audio and haptic feedback signals, recognising that users might have difficulty distinguishing between them.
- **Controllers and Quick Reference Guides**. Separate controllers, apps and quick guides can offer more details about the current injection status. For example, a controller might provide real-time status information and provide instructions on assessing and resolving an alert state.

Testing tip: If the wearable injector system includes a separate controller, include use scenarios that replicate system use with and without the controller to evaluate whether users can effectively use or monitor the device without the controller.

10. ADJUST THERAPY DURING INFUSION

Some wearable injectors enable setting adjustments during infusion. To do so, the device might offer physical buttons or functions on a controller.

- **Quick access**. Some wearable injectors include quick-access functions to adjust the therapy. For example, for a quick insulin bolus, users might have to remember how much insulin each press delivers, detect successful button actuation, and keep track of how many times they pressed the button. Such physical and cognitive demands can be overwhelming, leading to use errors.
- **Physical action**. Designing a button to be used on a soft, moving surface (i.e. the body) is inherently difficult. A button on the front surface might require the user to push the button into themselves, while a button on a side surface might require squeezing around the overall device for leverage. In either case, protect buttons with an unlock, recess, or raised lip to prevent accidental actuation. Importantly, consider users' hand sizes and grip strength, and provide an appropriate travel distance (~3 mm) and feedback (such as an audible and physical click) so that users can detect when they've successfully actuated the button.
- **Controllers**. Apps could mitigate some concerns related to quick access and physical buttons. When providing controls via an app, clearly present the device's status and most likely-used controls on screen (e.g. bolus function, pause therapy, increase/decrease infusion rate), while relegating other functions and information to a menu or secondary screen.

11. CONFIRM COMPLETED INJECTION

Users will want to know when the injection is complete. A device simply turning off upon completion is not only anticlimactic, but also flawed user interface design – users might not be able to determine whether the injection completed successfully or failed in the midst of infusion.

A controller screen should be able to provide a clear message, but the device should indicate its status as well. The device could provide haptic and audible feedback to get the user's attention, but it should also provide a visual signal. For example, a green LED to indicate "complete" (assuming that the same green light does not also indicate a "start" or "in progress" condition). Moreover, a physical mechanism – such as a plunger or gauge that changes colour, position, and labelling when complete – can create a unique physical "done" state.

12. REMOVE WEARABLE INJECTOR

Most wearable injectors are removed by peeling away the device. Make sure there is enough adhesive patch protruding from the device for users to grasp the patch's edge and get leverage to peel it away. In addition, when the injection is complete, the needle should retract into the device to reduce discomfort during removal and prevent a needle-stick injury.

13. DISPOSAL

Users might be unsure how to dispose of their wearable injector properly, especially when devices have a retracted (i.e. not visible) needle. Provide clear instructions for proper disposal.

- **Single-use components**. Users can be tempted to reuse single-use components due to the cost of some medications. Ideally, design all single-use components to prevent reuse. Provide training and explanation in instructional material regarding the risks of reusing components.
- **Durable components**. Inadvertently discarding a durable component can be costly and delay therapy. Components with a screen or buttons might be more easily recognised as reusable, but, in general, design durable components to be visually distinct, appealing, and dominant in appearance to help convey they should be retained after completing the injection.

14. STORE WEARABLE INJECTOR AND SUPPLIES

Storage instructions are typically provided when the user receives the device and supplies, but storage steps might also be relevant after each injection.

- **Clean after use**. Provide specific cleaning instructions for durable device components so that users do not damage the components with improper technique or cleaning agents.
- **Storage location**. Clearly indicate storage conditions, and seek ways to facilitate proper storage in common scenarios. For example, consider providing users with a carrying case designed to contain the device and related supplies for a week (or a day pack, if the drug is taken multiple times daily.)

CONCLUSION

Like any other medical device, developing wearable injectors that are safe, effective, and appealing requires a thorough user-centred design and human factors engineering

process. Thinking through the most common use steps and potential use-related issues is a foundational exercise that should be informed by research and continuously repeated and refined. In doing so, companies designing and developing wearable injectors can build on their understanding of the user's workflow through requirements definition, design, risk analysis, formative usability testing, instruction and training development, and ultimately human factors validation testing scenarios.

ABOUT THE COMPANY

Emergo by UL's experienced, global Human Factors Research & Design (HFR&D) team specialises in early-stage user research, product design, usability testing, and user interface design. With a primary focus on medical devices and combination products, the team helps clients bring safe and effective products to market and ensures best-in-class user experiences. The team includes more than 65 specialists and has offices in the US, the UK, the Netherlands, and Japan.

ABOUT THE AUTHORS

Cory Costantino is the Director of User Interface Design within the Human Factors Engineering group at Emergo by UL. Mr Costantino is a board-certified human factors professional. He received his MS in Human Factors in Information Design from Bentley University (Waltham, MA, US) and his BS in Industrial Design from Wentworth Institute of Technology (Boston, MA, US). Mr Costantino oversees and contributes to a wide range of projects including software user interfaces, instructional materials, hardware/ergonomic designs, and multi-phase projects, where he often contributes to user research and usability testing. Over the past 20 years, he has helped guide products, from hand-held consumer electronics to medical devices and software user interfaces, from concept to production.

Lauren Fennelly is a Senior Human Factors Specialist with Emergo by UL's Human Factors Research & Design (HFR&D) team. She has been with the team since 2013. As part of the Emergo HFR&D team, Ms Fennelly has experience applying HFE expertise to a variety of products, including drug delivery products, implantable devices, and medical devices used in-home and in-clinic. She leads a variety of human factors activities, including usability test protocol development, test conduct, data analysis, and HFE document development. Ms Fennelly holds a BS in Mechanical Engineering from the Northeastern University (Boston, MA, US) and a certificate in User Experience from Bentley University (Waltham, MA, US).

HOW LARGE-VOLUME WEARABLES ARE REVOLUTIONISING THE PATIENT EXPERIENCE

Victoria Morgan, Director, Segment Marketing, Global Biologics, West Pharmaceutical Services, looks at how the combination of large-volume medicines and the trend for wearable devices is transforming life for patients, highlighting the company's new-generation SmartDose 10 mL platform.

In recent times, various media outlets have promoted the comeback of flared trousers but, whilst they have been many a glam rock fan's chosen attire for years, the mainstream fashion-adhering public is yet to be convinced. The 1970s was the only decade to fully embrace flares with open arms until the trend was pushed aside for the skintight, drainpipe jeans of the 1980s. Today, the skinny jean (a young relative of the drainpipe jean), with the help of a generous dose of spandex, seems to have stood the test of time.

Trends are constantly influencing our way of life and preferences. The same is true for healthcare, and patient preference has never been more firmly rooted in pharmaceutical development. From implants revolutionising the choice of contraceptive dosing to pens for top-up insulin injections at the dinner table, significant steps forward have been made in health management, thanks to patient preference. Such steps have been supported by pharma companies to help improve patient compliance and stay ahead of the competition.

> "Designing a cost-effective drug administration process that offers a better experience for the patient is a radical change that will propel large-volume injection into a new era."

Large-volume medicines have traditionally been infused or administered intravenously due to the challenges of getting the required volume of drug into a patient's bloodstream. Patient self-administration of large volumes using traditional devices such as autoinjectors, pens or prefilled syringes has been unsuccessful for several reasons, such as the difficulty for a patient to hold a device in place for the required amount of time, the high viscosity of the drugs to be administered and the inability of subcutaneous tissues to absorb large drug volumes.

These challenges usually required patients to travel to health clinics and hospitals for treatment. Whilst the patient experience when visiting a hospital may vary, the interruptions to daily life, cost of travel, and the constant reminder of their disease state have driven the need for pharma manufacturers to consider the overall patient experience when developing alternative administration options.

While the patient always comes first, the cost of caregiving must also be considered during drug development. Designing a cost-effective drug administration process that offers a better experience for the patient is a radical change that will propel large-volume injection into a new era.

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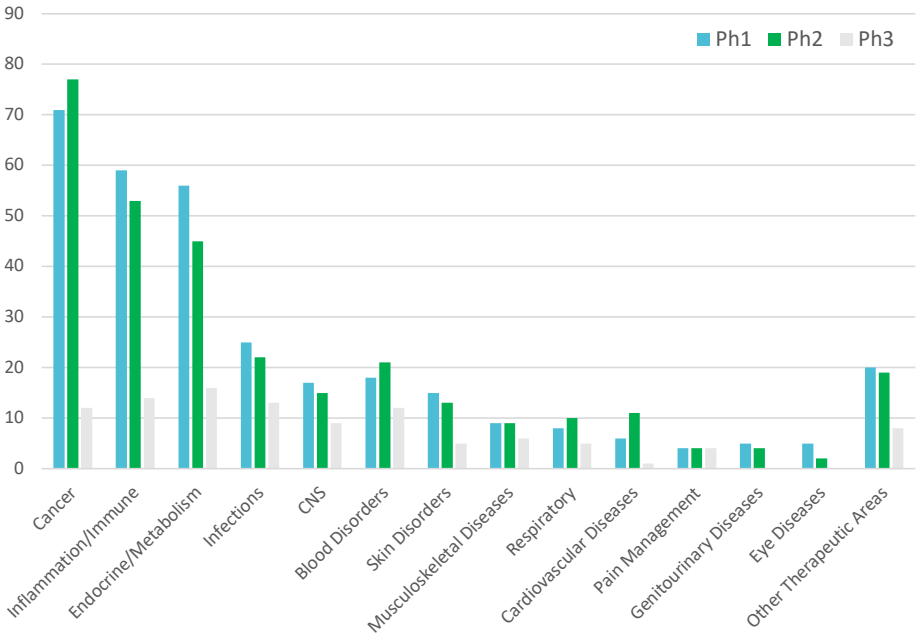

Figure 1: Number of new molecular entity subcutaneous biologics programmes in the clinic.[3]

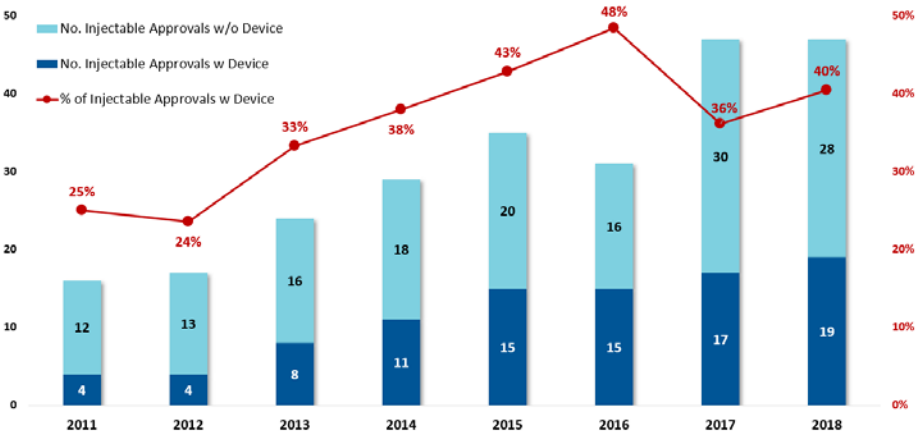

Figure 2: The increase in combination products means more opportunities for device innovation.

> "The increase in combination products means more opportunities for device innovation for pharma companies, patients and payers."

The invention of wearable devices and the availability of Enhanze® drug delivery technology from Halozyme (San Diego, CA, US) have been upstream changes that have met with the downstream desire of patients to have more influence over their disease management. These two technology advancements have allowed larger volumes to be administered subcutaneously, over a longer period, in a non-clinical setting by ensuring user requirements are at the heart of the patient experience.

This step change in drug packaging has been most applicable for biologic drug administration where viscous formulations and higher volumes are common. The new biologics pipeline continues to grow, with a focus on lifecycle management and total cost reduction. The number of preclinical and Phase I/II pipeline products increased 70% and 32%, respectively, from 2016 to 2018.[1]

Pipeline biologic molecules are focused on narrowly targeted therapies and small patient populations with reduced side effects and reduced dosing. The current trend is for consistent growth in combination products coming to market with a CAGR between 2014 and 2018 of 12%.[2] Subcutaneous injections have rapidly expanded beyond diabetes and autoimmune therapy areas into cancer, cardiology and blood diseases, amongst others (Figure 1).

Not only are the number of new molecular entities in development increasing, but we also see drug development companies looking to reformulate existing commercial molecules into volumes suitable for wearable injectors. These companies are increasingly comfortable with bringing combination products to market (Figure 2).[3]

This sustained strong growth in the number of combination products means more opportunities for device innovation for pharma companies, patients and payers as follows:

- For the pharma company, drug delivery methods can be used to protect market share from biosimilar competition (such as with Amgen's Neulasta® Onpro®)
- For the patient, higher-volume chronic disease subcutaneous injections offer advantages with less frequent injections, improved adherence and a home setting
- For the clinic/payer, a move from intravenous to subcutaneous drug delivery offers cost savings since:
  - Faster drug prep time improves pharmacy efficiency[4]
  - Fixed dosing reduces drug waste and medication error[5]
  - Less set-up reduces nurses time.[4]

West Pharmaceutical Services recognised these trends over a decade ago and invested in wearable technology in 2010. West's first offering was the wearable and programmable SmartDose® drug delivery device, the technology of which Amgen incorporated into its Pushtronex® device (Figure 3). In 2016, the US FDA approved the use of Amgen's Repatha® for hyperlipidaemia in the Pushtronex device, which was the first FDA-approved commercial-use wearable. Human factors showed the design, functionality, size and comfort were all conducive to the patient whilst allowing Amgen to differentiate its offering to the market.

West's SmartDose wearable first-generation device revealed the need for higher-volume, subcutaneous delivery with programmable features to suit the dosing regime of the therapy. As a result, West expanded its commitment to wearable technologies with the development of a platform of devices. In January 2019, scPharmaceuticals (Burlington, MA, US)

Figure 3: Amgen's Pushtronex® system that incorporates West's SmartDose® drug delivery technology.

announced a development agreement with West for its Next-Generation FUROSCIX® On-Body Infusor, featuring second-generation technology of the SmartDose device.

FUROSCIX is a proprietary furosemide solution formulated to a neutral pH to allow for subcutaneous infusion via a wearable, pre-programed drug delivery system that is applied to the abdomen for subcutaneous drug administration. FUROSCIX is being developed for treatment of oedema, or fluid overload, in patients with heart failure. FUROSCIX has the potential to provide an outpatient alternative for the treatment of worsening heart failure due to oedema.

With considerable market traction around the SmartDose drug delivery platform, it is not surprising to see the results from West's early recognition of the trend for larger volume delivery. The new-generation platform (Figure 4) offers usability and feature enhancements, including:

- Up to 10 mL delivery
- Better usability
- Faster Injection
- Quieter
- Training system (Figure 5)
- Filling pathway.

These usability and feature enhancements have been examined in extensive human factors testing. The extensive design incorporated body mass index (BMI), age, health status and experience and was arranged to test design usability, acceptability, comfort, whether the device addressed the patient needs and what was the monthly preference for administration. Study users chose the SmartDose 10 mL as an acceptable treatment, and rated it higher than all of the alternatives (Figure 6), which included autoinjectors, visiting a clinic for intravenous injection or infusion and even multiple doses with the lower-volume first-generation SmartDose device.

FILL-FINISH IS A CRITICAL BRIDGE FROM DEVELOPMENT TO DELIVERY

Fill and finish services for wearable containers are a complex yet critical part of the drug development supply chain. Requirements for fill and finish services range from small-scale fills suitable

"Fill and finish services for wearable containers are a complex yet critical part of the drug development supply chain."

Figure 4: Second-generation SmartDose® 10 mL wearable device.

Figure 5: Training pack for onboarding caregivers and patients.

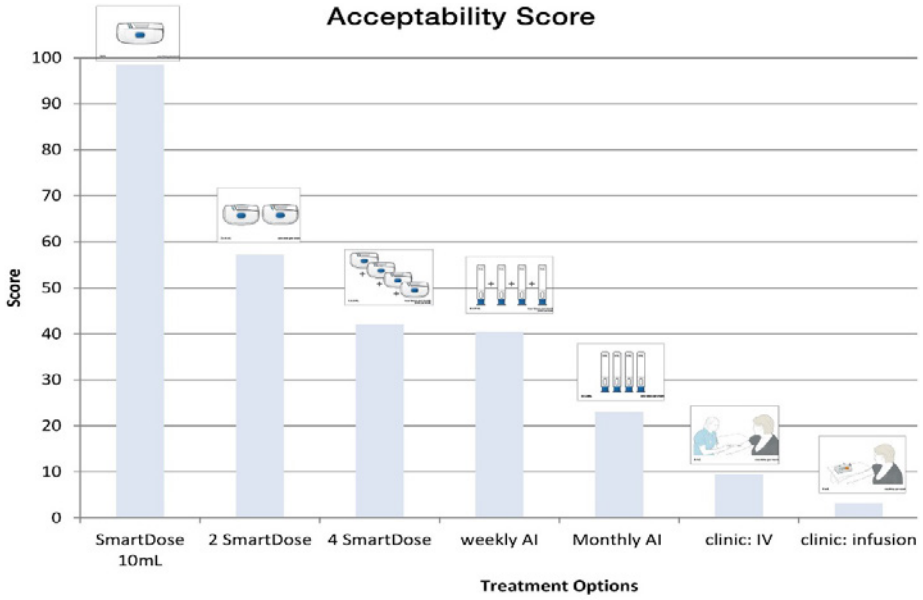

Figure 6: Human factors study results showing SmartDose® 10 mL was the preferred device.

for taking to the clinic, through to commercial-scale production volumes. Finding a partner who can support a drug developer's requirements in the right way, at the right time, without risk to the overall development timelines can be time consuming.

Recognising the need to strengthen the device offering and taking more of a collaborative, integrated approach to supporting a customer has been a key driver for West. The company offers in-house small-scale laboratory filling services to help customers from sample preparation for product testing through to product and process characterisation. West can support a drug development company with GMP filling at established contract manufacturing organisations or enable a customer's new fill line or retrofits in-house.

Earlier this year, West announced that it had commenced discussions with Swissfillon (Visp, Switzerland) – a provider of aseptic fill and finish services to pharma and biotechnology companies, that are intended to lead to a non-exclusive global collaboration to provide fill-finish capabilities to customers using the SmartDose® platform for complex molecules.

Through the collaboration, it is anticipated that West will be able to deliver an integrated solution with filled Crystal Zenith® cartridges for the SmartDose drug delivery platform, which is expected to accelerate clinical development and enable customers to bring their innovative injectable drugs to market quickly. This new collaboration is expected to offer customers a robust clinical fill-finish capability later this year.

West has seen many changes over the past decade from building out its device platform, enabling fill and finish capabilities and leveraging a wealth of expertise in componentry, devices, regulations and testing as an integrated solution to customers. The appetite for wearables is considerable and West will continue to grow and evolve, to predict and respond to the trends to help ensure our customers are providing up-to-date and innovative options for patients.

ABOUT THE COMPANY

West Pharmaceutical Services, Inc. is a manufacturer of packaging components and delivery systems for injectable drugs and healthcare products. Working by the side of the world's leading pharmaceutical, biotechnology, generic drug and medical device producers from concept to patient, West creates products that promote the efficiency, reliability and safety of the global pharmaceutical drug supply. In addition, West provides a comprehensive Integrated Solutions Program that combines high-quality packaging and delivery systems with analytical testing, device manufacturing and assembly, and regulatory services to support customers throughout the drug development lifecycle.

West is headquartered in Exton, PA, US, and supports its customers from locations in North and South America, Europe, Asia and Australia. West's 2018 net sales of US$1.7 billion reflect the daily use of approximately 112 million of its components and devices, which are designed to improve the delivery of healthcare to patients around the world.

REFERENCES

1. *Pharmacircle, January 2019.*
2. *IQVIA Data.*
3. *US FDA CDER / CBER Data.*
4. *De Cock E et al, "A time and motion study of subcutaneous versus intravenous trastuzumab in patients with HER2- positive early breast cancer". Cancer Med, 2016, Vol 5(3), pp 389-397.*
5. *Jeroen J et al, "Fixed Dosing of Monoclonal Antibodies in Oncology". The Oncologist, July 28, 2017.*

ABOUT THE AUTHOR

Victoria Morgan has been in the pharmaceutical industry for more than 25 years with extensive experience in the area of injection drug delivery products, such as primary packaging and combination products for vial, prefilled syringe systems, cartridges and devices. Throughout her tenure at West, she has served in various functions across sales and marketing. Ms Morgan spent more than 17 years in global sales roles, with her most recent position being Director of Segment Marketing, Biologics, where she has responsibility for global biological strategy development and implementation.

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January 2020	Ophthalmic Drug Delivery	Dec 5, 2019
February 2020	Prefilled Syringes & Injection Devices	Dec 23, 2019
March 2020	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 6, 2020
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Elcam
Drug Delivery Devices

EVOLUTION OF AN ON-BODY BOLUS INJECTOR: FROM DRUG-SPECIFIC DEVICE TO PLATFORM TECHNOLOGY

Here, Tsachi Shaked, Managing Director and Chief Business Officer of E3D, introduces the company's On-body Bolus Injector, OBI, a versatile wearable injector platform that uses gas generating microcells as its engine, has no electromechanical components, only one moving part, and can be supplied to the patient prefilled and preloaded or filled and loaded at the time of application.

Some of medicine's greatest innovations started with a simple question, "What if?" What if tiring hospital visits could be completely eliminated by creating an on-body injector which could allow patients to receive vital drug dosages at home?

As the trend to transition patient care from the clinic to the home continues, and as a growing number of parenteral biologic products are developed for a wide range of medical conditions, there is an ever greater need for devices which enable patients or other non-clinicians to administer injectable medications themselves, safely and effectively.

MOVING CARE FROM THE PATIENT CHAIR TO THE SOFA

Elcam Drug Delivery Devices (E3D), a division of the Elcam Medical Group, is at the forefront of moving elements of patient care out of the clinic and into the home, where it is appropriate and safe to do so. The move into on-body bolus injectors was a natural progression for E3D, an established player in the injectable medications market (see Figure 1) and best known for its Flexi-Q PFS disposable mechanical autoinjector which is partnered with a big pharma "blockbuster" drug.

Figure 1: E3D's family of products.

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"The first version of the OBI, the OBI-1 provides subcutaneous delivery of a 0.6 mL dose of pegfilgrastim in the familiarity, comfort and convenience of the patient's home, saving them the inconvenience and discomfort of yet another hospital visit."

Figure 2: OBI on-body injector.

MARKET DRIVERS

In recent years there has been considerable interest in on-body injectors from pharma companies developing biosimilars of Amgen's Neulasta (pegfilgrastim). This drug is delivered as a single 0.6 mL subcutaneous injection one day after a course of chemotherapy, in order to prevent neutropenia and therefore reduce risk of infection. Amgen's Onpro on-body injector device was adapted from an insulin pump technology. If an insulin pump delivers too much insulin too quickly, it can result in the user entering into a hypoglycaemic condition – which could lead to serious injury or death. Consequently, an insulin pump must have the appropriate means to deliver very small (but variable) amounts of insulin, very accurately, over extended periods – with associated sophisticated monitoring and control systems to ensure clinical efficacy and user safety.

By contrast, one-time delivery of a 0.6 mL bolus of pegfilgrastim takes place over a period of minutes. While the drug must undoubtedly be delivered accurately and safely, this does not present the same level of challenge as delivery of insulin – and can therefore be achieved with a device that is smaller, less sophisticated and less costly than a modified insulin pump or other relatively complex electromechanical technology.

I was intrigued by this possibility, as was our development team. Creating on-body delivery devices represented the next step in E3D's drive to solve injection-related challenges by delivering suitable device platforms for subcutaneous or intramuscular delivery of medications outside of a clinical environment. Beyond the strong business case, I had a personal motivation. I was driven by the words of a close friend suffering from skin cancer who said, "Wouldn't it be nice if I could do that simple shot in my own home?"

Patients taking pegfilgrastim are already weakened from chemotherapy. Creating a convenient injector for home use spares them the tiring trip to the hospital, finding a parking space, and waiting in line. Instead, they can rest comfortably at home while the on-body injector does its job. It also spares valuable hospital resources, providing a cost-effective alternative to outpatient treatment.

TOWARDS AN ON-BODY PLATFORM TECHNOLOGY

While working on the new on-body device, the E3D team looked at several key issues including the device's size, relative complexity and estimated manufacturing costs. Our research determined that reliable and robust on-body devices for drug delivery should ideally meet the following criteria:

- **Usability** – replicate the user experience already introduced to market, ensuring it is both easy to use and user-friendly
- **Pre-loading** – the device can be loaded with the drug by hand from a PFS and applied to the patient's skin by a healthcare professional on the day of the patient's last clinic visit for chemotherapy
- **Delivery** – the bolus injection will be administered within a specified time, automatically starting 27 hours after being applied to the patient's skin
- **Stable** – doesn't protrude too much from the patient's skin and cannot be easily dislodged from a patient's body in the 27 hours between device placement and injection
- **Reduces risk** – if the device is not properly attached to the patient or the intended site of injection has to be changed because a nerve end or blood vessel had been hit by the injection cannula, it will not result in losing the drug dosage
- **Simplified design** – reduce the size and complexity of the device to enable cost-effective manufacture.

BOLUS SC DELIVERY WITH ON-BODY INJECTORS

Following extensive R&D and usability testing, E3D recently introduced its On-body Bolus Injector (OBI), which met all the defined criteria. The OBI platform (Figure 2) has been specifically developed to deliver bolus subcutaneous injections at the desired injection rates — as cost-effectively as possible and with minimal need for patient intervention. Drawing on E3D's extensive experience in the design of wearable, smart and mechanical injectors, the first version of the OBI, the OBI-1 provides subcutaneous delivery of a 0.6 mL dose of pegfilgrastim in the familiarity, comfort and convenience of the patient's home, saving them the inconvenience and discomfort of yet another hospital visit.

OBI-1 is configured to be used in a similar manner to the Onpro device which is already approved and used with the originator's Neulasta product. OBI-1 for pegfilgrastim is manually filled from a prefilled syringe by a healthcare professional in the clinic and is then attached to the patient by an integrated adhesive patch. As with the Neulasta Onpro

"In addition to avoiding the need for complex and expensive motors, gears and their associated power sources and controls, the use of such microcells in this way results in a device technology which is small, light, inherently robust, with only one moving part."

injector device, OBI-1 incorporates a timer which results in the patient automatically receiving their bolus injection over approximately one hour – 27 hours following attachment of the device and after the patient has returned home from the clinic.

COMPACT, ECONOMICAL AND EFFICIENT TECHNOLOGY PLATFORM

The key to the OBI technology platform is its use of gas generation by microcells as the basis for its "engine" – a system which is well-established to move liquids and deliver fluids in numerous medical and consumer products. Once an OBI device has been activated, gas is automatically generated at a controllable rate and its pressure is utilised to move a plunger and deliver the bolus of drug. In addition to avoiding the need for complex and expensive motors, gears and their associated power sources and controls, the use of such microcells in this way results in a device technology which is small, light, inherently robust, with one moving part (the elastomeric plunger which delivers the drug) and very cost-effective.

The OBI device technology platform offers significant advantages in the delivery of other injectables. Because OBI has no electromechanical components, and has only one moving part, it represents a device platform which is compact, inherently robust, economical, readily scalable for any dose volume, and suitable for either manual filling of drug or preloaded with the relevant drug.

Whilst the OBI-1 is designed specifically for the delivery of a 0.6 mL dose of pegfilgrastim, and for manual filling of its reservoir by a healthcare professional, E3D recognises that application of the OBI platform (Figure 3) for other drugs will typically require injection of higher dose volumes. An OBI device with a single microcell is capable of delivering a liquid bolus of up to 20 mL, allowing OBI devices to be readily scaled for such dose volumes. Should it be necessary to administer even higher dose volumes, additional microcells can be easily incorporated as necessary. The microcell "engine" is also well suited to delivering viscous liquids, addressing an increasingly prevalent requirement for emerging drug products.

> "Because OBI has no electromechanical components, and has only one moving part, it represents a device platform which is compact, inherently robust, economical, readily scalable for any dose volume, and suitable for either manual filling of drug or preloaded with the relevant drug."

Figure 3: OBI platform technology.

> "The OBI platform can provide the required capabilities to meet the needs of specific drugs, therapies and patient populations. Its versatility is set to provide significant added value to pharma companies seeking cost-effective on-body alternatives."

PRELOADED DEVICES WILL OFFER SIGNIFICANT PATIENT ADVANTAGES

Additionally, and in common with other injector devices, there are clear advantages in having an injector which is intended for use by patients to be supplied with the drug product already preloaded within the device – in order to make its use as simple and intuitive as possible. Whilst OBI-1 for pegfilgrastim is designed for manual filling, the simplicity of the OBI platform allows E3D to offer OBI devices in a configuration that incorporates prefilled primary containers (in glass or other materials), which are suited to established drug filling, handling, sterilisation and assembly processes.

While OBI-1 for pegfilgrastim incorporates a timer to enable automatic activation and initiate an injection 27 hours post-attachment of the device to the patient, it is not anticipated that this feature will be widely required for other drugs and indications, with OBI devices typically therefore being activated by the user pressing a button following placement of the device on the injection site tissue. Once activated, the OBI device communicates with the patient by means of audible and visual indicators, making it clear when an injection has been completed and when the used device can be peeled from the skin for disposal.

Since it generates no electromechanical waste, OBI can be disposed of simply and without the need for complex and expensive "back to base" logistical operations.

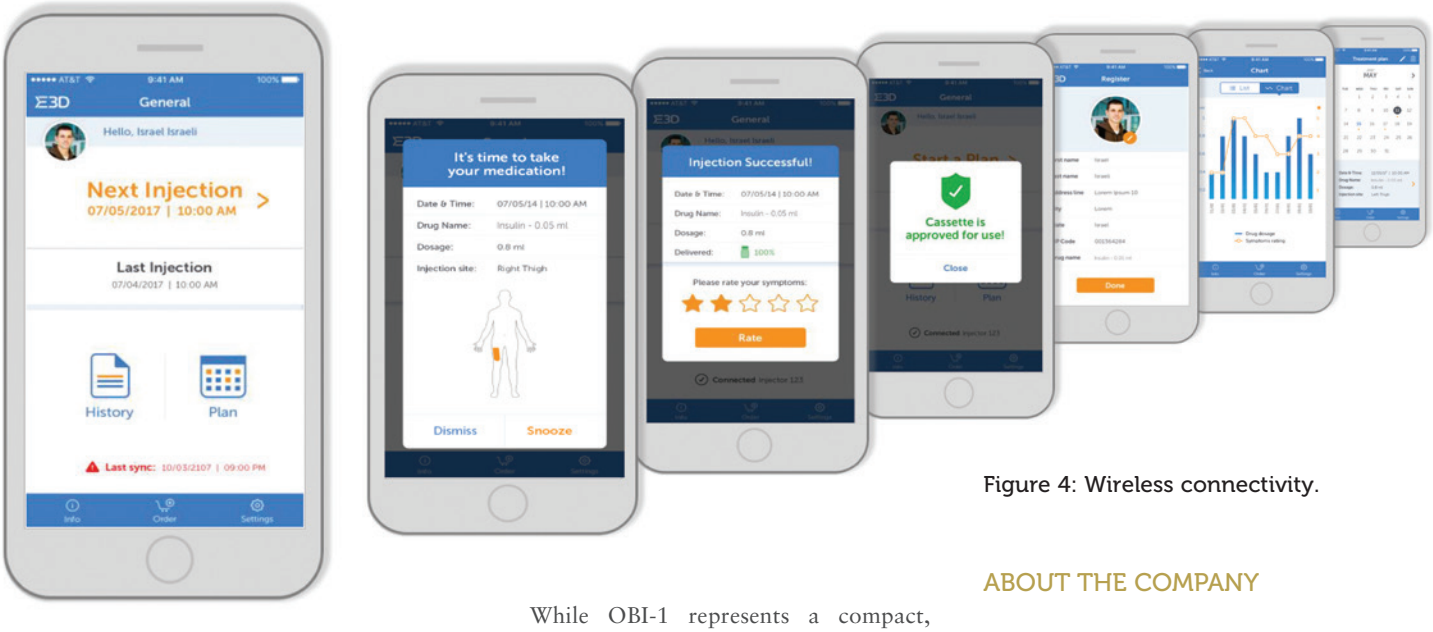

Figure 4: Wireless connectivity.

E3D's technology portfolio includes "smart" injector devices which are configured for generation, storage and wireless communication (e.g. to central data storage and/or mobile phones) of comprehensive data regarding each injection (Figure 4).

The OBI platform can provide the required capabilities to meet the needs of specific drugs, therapies and patient populations. Its versatility is set to provide significant added value to pharma companies seeking cost-effective on-body alternatives.

EXPANDING THE BOUNDARIES OF ON-BODY TECHNOLOGY

With more injectables requiring high dose volumes and with more of these drug products having elevated viscosities, all of the signals from the marketplace suggest that on-body injector devices will have an increasingly important role to play in providing, effective, safe and convenient patient care.

While OBI-1 represents a compact, robust, flexible and cost-effective on-body injector for delivery of pegfilgrastim, devices based on E3D's OBI technology platform create significant advantages for a broad range of drugs for a wide variety of indications including autoimmune conditions, diabetes, oncology, multiple sclerosis and more.

On-body injectors will represent an increasingly attractive alternative to handheld injector devices for higher dose volumes and viscous drugs. Our goal is to provide a robust, scalable and economic platform that serves many applications.

ABOUT THE COMPANY

Elcam Drug Delivery Devices (E3D) portfolio encompasses a wide range of injectables produced in the company's manufacturing facilities in Europe, the US and Israel. These devices include single-use and multi-use, spring-powered autoinjectors designed for 1 mL and 2.25 mL prefilled syringes; wearable injectors for bolus, high-volume and viscous drug delivery; electromechanical and mechanical "smart" injectors with wireless connectivity; autoinjectors for viscous formulations; emergency-use injector devices; and injectors with both automated and manual reconstitution for lyophilised products.

ABOUT THE AUTHOR

Tsachi Shaked is the Managing Director and Chief Business Officer at E3D (Elcam Drug Delivery Devices), a subsidiary of Elcam Medical. Mr Shaked holds an MBA from Bar-Ilan University, Israel, specialising in Marketing. As part of the company's portfolio, he is deeply involved with the development of E3D's new drug delivery devices incorporating connectivity and electronic applications. Mr Shaked has been with the company since 2006.

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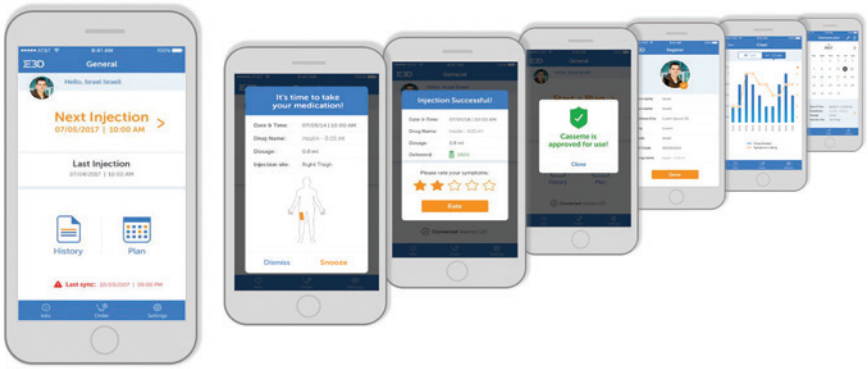
Elcam Drug Delivery Devices

Adding connectivity to drug delivery devices

Evolution of an On-Body Bolus Injector

From drug-specific device to platform technology



Elcam
Drug Delivery Devices

Elcam MEDICAL
Where everything connects

COMPANY SHOWCASE: Sensile Medical

SENSILE MEDICAL
A Gerresheimer Company

Sensile Medical has achieved a lot since its acquisition by Gerresheimer last year. Here we provide an update on two recent projects: the recent market launch of our first micropump, an infusion pump for Parkinson's disease patients; and our latest project with SQ Innovation for a 3 mL furosemide patch pump. With these tangible results and achievements, we demonstrate our world-class capabilities in the development of large- and small-volume wearable injection devices.

ONCE-A-DAY SET-UP OF A FULL DAY'S TREATMENT

The first micropump from Sensile Medical is now available on the market. It may give Parkinson's patients more autonomy in their day-to-day lives by enabling once-a-day set-up for a full day's treatment.

Figure 1: 20 mL wearable platform has recently been launched in Europe with apomorphine for advanced Parkinson's disease.

> "For most patients a full day's treatment can be set up just once a day, giving them more autonomy in their daily lives."

Developed by Sensile Medical especially for EVER Pharma (Unterach, Austria) under the brand name D-*mine*® Pump, this 20 mL wearable infusion device with a micropump (Figure 1) recently received European CE certification and has already been launched in several European countries. The compact, patient-friendly infusion pump is used for the continuous subcutaneous administration of apomorphine to treat the advanced stages of Parkinson's disease.

Looking at currently available treatments, patients often have to swallow multiple oral dosage forms while adhering to a strict schedule. Additionally, one or more self-injections of medicine were required. All this compromised their quality of life. In order to ease the control of the disease, a continuous infusion using the pump offers a beneficial option. For most patients a full day's treatment can be set up just once a day, giving them more autonomy in their daily lives.

A Perfect Fit: Modular and Flexible Components

Sensile's modular and flexible system, providing a multi-use reusable module containing the software and electronics as well as motor, feedback elements and power source, together with the single-use disposable component that is exchanged with every new drug filling, are a perfect answer for this specific therapy.

Considering the impairments caused by the disease, it was crucial to develop a device which is safe and easy to handle for those having difficulties co-ordinating their movements. Small, discreet and easy to carry portable were further goals which were achieved from a device look and feel perspective.

Fully Patient Centric – Basal and Bolus Fit to Each Individual Patient's Needs

It was mandatory to have built-in automated drug transfer from the vial to the device. A minimal number of buttons and a multicolour screen interface allow adjustment of the pump according to every single patient's needs for basal and bolus drug flow, as well as adapting the dose whenever needed. Plain text menus improve usability. With Sensile's micropump technology these features and settings are an integral part assuring precise and accurate dosing.

The integrated software and electronics, fully adapted to the specific therapy, allowed us to integrate multiple languages supporting launch in various countries. Patients have

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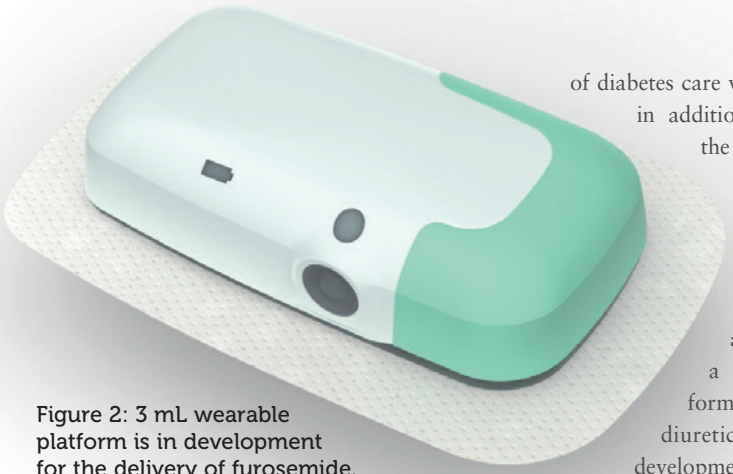

Figure 2: 3 mL wearable platform is in development for the delivery of furosemide.

the freedom to choose their language of choice. To avoid complicated flow-rate calculations for this specific treatment the device flow rate was set to mg instead of ml/h for delivery. Data history can be looked up and supports better management options to healthcare professionals with no additional daily paperwork for the patient.

Based on its excellent dedicated team, technology and experience Sensile Medical has delivered an ambitious 20 mL infusion pump with highly innovative user requirements fully customised to the patient and pharma company's needs and the pump has successfully entered the market.

3 ML MICROPUMP FOR CONCENTRATED FUROSEMIDE – A NEW TREATMENT OPTION

Sensile Medical is in the advanced stages of development of a 3 mL micropump (Figure 2) providing extremely accurate dosing over time. The most obvious therapeutic application for such a pump is in the area of diabetes care with insulin. However, in addition to insulin therapy, the 3 mL pump platform is being developed for multiple other therapeutic applications. One of these is for ultra-accurate delivery of a novel concentrated formulation of the loop diuretic furosemide under development by SQ Innovation (Zug, Switzerland) for the treatment of oedema in heart failure.

In partnership with SQ Innovation, Sensile is utilising its 3 mL platform, based on a standard 3 mL cartridge, to enable a cost-effective drug delivery solution that will help improve outcomes and reduce costs in the treatment of heart failure. The device design comprises reusable motorised component and disposable cartridge, which minimises waste and creates cost-effective treatment options across therapy areas.

Heart failure is a common, complex and serious condition affecting approximately 6.2 million people in the US and 26 million people worldwide. Many patients with heart failure experience episodes of worsening symptoms due to fluid overload (oedema). Current therapy options for these episodes include an increase in oral medication or, when oral treatment is not sufficiently effective, intravenous (IV) treatment, typically delivered in an emergency room or other clinical setting. Subcutaneous infusion by means of a mini pump adhered to the skin may offer a solution for patients who otherwise do not require hospital care.

Fluid overload in heart failure is responsible for approximately US$14 billion (£11.5 billion) in Medicare spending, or approximately 3.9% of the Medicare budget, making it one of the most expensive therapies for the elderly. The high spending is attributable to in-patient care for diuretic treatment which accounts for approximately 7% of Medicare hospital admissions. In addition, a hospital stay is associated with risks of adverse outcomes due to rapid muscle loss and functional decline experienced by many elderly patients during their hospital stay and recovery.

"A heart failure patient should not have to be in hospital to receive effective diuretic therapy for fluid overload," said Bertram Pitt, MD, Professor of Medicine (*emeritus*) at the University of Michigan School of Medicine (Ann Arbor, MI, US). "A treatment option that provides IV strength diuresis without the need for venous access would enable the development of novel strategies, which could reduce hospitalisations with a resultant improvement in quality of life and a reduction in healthcare costs."

Sensile Medical is proud to be involved at the centre of exactly such a treatment option.

CONCLUSION

The interest in small- and large-volume patches, and off-body worn devices, is constantly growing in the industry. Modular and flexible platforms support individual requirements in various treatment areas. Sensile Medical is the right partner building bridges from drugs to patients.

SORREL medical

A VIAL-BASED SOLUTION FOR WEARABLE DRUG DELIVERY

In this article, Mindy Katz, Director of Product, and Michael Ratigan, Chief Commercial Officer, both of Sorrel Medical, describe how, due to the inherent challenges of integrating vials into wearable devices, there has not been a viable, patient-centric option for wearable devices using vials ... until now.

With the continued shift to value-based care, increased emphasis on patient drug delivery experiences, and rising healthcare costs, pharmaceutical companies are under mounting pressure to offer solutions capable of addressing the varied needs of both patients and healthcare providers. Innovations in the drug delivery and combination product industry have seen standard primary containers incorporated into prefilled and preloaded drug delivery devices, with the intention of creating a patient-centric solution that benefits both healthcare providers and pharma companies.

> "Maintaining a vial as the primary drug container can significantly improve time to commercialisation, while reducing both cost and overall risk for pharma companies bringing new biologics to market."

A recent example is the use of a standard vial as the primary container for wearable drug delivery devices. Maintaining a vial as

Figure 1: Primary containers for injectables: vials and cartridges.

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the primary drug container can significantly improve time to commercialisation, while reducing both cost and overall risk for pharma companies bringing new biologics to market. However, the complexities involved in using a vial for wearable drug delivery devices have – until now – made such solutions impractical for pharma companies and patients alike.

CHOOSING A PRIMARY CONTAINER

There are numerous considerations drug developers must take into account when selecting a primary container.[1] Volume, material, manufacturer, previous regulatory approvals, procurement concerns and costs – as well as any chemical interactions with the specific medication – are all in the mix when it comes to choosing an ideal container closure system (Figure 1). Consequently, one of Sorrel's initial goals was to allow pharma partners the freedom to use a variety of drug reservoirs. The technology was thus designed with the necessary flexibility to allow drug developers to integrate the primary container of their choice.

THE BENEFITS OF A VIAL

Over the past decade, the drug delivery industry has seen new primary containers and drug delivery devices introduced to the market, bringing to light innovations, including novel materials and drug containers, for the benefit of both patients and drug manufacturers. Despite this, for the vast majority of injectable medications, drug formulation and development continues to occur in a vial. Compared with prefilled syringes and cartridges, the vial is still the standard and most widely used primary container for injectables.

Accordingly, vials are being manufactured in larger numbers and with the lowest cost per unit, compared with other primary containers. Additionally, filling lines for vials are the most common, and many contract manufacturing organisations (CMOs) offer vial filling capabilities, as opposed to less-popular cartridge and prefilled syringe filling lines. Many of the large pharma companies have established internal capabilities for handling vials, while needing to outsource the knowledge and filling of other primary containers.

Pharma companies have traditionally encountered the need to transition from one primary container to another ahead of a commercial launch. This generally involves transferring the medication from a vial to either a cartridge or prefilled syringe to allow for a more patient-friendly and ready-to-inject application. However, this transition to a new primary container introduces new challenges and risks to the development project.

> "Any transition from one primary container to another introduces cost and time needed for activities on all fronts – technical, procurement, supply chain and regulatory, to name but a few."

First, the addition of any new container closure component – specifically plungers which are integral to both cartridges and prefilled syringes – is another material that comes in contact with the medication and must be vetted and tested accordingly. This may require bringing in an additional manufacturer, and possibly a dedicated development project, to supply a proprietary plunger for the system. Additionally, both prefilled syringes and cartridges generally require siliconisation to support the plunger movement, which can pose a challenge for medications known to interact with silicone.

Regardless of these specific challenges, any transition from one primary container to another introduces cost and time needed for activities on all fronts – technical, procurement, supply chain and regulatory, to name but a few. These activities introduce inherent risks to a development project and may cause delays in launching a new drug product to market.

Pharma companies are therefore faced with a challenging decision when launching a new medication – deciding in which primary container, together with an appropriate drug delivery device, their product will be introduced to the market.

WEARABLE DEVICES MEET VIALS

Wearable drug delivery devices (also referred to as patch pumps, wearable injectors, on-body devices, large-volume injectors or bolus injectors) have gained popularity in recent years and can provide a significant value proposition for the delivery of large-volume and high-viscosity medications. Moreover, therapies requiring a more complex treatment profile than the traditional manual injection can benefit from such devices, providing options for timed treatment initiation, alternating flow rates, patient-controlled boluses, paused injections and more. Accordingly, we see many pharma companies partnering with medical device manufacturers, as well as developing in-house capabilities, to support the launch of combination products with wearable injectors in the upcoming years.

Looking at such devices, both commercially available and those currently in development or in clinical trials, we see wearable device manufactures recognising the importance for their pharma partners of maintaining the vial as the primary container. Accordingly, there have been several attempts to introduce vial-based wearable drug delivery solutions to the market. However, such solutions generally shift the focus from the patient to the partner. While allowing pharma companies to maintain the vial as the primary container, these generally result in the patient having to perform additional actions in order to transfer the drug out of the vial and into the drug delivery device – affecting the patient centricity of the overall solution.

Patients will often have to purchase the medication and device separately or receive the two components separately but co-packaged. In order to transfer the medication from the vial into the device, one option will be for the user to manually fill the device. This will entail withdrawing the medication from the vial with a dedicated syringe and then transferring it via a dedicated fill hole into the device (Figure 2).

Figure 2: Filling certain wearable devices today requires manually transferring medication from a vial via a syringe.

> "The overriding challenge for a vial-based wearable device derives from the inherent properties of a vial as a non-collapsible drug reservoir."

Alternatively, a dedicated transfer accessory is an option for some devices, allowing the medication to be transferred out of the vial and into the wearable device in a semi-automatic manner. Another option, introduced with some wearable devices, is to have an external filling port through which the medication is extracted from the vial and transferred into the device.

While these solutions enable a vial-based wearable drug delivery solution, they also introduce a new set of complexities and challenges for the user. This is especially true for first-time patients, the elderly or those with limited dexterity. In such cases, this may prevent patient adherence to therapy – with the added risk of potential dosing errors.

To date, pharma companies have therefore been left with two options, neither of which are ideal. The first is to introduce a vial-based solution which adds further complexity to the patient experience. The second requires taking on the task of transferring to a new primary container, enabling a more patient-centric approach but introducing additional risk and delaying time to commercialisation.

THE VIAL CHALLENGE

The overriding challenge for a vial-based wearable device derives from the inherent properties of a vial as a non-collapsible drug reservoir. In comparison, a cartridge or prefilled syringe is collapsible, comprising an open-ended glass or plastic barrel with a plunger that moves as the delivery progresses, continuously reducing the overall volume of the reservoir as the drug is expelled.

When examining the different types of drug delivery mechanisms, one can either push or pull the drug out of a primary container to transfer the fluid from the reservoir through the device fluid path and into the patient. Pushing requires exerting a force on the back end of the plunger and so is not a suitable mechanism to be used with a vial.

On the other hand, drawing the medication out of the primary container poses a new challenge. As the drug is drawn from the vial, air pressure inside the vial is reduced and vacuum is created – making it more challenging to withdraw fluid from the vial. As an example, when using a syringe to manually draw directly from a vial, users are instructed to inject air into the vial prior to withdrawing medication – allowing the medication to be withdrawn more easily, and preventing vacuum forming.

Another inherent challenge pertains to the orientation of the vial during the withdrawal of the medication. As the vial is comprised of both air and liquid, in order to withdraw the medication out of the vial, the vial's orientation needs to be with the cap facing down, relying on gravity for maintaining the flow of medication.

These dual requirements, avoiding creation of vacuum in the vial while maintaining the vial's correct orientation when drawing out the medication, introduce technical challenges for any vial-based wearable device.

A PLATFORM SOLUTION FOR WEARABLE DRUG DELIVERY

Sorrel's pumping mechanism, integrated with the platform's smart sensing capabilities along with audio, visual and tactile indicators, is able to address the challenges of a vial-based wearable device. A key component of the platform solution involves the ability to decouple the device's pumping mechanism from the primary container, enabling the flexibility to accommodate a wide range of drug reservoirs, cartridges and vials alike.

Having established that a device platform must comprise a truly patient and partner-centric solution,[2] it was important to base this solution on Sorrel's platform, without compromising the ease of use of its prefilled and preloaded wearable devices (Figure 3).

As previously noted, Sorrel's platform solution enables a prefilled and preloaded device configuration, by using a disinfection chamber with an integrated UV-C LED, for disinfection at point of care.[3] The LED disinfects the primary container's septum prior to engagement between the primary container and the rest of the device's fluid path (Figure 4).

Sorrel's proprietary UV-C LED technology provides disinfection at the point of care; meets the size, cost and energy requirements of a fully disposable wearable device; and fits both vials and cartridges – thus complementing Sorrel's vial-based solution.

SUMMARY

Despite the introduction and popularity of new primary container configurations, pharma and biotech companies have nevertheless long held a clear and vested interest in the direct use of vials for drug

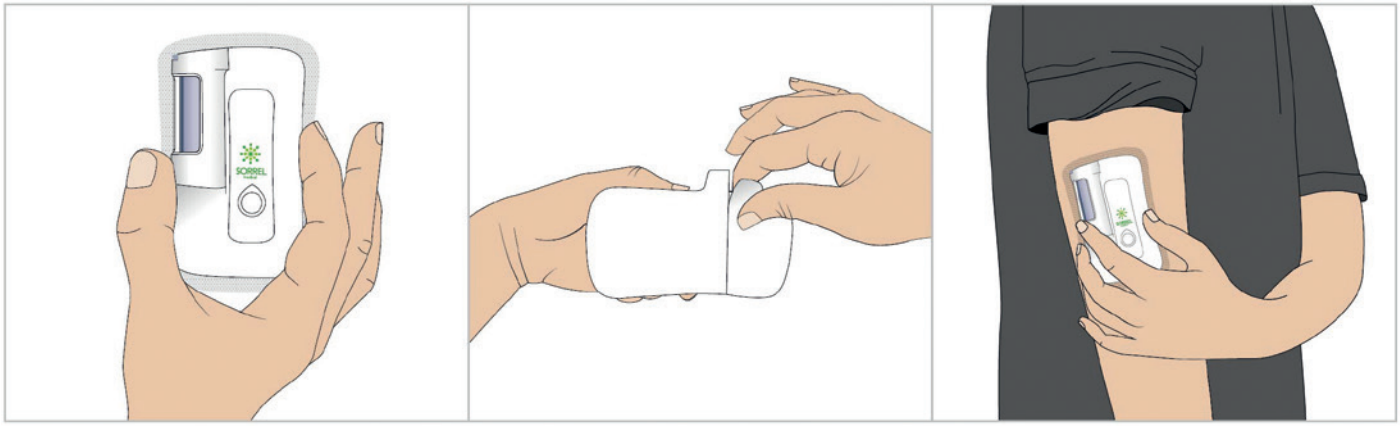

Figure 3: Prefilled and preloaded wearable device user flow: peel and stick.

Figure 4: UV-C LED-based disinfection chamber, enabling a prefilled and preloaded device.

delivery. Due to the inherent challenges of integrating vials into wearable devices, there has not been a viable, patient-centric option for wearable devices using vials – until now.

The option of using a vial as the primary container, complementary to the cartridge-based device offering, is a strategic new component of Sorrel's commitment to providing a patient-centric and partner-focused platform solution to the world of drug delivery (Figure 5).

ABOUT THE COMPANY

Sorrel Medical is a medical device company focused on prefilled wearable injectors. Sorrel is one of three privately held companies operating under the Eitan Group, all in drug delivery devices, including Q Core Medical, Avoset Health and Sorrel Medical. The joint experience shared amongst the Eitan Group's three companies includes commercialisation of drug delivery products across the continuum of care, multiple US FDA approvals, market presence in over 20 countries worldwide, and a team of R&D innovators that are experts in parenteral drug delivery.

Figure 5: Sorrel Medical's wearable device platform, compatible with both cartridges and vials (pictured: 5, 10 and 20 mL).

REFERENCES

1. *Siew A, "Container Selection for Biologic Formulations". Pharmaceutical Technology, 2016, Vol 40(4), pp 24–26.*
2. *Katz M, "Prefilled wearable drug delivery: harnessing technology for patient & partner centricity". ONdrugDelivery, Issue 91 (October 2018), pp 32-36.*
3. *Katz M, "UV sterilization & the case for prefilled &preloaded drug delivery systems". ONdrugDelivery, Issue 95 (February 2019), pp 80-84.*

ABOUT THE AUTHORS

Mindy Katz is Director of Product at Sorrel Medical, responsible for product management and marketing. Ms Katz previously served as Program Manager at Q Core Medical, where she worked across multidisciplinary teams to build structured and collaborative partnerships between companies in the world of drug delivery. Mindy holds a BSc in Biomedical Engineering from the Technion – Israel Institute of Technology.

Michael Ratigan is Chief Commercial Officer at Sorrel Medical, responsible for global business development and partnering initiatives. Mr Ratigan joined Sorrel from Phillips-Medisize, where he served as Vice-President Global Sales and Marketing. Prior to Phillips-Medisize, he served as Senior Vice-President and Chief Commercial Officer at Unilife Corporation, a provider of injectable drug delivery systems. Mr Ratigan also served as Worldwide Business Platform Leader at Becton Dickinson.

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safer, easier and faster drug delivery

LARGE-VOLUME WEARABLE DRUG DELIVERY: A VISION BECOMES REALITY

In this article, Hans Peter Manser, Chief Executive Officer; Christoph Egloff, Chief Technology Officer; and Martin C King, Head of Quality & Regulatory; all of Weibel CDS, introduce LV DDS , a flexible-form, low-profile wearable injector platform, for large-volume drug delivery.

Pharmaceutical companies around the globe are focusing on simplified, affordable, large-volume delivery of parenteral drugs. There is a strong trend for subcutaneous delivery and self-administration that is leading to even larger injection volumes and higher viscosity formulations.

Weibel CDS recently delivered the first prefilled customer units of a new low-profile (22.3 mm) large-volume (25 mL) wearable injector with a flexible form drug reservoir (Figures 1 and 2). It is a single-use disposable device that is worn attached directly to the skin with an integrated fluid path, automatic needle insertion, soft cannula placement and infusion/injection system. The drug reservoir is capable of containing volumes up to 50 mL.

The units were the first from Weibel CDS's new Large-Volume Drug Delivery System (LV DDS) platform, based on proven Weibel CDS innovations:

- The Drug Delivery System, DDS, a valveless volumetric continuous micro-displacement pump
- The MiniBag, a flexible form primary container with similar drug contact properties to glass.

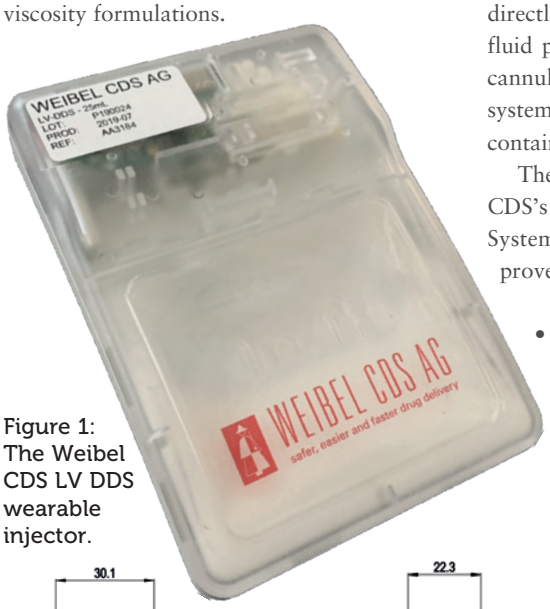

Figure 1: The Weibel CDS LV DDS wearable injector.

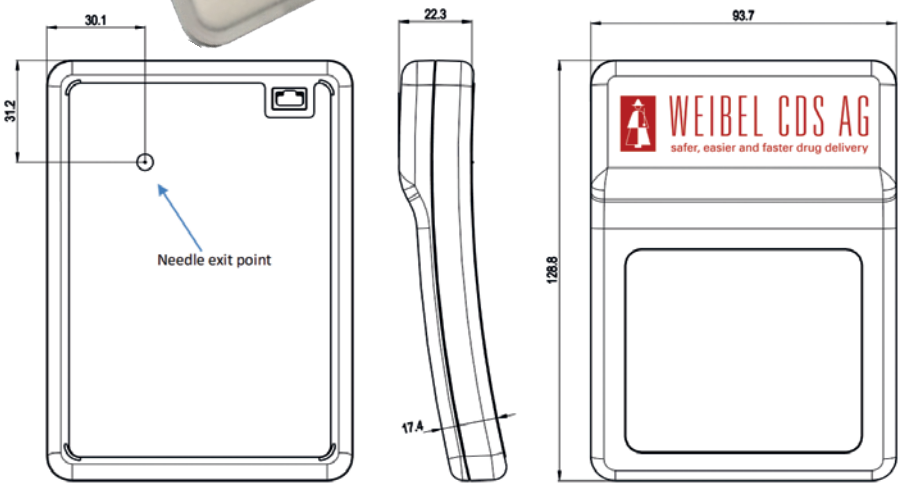

Figure 2: Example based on 25mL and fully disposable LV DDS.

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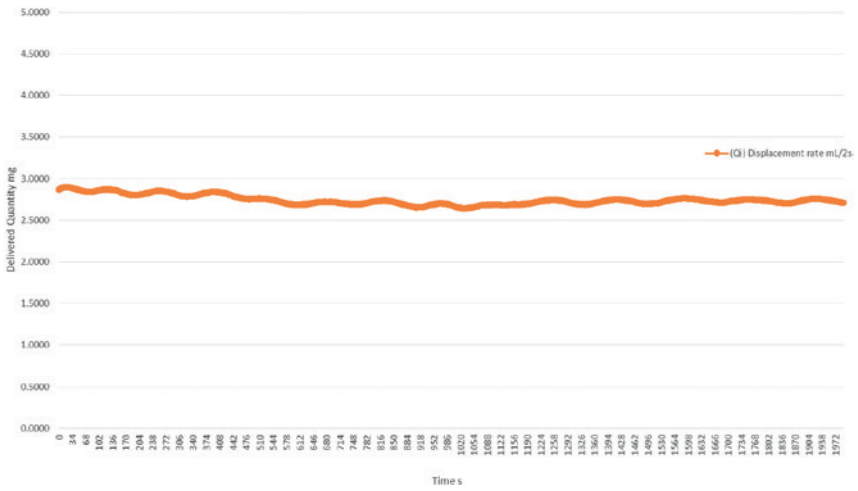

Figure 3: The pump has a constant displacement rate in compliance with IEC 60601-2-24.

LARGE-VOLUME DRUG DELIVERY: SIMPLIFIED

User-filled or prefilled, the single-use Weibel CDS LV DDS simplifies drug administration at home, or in the clinical environment by healthcare professionals, to three steps:

1. Peel-off backing
2. Attach device to body
3. Start injection.

Ready for Customisation

The LV DDS platform is ready for customisation to specific "intended-use" user- or drug product-specific requirements. With unsurpassed dose accuracy (Figure 3), its continuous volumetric displacement pump (Figure 4) supports a range of high viscosity large molecule drug products.

The Weibel CDS LV DDS supports the following features:

- Safe, user-friendly simple to use system with minimised steps.
- Automatic needle insertion system (ANIS), with all needle safety steps performed automatically. The needle remains hidden at all times and is made safe after injection and device removal.
- Automatic soft cannula placement as an option for long duration injections and patient comfort.
- Automatic injection commences when attached to the skin and the drug is ready for injection.
- Suitable for combination therapies from a single device.
- Suitable for continuous flow slow injection, bolus and long duration injections
- Unique high dose accuracy, continuous volumetric pump supporting a range of high viscosity drug products.
- Programmable electronics provide:
  - Personalised patient feedback and connectivity
  - "patient-personalised" programmable injection time and rate profile for the healthcare professional.
- Customisable device shell supporting customer-specific branding schemes.
- Preloaded or loaded at time of use without the need of a cleanroom environment.

The key parameters and technical specs of the LV DDS are summarised in Table 1.

Low-Shear-Force Volumetric Displacement Pump

The Weibel CDS valveless volumetric displacement pump (Figure 3) performs well with highly viscous products and offers good compatibility with shear force-sensitive drugs resulting in no measurable change to the protein structure. Weibel CDS provides Test Platforms for Pharmaceutical Companies to evaluate the delivery characteristics of drug products in the security of their own laboratories.

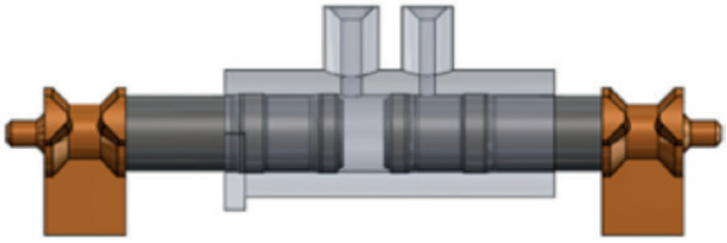

Figure 4: Valveless volumetric displacement pump.

KEY PARAMETERS

Primary Packaging: **2-50mL MiniBagSystem (Larger Volumes on Request)**
Needle System: **27G cannula with a 25G soft cannula, automatic insertion**
Dimension: **128.8mm x 93.7mm x 22.3mm**

	Min.	Typ.	Max.	Units
Water Proofing		IP 33		
Device Weight (Empty Reservoir)		100		g
Operating Temperature	+4	+23	+37	°C
Operating relative humidity range	20		90	%
Non-condensing Operating atmospheric pressure	600		1065	hPA
Viscosity of forwarded Medium			100*	cP
Reservoir		40		mL
Dosage Range with liquid viscosity of 10cP	tbd		360,000	µL/h
Single Stroke Pump Volume	10		200	µL

Depending on the drug delivery rate required, higher viscosities may be possible.

Table 1: Key parameters and technical specs of the Weibel CDS LV-DDS.

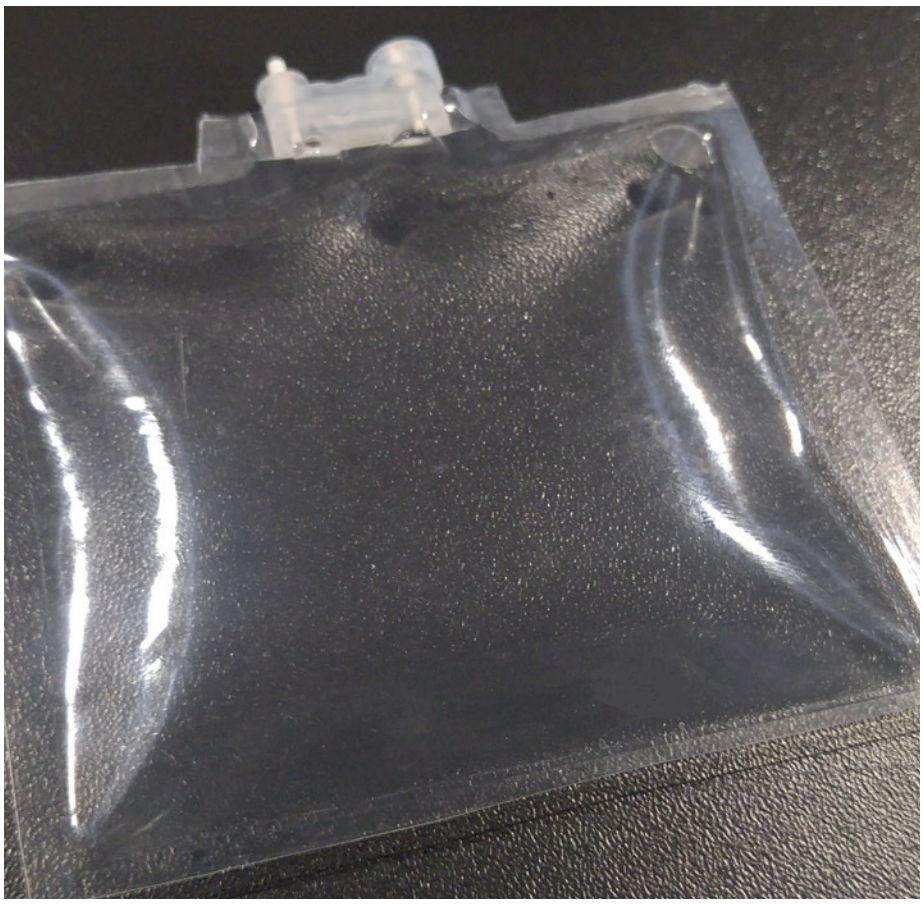

Figure 5: MiniBagSystem is a primary packaging solution with similar drug contact properties to glass.

MiniBagSystem

MiniBagSystem (Figure 5) has undergone rigorous mechanical characterisation and stability testing with large-molecule drug products confirming it as a primary packaging solution with similar drug contact properties to glass, and resilience to pharmaceutical industry standard sterilisation processes.

Exclusive to Weibel CDS, this cyclic olefin copolymer/polychlorotrifluoroethylene (COC/PCTFE) flexible film, CETA160, has been specially developed to store drug product. Manufactured to cGMP standards, the film is high-barrier, transparent, radiation sterilisation stable, non-yellowing and US FDA-compliant.

The PCTFE element is Aclar® from Honeywell International, which gives the film its high barrier to moisture and to aromatic and aliphatic hydrocarbon species and excipients (Table 2).

ABOUT THE COMPANY

Weibel CDS is a privately owned, ISO-certified medical technology company developing, manufacturing and supplying affordable, innovative, user-friendly injection systems and devices to ensure safer, easier and faster delivery of parenteral drugs for home, point-of-care and clinical users around the world. The company is situated at the heart of a medtech cluster based in Schaffhausen, Switzerland.

Weibel CDS holds numerous international patents covering its product portfolio of parenteral drug delivery platform technologies. LyCaJect is a patch injector with in-device automatic reconstitution. The Large-Volume Drug Delivery System (LV DDS) is a low-profile, on-body injector or infusion system capable of delivering up to 50 mL. SuperCapSyringe® is an advanced safety syringe platform based on a modular design with sharps protection, reuse prevention, and an integrated drug transfer vial-to-syringe fluid path. Reconstyringe® is the first to offer fully automated in-device reconstitution of lyophilised drug. Contained in its original vial, the solvent is automatically transferred into the vial. Like a Swiss watch, it runs through the full reconstitution cycle. After this, the drug is drawn through the integrated fluid path into the SuperCapSyringe® ready for injection.

Water vapour transmission rate (@38°C, 90% RH)	0.06 g / m² / 24 h	0.004 g / 100 in² / 24 h
Oxygen transmission rate (@23°C, 50% RH)	19 cm³ / m² / 24 h	1.23 cm³ / 100 in² / 24 h

Table 2: Barrier properties of Aclar® film used for the MiniBagSystem.

ABOUT THE AUTHORS

Hans Peter Manser, Chief Executive Officer at Weibel CDS, holds a diploma in Business Administration and Applied Technical Management. After perennial stays in the UK, Australia, the US, France and Germany, he assumed sales management and executive functions in the communications industry with global responsibilities. Mr Manser transitioned to the pharmaceutical packaging industry in 2001 and subsequently joined Weibel CDS in May 2011 as Business Director, responsible for setting up and management of all administrative and commercial aspects of the company, taking over the overall responsibility of the company in October 2016.

Christoph Egloff is the Chief Technology Officer at Weibel CDS. His role covers innovation, technical design, management of the engineering department and project management. Mr Egloff worked on the design, manufacture, installation and qualification of the company's precision drug delivery, injection, micro-infusion and automatic reconstitution devices.

Martin C King is Head of Quality and Regulatory at Weibel CDS. He has extensive experience in the fields of international medical device development and pharmaceutical management, encompassing all aspects of quality management and regulatory affairs. Mr King has served as a Deputy Swissmedic Responsible Person and Certified Lead Auditor under ISO 13485:2016, with specific expertise in ISO 62304, ISO 14971, 21 CFR 820 and MDSAP.

The vision of Large Volume Wearable Drug Delivery becomes reality

Large Volume Wearable DrugDeliverySystem

safer, easier and faster drug delivery

International patents pending

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TRAINING PATIENTS IN THE USE OF WEARABLE INJECTORS

Advancements in biologics, coupled with the shift to patient self-care in the home setting, have driven the need for self-injection systems. With the continued expansion of the biologics market, it is projected that wearable injection devices will continue to grow in popularity as well. With this growth, it is imperative that healthcare providers (HCPs) both properly train their patients in the office and offer training devices that patients can take home and practice with. Joe Reynolds, Research Manager at Noble, outlines the key features of the company's training devices and explains how they can improve patient outcomes.

Millions of patients worldwide living with rare, debilitating conditions are benefiting from developments in biopharmaceuticals and complex chemical entities as well as novel approaches to drug delivery. For example, many therapeutics administered in a subcutaneous injection are suitable for at-home administration by patients themselves, rather than in a healthcare facility.

More recently, electromechanical on-body injector devices that provide extended dosing – such as those that can provide delivery over 45 minutes at specific time intervals – are making it possible for patients to undergo longer injections while at home or even out and about. These devices allow patients with chronic conditions to administer medications at home in private, while also providing an advanced, timed-dose alternative to daily prefilled syringe injections, autoinjector injections and infusions. As a result, there has been a steady rise in the popularity of these devices and the overall wearable devices market is expected to continue to drive approximately US$32 billion (£26 billion) in global revenue this year.

To address the demand for this emerging market, Noble has developed on-body training solutions and platform technologies that can be used by manufacturers to meet specific onboarding needs. Designing optimal training devices comes down to the unique needs of patients and other user populations. This is why Noble's development process and proprietary portfolio of multisensory, error-detecting, wireless and smart technologies support manufacturers in prioritising requirements and developing solutions that maximise training value for patients and other stakeholders.

HOW THE TRAINERS WORK

A typical on-body self-injection system is affixed via adhesive onto a patient's body (typically the abdomen or the back of the arm), either by the HCP or by patients themselves. For instance, following the administration of chemotherapy, an on-body device will be attached to the patient's body to ensure delivery of a dose of medicine the next day in the form of a subcutaneous injection.

During the interval between the device being attached to the body and the actual time of dosing, the system will signal to the patient via feedback, such as sounds or lights, that it is operating properly. As the time of dosing approaches, the device will indicate that dosing is about to begin. Additional feedback may also show that dosing is currently underway. A window built into the device may display that dosing has been completed satisfactorily.

Key Features

Many of these helpful auditory and visual modes of feedback are known as "smart" features, and just like the true device,

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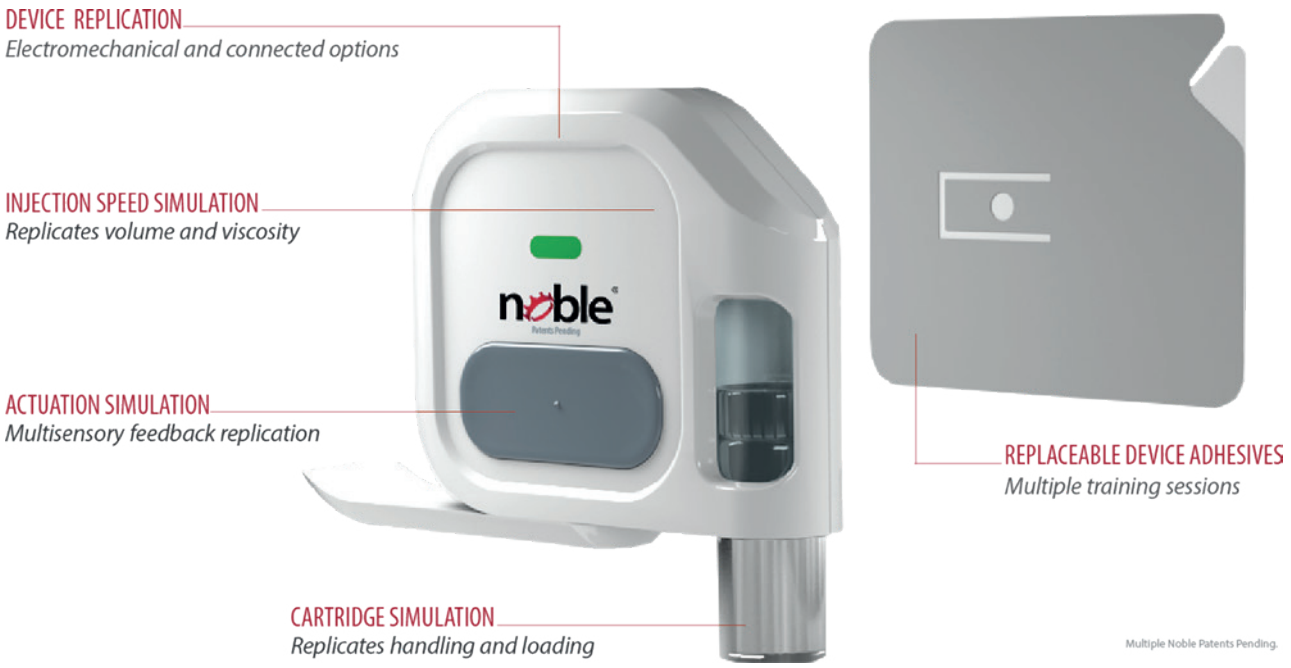

Figure 1: Noble on-body training devices replicate the form and function of specific on-body devices to help patients onboard easier.

Noble's trainers incorporate many of these to foster a more robust and accurate training experience (Figure 1). Some smart features include the design form and the LED signals that provide crucial operational information to users, as well as the small window on the side of the device that indicates whether the entire dose has been delivered. Further, the Noble trainer effectively mimics the tactile feedback and actuation force that is featured by such a platform. These are designed to work in tandem with smartphone apps and can provide real-time feedback to the patient regarding any errors associated with the use of the device as they occur. This information can also allow drug manufacturers to learn how well their devices are being utilised by patients.

In addition to smart features, the trainers are also capable of injection speed simulation, which mirrors a variety of customisable drug delivery times and replicates the volume and viscosity of the drug as it is delivered to the patient. Meanwhile, actuation simulation is made possible by components developed to simulate visual, auditory and haptic feedback through LED light signals, sounds and clicks, as well as actuation button resistance.

Furthermore, the trainers are designed to allow cartridge simulation, providing patients with a realistic device-loading experience prior to the injection part of the training. Noble's trainers also include a number of replaceable device adhesives, which allow patients to train multiple times and to gain familiarity with device initiation pull tabs, adhesive backings and the proper placement of the device on the body.

BENEFITS PROVIDED BY USING THE TRAINERS

Comfort

Collectively, the trainers' features enhance user experience in numerous ways, including setting patient expectations of the comfort level associated with the device. Typically, on-body self-injection devices require needle insertion for an extended period while affixed to the body. Using a training device can be an effective way to convey to the patient that there may be less discomfort than anticipated while using the actual device. Trainers can also assure patients that the protection features built into on-body injection devices can prevent needlestick injuries when used correctly.

Correct Usage

As with all therapies involving drug delivery devices used outside a healthcare setting, the course of treatment cannot achieve expected efficacy if the patient does not use the device correctly. Misuse may result in a less-than-complete dose, or other consequences that lead to suboptimal health outcomes. Studies indicate that improved outcomes may be achieved with the use of training devices for injection-based delivery systems. Such trainers allow patients to practise wearing an on-body device and experience its operation before actually going through dosing with the prescribed therapeutic. The goals are to help patients feel comfortable in advance of using the on-body device, reduce any undue anxiety and ensure that they will utilise the device correctly.

Adherence and Confidence

It is also vital to ensure that patients are truly comfortable with their on-body device and can oversee its operation on their own. Studies have suggested that more comprehensive educational strategies surrounding the use of injection devices is required to improve the patient experience and to encourage adherence. Although HCPs have traditionally instructed patients to read the Instructions for Use (IFU) that come with a device, this measure alone is often not effective in boosting adherence and overall confidence using the device.

In fact, a study conducted by Noble and analysed by Auburn University (AL, US) found that more than 60% of patients self-reported that they did not thoroughly read the required steps outlined in a self-injection's IFU prior to beginning treatment, potentially leading to administration errors and impacting compliance with prescribed therapies. Similar outcomes can occur with on-body injection devices as well, and advanced training devices that better prepare patients for the true injection may help reduce these errors while simultaneously increasing patient confidence.

Fostering overall patient confidence is vital, which is why – for on-body devices in particular – trainers are an important tool to help patients understand how the device may be concealed by clothing when in use. This can alleviate apprehension about stigmatisation resulting from the use of the device that they may initially believe would be noticeable (Figure 2).

Figure 2: On-body trainers allow patients to become familiar with the operation process before using the true device.

ADVANCED DESIGN FEATURES

Adhesion

From a user-experience standpoint, one of the most distinguishable differences between on-body systems and conventional injectors is that they are held in place on a patient's body using adhesives. Incorporating this into reusable training devices requires careful consideration for sanitation, biocompatibility and other design trade-offs. To assist manufacturers through the process, Noble has developed proprietary adhesive and alternative simulation methods that balance these trade-offs and optimise training. This is done so that patients can realistically learn how to adhere and remove devices from their body and understand how long it takes the medication to deploy and be fully delivered.

Forces

In addition to addressing device adhesion, all functions requiring force application by the user must accurately represent the real device. Force profiles can also play a significant role; some forces may ramp up slowly, while others have a fast onset for activation. Within the on-body market, there are also devices that have unique steps for loading, priming, unlocking and other functional features that need to be replicated by a trainer.

Sensory

Other considerations include representing the audible and haptic feedback levels that are present and integrating tactile feel elements, such as subtle internal vibrations associated with drive elements. In addition to these items, the training device must be easily resettable (versus just a single-use product) and must also maintain a 1:1 size ratio (i.e. it cannot get any larger than the real drug delivery device).

BENEFITS FOR HCPS & PHARMA MANUFACTURERS

Patients are not the only group that reap benefits from training devices. When patients are better trained and more informed, they are statistically more likely to adhere to their therapies, which is a boon for HCPs, pharmaceutical companies and manufacturers. Annually, pharmaceutical revenue loss is $637 billion due to non-adherence. One way to help mitigate this staggering loss is through empowering patients to stay involved with their therapies through repeated use of training devices and other advanced training solutions.

It is in HCPs' best interest to ensure that on-body devices are used properly and deliver the optimal dose of drug to their patients. By augmenting traditional patient onboarding methodologies, trainers can help facilitate this goal.

Meanwhile, on-body trainers can enhance a pharmaceutical manufacturer's standing within the rapidly expanding on-body drug delivery market. Debuting a new on-body device in tandem with a trainer can allow the company to distinguish itself from competitors and build a positive reputation among potential patients. Additionally, utilising training devices in clinical trials can help solidify their importance in a strong patient training programme.

SUMMARY

Noble aims to improve the patient experience, reduce errors and anxiety and help increase adherence to prescribed injectable therapies by offering advanced technologies and education materials informed by human factors analysis. It has also developed a portfolio of support materials – such as IFUs, instructional videos and more – to bolster the patient onboarding experience further.

As an increasing number of innovative on-body therapies continue to reach the market, onboarding and training can help to improve patient acceptance, confidence, satisfaction and outcomes with therapy.

ABOUT THE COMPANY

Founded in 1994, Noble is a global leader in medical device training solutions, patient onboarding strategies and multisensory product development for the world's top pharmaceutical brands and biotechnology companies. Focused on driving innovation, Noble works closely with brand, device and commercialisation teams to develop turnkey solutions that improve onboarding and adherence, bringing value to clients and patients alike.

BIBLIOGRAPHY

- *Evans C, "Device training: Maximizing patient adherence by minimizing the forgetting curve". Drug Development & Delivery, 2018, Vol 18(1), pp 22-25.*
- *McLean T, "West's SmartDose platform: a wearable engineered with both patient & pharma partner in mind". ONdrugDelivery, Issue 70 (September 2016), pp24-27.*
- *"On-body training and onboarding platforms". Company Web Page, Noble, August 2019.*
- *"Pharmaceutical & healthcare leaders collaborate to improve the patient journey". Press Release, Noble, October 17, 2016.*
- *"Pharmaceutical Companies Lose $637 Billion in Revenue Annually Due to Medication Nonadherence." Press Release, HealthPrize Technologies, April 26, 2019.*
- *Salazar D, "From 'wearables to ther-ables.'" Drug Store News, April 14, 2016.*
- *"West and Noble collaborate to improve patient education and training for self-injection systems". Press Release, West Pharmaceutical Services, January 20, 2016.*

ABOUT THE AUTHOR

Joe Reynolds is Research Manager at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximise value for stakeholders. Mr Reynolds earned his Bachelor of Science in Business Administration from the University of Central Florida, a Master of Science in Marketing from the University of South Florida, and a Master of Science in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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THE CHANGING DRUG DELIVERY PARADIGM

In this article, Beth DiLauri, Director, Strategic Marketing, Self-Administration Injection Systems BD Medical – Pharmaceutical Systems, sets out the fundamental case for the adoption of wearable injectors, outlines the specific barriers they overcome that pens and prefilled syringes cannot, and describes how the design and development of the BD Libertas™ wearable injector platform, paired with the company's unparalleled parenteral delivery device experience and know-how, make BD Libertas™ an attractive proposal for pharma companies seeking a wearable injector.

Recent years have seen ground-breaking advances in pharmaceutical development with increasingly innovative medicines being brought to market. However, the cost of these novel drugs has intensified the pressure to shift medication administration from traditional settings to more cost-effective alternatives. One such alternative is the patient's own home, where novel molecules are now regularly self-administered subcutaneously to treat chronic diseases such as rheumatoid arthritis, multiple sclerosis and dyslipidaemia, among others.

Pharmaceutical companies have worked to develop highly concentrated monoclonal antibodies (mAbs) to improve treatment options for these chronic diseases.[1] At the same time they are looking to ease the burden on patients by reducing injection frequency and enabling home-based delivery. Although this new paradigm holds tremendous potential it also brings new challenges in drug delivery which require innovative solutions to address them effectively.

LIMITATIONS OF CONVENTIONAL DELIVERY SYSTEMS

Historically, delivering the small-molecule drugs developed to treat conditions such as infection, hypertension, and hyperlipidaemia was of little concern, as most of these medicines could be administered orally. Moreover, when the oral route was not an option, most traditional therapies could be easily solubilised and delivered via intravenous (IV), intramuscular (IM), and/or subcutaneous (SC) injection in a relatively small volume of fluid.

Recent developments in biotechnology have produced a plethora of protein-based molecules (e.g. mAbs) that must be injected to achieve their therapeutic effects. To accommodate the volume limitations of current IM and SC delivery methods, manufacturers must concentrate these formulations, thereby creating an additional challenge of high viscosity.[2]

This trend poses a fundamental problem with two possible

> "Wearable injectors effectively address the volume and viscosity challenges of prefilled syringes and auto-injectors, allowing highly-concentrated drugs to be diluted into larger volumes and administered over longer periods (minutes rather than seconds) without saturating the SC space."

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Figure 1: BD Libertas™, a pre-assembled, fully-integrated, mechanical wearable injector designed to deliver 2-10 mL doses of high-viscosity biologics of up to 50 cP.

"Optimising performance early saves time in the development process and gives us a much better understanding of our users' needs sooner."

solutions, addressed individually or together: 1) increase the injection volume; or 2) increase the injection duration. While these options may be feasible for IV administration, they pose significant impediments to SC delivery, especially when administered by a caregiver or a patient themselves. Practically speaking, humans have a finite ability to self-inject over long periods with traditional delivery devices, as factors such as fatigue, concentration, and the urge to move eventually cause their ability to hold the injection device steadily in place to waver. Physiologically, the SC tissue has a limited physical and absorptive capacity for a rapid influx of large volumes (e.g. >10 mL),[3] and associated injection pressure may lead to drug leakage and injection pain.[4–6] Thus, the clear majority of commercially-available delivery devices (i.e. prefilled syringes and auto-injectors) are designed to administer small drug volumes (≤2 mL) in under 15 seconds.

WEARABLE INJECTORS PRESENT A SOLUTION

Wearable injectors are delivery systems that adhere to the body to administer larger volumes (more than 2 mL) of drug subcutaneously over an extended period. For more than a decade, numerous pharmaceutical and medical device companies have led development efforts to bring wearable injectors to market, including the BD Libertas™ large-volume wearable injector (see Figure 1). While there is variability amongst products, all wearable injectors provide a reservoir for the medication, a cannula for delivery to the tissue, adhesive to fix the device to the patient's skin (Figure 2), and a drive system to deliver the appropriate drug volume.

Figure 2: Wearable injectors provide a drug reservoir, cannula , and adhesive to fix the device to the patient's skin.

Wearable injectors effectively address the volume and viscosity challenges of prefilled syringes and auto-injectors, allowing highly-concentrated drugs to be diluted into larger volumes and administered over longer periods (minutes rather than seconds) without saturating the SC space. Although the potential benefits of these delivery systems are numerous, perhaps the most notable is the ability to self-administer high-volume, high-viscosity drugs in a non-clinical setting.

THE VALUE OF EXPERIENCE

Like all drug delivery devices, a successful wearable injector must be designed to meet the needs of a variety of healthcare stakeholders. Most importantly, it must meet patients' needs for simplicity in the non-clinical setting.

These devices must also meet the pharmaceutical manufacturer's needs for a solution that offers proven, well-integrated components that fit into existing fill/finish processes. This is a significant requirement that demands partners with experience in producing drug delivery devices.

As a leader in delivering high-quality medical devices for over 100 years, BD can leverage its broad experience to meet these requirements effectively and

Figure 3: The BD Libertas™ device has a unique fluid transfer valve built in, enabling the primary container to be filled, assembled, and packaged in a standard Class 8 manufacturing facility.

successfully introduce new drug delivery systems. "BD's extensive expertise in medical device development, primary containers and needles allows for the seamless addition of a wearable injector to any pharmaceutical partner's portfolio," said Kevin Kelly, Vice-President of BD Medical – Pharmaceutical Systems' Self-Administration Injection Systems business.

BD LIBERTAS™, THE NEXT GENERATION OF WEARABLE INJECTORS

BD Libertas™ is a pre-assembled, fully-integrated, mechanical wearable injector designed to deliver 2-10 mL doses of high-viscosity biologics of up to 50 cP. Its unique design and interface were informed by extensive preclinical and clinical research, resulting in a device with minimal steps and little complexity.

Simplicity in Design

Unlike some other wearable injectors, BD Libertas™ does not require user assembly or filling, significantly reducing the potential for human error and contamination. Devices that require user assembly and filling introduce the potential for dropping (and breaking) the primary container, incorrect assembly, touching aseptic areas, and increasing patient and caregiver confusion. Conversely, BD Libertas™ comes completely pre-assembled and ready to use out of the package, eliminating the greatest source of contamination: human interaction.

> "BD Libertas™ incorporates BD Neopak™ primary container technology and employs the same cannula technology found in BD's world-class needles."

"The convenient presentation is enabled by a unique fluid transfer valve built into the injector. The valve enables the primary container to be filled, assembled, and packaged in a standard Class 8 manufacturing facility [Figure 3]," explains Peter Quinn, BD's Wearable Injector Product Platform Leader.

Pioneering Injection Research

BD has conducted rigorous preclinical and clinical research to ensure effective SC delivery of large-volume injections. The Translational Sciences Center of Excellence at BD Technologies has partnered with BD Pharmaceutical Systems to provide *in vivo* testing of BD Libertas™. This collaboration provides valuable insights to impact device design directly, and offers early information on performance in a living system that is not easily replicated on the bench.

Approximately 40 preclinical studies were conducted to characterise the tissue response to large-volume SC deposition, investigate effects that could influence patient perception of the device, and optimise design and system components. These studies evaluated device performance across a broad range of injection conditions that pharmaceutical companies may need to deliver their molecules (e.g. varying viscosities, flow rates, injection times, or body locations). "One extraordinarily valuable aspect of *in vivo* testing is the ability to develop a model that is a good predictor of human outcomes. With rigorous preclinical testing, we can quickly gain the information we need to understand delivery dynamics and device footprint, and optimise device performance before we move on to human testing," commented Natasha Bolick, Manager, BD Technologies.

BD has used this extensive preclinical research to inform four clinical studies. Two of these studies were specific to BD Libertas™ design component optimisation, while the remaining were large-volume injection studies that employed a surrogate system to mimic BD Libertas™ delivery. Through these clinical studies BD gained a comprehensive understanding of the large volume SC injection experience across a variety of injection conditions and valuable insight into patient acceptance and preference. "It's important that we provide the best possible

"Purely mechanical systems provide reliable and known mechanisms for administration, which may help to reduce risk and increase reliability. In contrast, electromechanical devices typically require pumps, which may introduce technical complexities and unknown sources of error."

experience for our end users," Bolick emphasised. "Optimising performance early saves time in the development process and gives us a much better understanding of our users' needs, sooner."

Integrating Trusted Components

Paired with these novel innovations and capabilities, BD leverages the technologies it already delivers to pharmaceutical manufacturers by the millions every day. BD Libertas™ incorporates BD Neopak™ primary container technology and employs the same cannula technology found in BD's world-class needles. "Libertas was purpose built to provide a complete solution, anticipating both patient and manufacturer needs," said Theresa Bankston, Associate Director, Technical Services.

Benefits of Mechanical Systems

A mechanical drive system, like that found in BD Libertas™, provides a robust, industry-tested method of delivering medication. Purely mechanical systems provide reliable and known mechanisms for administration, which may help to reduce risk and increase reliability. In contrast, electromechanical devices typically require pumps, which may introduce technical complexities and unknown sources of error.

Moreover, purely mechanical devices may deliver more comfortable injections compared with electromechanical devices, as they are responsive to tissue back-pressure. As fluid diffuses into the subcutaneous space, pressure in the tissue slowly builds, which may induce pain at the injection site. When this occurs during mechanical delivery, the device responds by naturally slowing the medication delivery toward the end of the injection, reducing the potential for pain. Conversely, electromechanical devices are designed to deliver medication at a constant delivery rate regardless of tissue back-pressure. A final advantage of purely mechanical devices is simply the absence of electronics from the core device. This is particularly beneficial when it comes to device disposal.

Customisation Options

BD offers the ability to adapt several aspects of the BD Libertas™ device, including the look and feel and injection volume, while keeping the core footprint standardised. It will be available in two volume formats, 2-5 mL and 5-10 mL, both housed within a similar device design.

The BD Libertas™ design features customisable outer-facing components, enabling further flexibility without impacting on the functionality of the device. For example, grip and button colours can be changed to reflect branding. The device's outer cover can also be modified with components that contain enhanced functionality. In this way, any BD Libertas™ device can be easily modified or upgraded as needed, without any changes to the core device module.

Flexibility to Become "Smart"

The BD Libertas™ design is future-proofed to meet evolving industry trends. More developers are looking to enhance the injection experience by incorporating "smart" features and connecting with the digital health ecosystem (Figure 4). Although a limited number of commercially-available drug delivery devices currently have smart features, connected devices are poised to become the norm over the next 5-10 years.[7]

According to Kelly, BD believes that smart devices should encompass both local and global connectivity: local, in that a smart device should help facilitate better interactions with individual users; and global, in that the device should enable communication with others about its state and usage. BD has taken this approach in the development of BD Libertas™, while also recognising that not every situation requires the same degree of connectivity.

BD Libertas™ was designed from the outset with the capacity for smart features, simply by adding a smart module to the core device. In this way, one platform can accommodate both local and global connectivity for the same molecule or across molecules within one customer. BD Libertas™ truly offers a platform solution for pharmaceutical companies.

Figure 4: BD Libertas™ was designed from the outset with the capacity for smart features, simply by adding a smart module to the core device.

SUMMARY

Wearable injectors present a comprehensive solution to the challenge of delivering SC injections of increasing dosing volumes and viscosities in non-clinical settings. Introducing robust, innovative technologies will allow more patients to enjoy the convenience of injecting at home. In addition, the ability to accommodate new formulations with higher volume and/or viscosity will enable less frequent injections, improve the patient experience, and potentially increase adherence to therapies.

Bringing new injection technologies to market introduces complexities that pharmaceutical companies must consider as they select the right wearable injector platform for their portfolio. However, experience in providing prefillable injection technologies, delivering well-integrated primary container and device systems, and working with partners who understand the intricacies of delivering drugs into the subcutaneous space all help to increase peace-of-mind for pharmaceutical companies in bringing combination products to market.

BD Libertas™ represents the newest addition to BD's platform of integrated device components to support the development of combination products to enable a variety of options for delivering self-administered biologics.

BD Libertas™ is a product in development; some statements made are subject to a variety of risks and uncertainties.

REFERENCES

1. *Li L, Kumar S, Buck PM, et al, "Concentration dependent viscosity of monoclonal antibody solutions: explaining experimental behavior in terms of molecular properties". Pharm Res, 2014, Vol 31(11), pp 3161-3178.*
2. *Galush WJ, Le LN, Moore JMR, "Viscosity behavior of high-concentration protein mixtures". J Pharm Sci, 2012, Vol 101(3), pp 1012-1020.*
3. *Buxton ILO, "Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination". In Brunton LL, Knollmann BC, Hilal-Dandan R, (eds). Goodman & Gilman's: "The Pharmacological Basis of Therapeutics", McGraw-Hill Education, 2017.*
4. *Doughty DV, Clawson CZ, Lambert W, Subramony JA, "Understanding subcutaneous tissue pressure for engineering injection devices for large-volume protein delivery". J Pharm Sci, 2016, Vol 105(7), pp 2105-2113.*
5. *Heise T, Nosek L, Dellweg S, et al, "Impact of injection speed and volume on perceived pain during subcutaneous injections into the abdomen and thigh: a single-centre, randomized controlled trial". Diabetes Obes Metab, 2014, Vol 16(10), pp 971-976.*
6. *Jørgensen JT, Rømsing J, Rasmussen M, Møller-Sonnergaard J, Vang L, Musæus L, "Pain assessment of subcutaneous injections". Ann Pharmacother, 1996, Vol 30(7-8), pp 729-732.*
7. *Krishnamurthy R, Sastry A, Balakrishnan B, "How the Internet of Things Is Transforming Medical Devices". Whitepaper, Cognizant, May 2016.*

ABOUT THE AUTHOR

Beth DiLauri is Director, Strategic Marketing at BD Medical – Pharmaceutical Systems, responsible for developing portfolio strategies and leading commercialisation for self-injection devices with the Pharmaceutical Systems business. She has dedicated her 18-year career at BD to developing and executing portfolio strategies based on deep market and customer insights, across multiple segments of the healthcare industry including pharma/biotech, medical devices, diagnostics and healthcare IT. Prior to BD, DiLauri was responsible for business development at Transcend Therapeutics, a venture-backed development-stage pharmaceutical company, from inception through its Initial Public Offering on the NASDAQ in 1997. She received an MBA from the Tuck School of Business at Dartmouth College (Hanover, NH, US), and a Bachelors' degree in Psychology from Boston College (MA, US).

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LARGE-VOLUME PATCH-INJECTION VIA YPSODOSE: SIMPLER FOR PHARMA COMPANIES & PATIENTS

Here, Ian Thompson, Vice-President Business Development at Ypsomed Delivery Systems, updates us on the company's prefilled large-volume patch injector platform, YpsoDose, which simplifies the approach to wearable patch injectors for both pharma companies and patients.

PATCH INJECTORS MEET MARKET DEMAND

The evaluation and selection of a wearable patch injector continues to compete against more frequent dosing based on standard prefilled syringe-based auto-injected therapies. And, for pharma companies to consider and invest in patch injectors they need to be able to access reliable device technology, utilise standard filling processes and, last but not least, fully understand patient and healthcare practitioner (HCP) preferences.

Fulfilling these requirements with the appropriate device technologies will allow the patch injector market to grow significantly over the coming years and become established as a third self-injection device class to complement the well developed markets for pens and autoinjectors.

The number of large-volume injectable drugs, mainly antibody-based, in pharmaceutical development is large and growing. They are in development for the treatment of diseases such as rheumatoid arthritis, psoriasis, IBD/Crohn's disease, asthma, dermatitis, cardiovascular diseases and migraine. Looking into the future their demand will be further increased by immuno-oncology drugs as maintenance therapies for treated cancers.

General expectations for these drugs is that they will be dosed subcutaneously every two weeks, monthly or even less frequently; that they will be in the range 3-10 mL; and that the injection time will be in the range 3-30 minutes.[1] The large injection volume and longer injection time compared with autoinjectors means that the injection system needs to be worn on the skin during administration. For larger injectable volumes, patch injectors require a new drug reservoir, and the prefilled cartridge is the drug container of choice. As a cartridge does not have an integrated fluid path/needle, the patch injector provides the sterile fluid path and injection needle.

LARGE-VOLUME SC INJECTION CHARACTERISTICS

Biologics and mAbs have a large therapeutic window and allow the use of a large fixed-dose drug payload compatible with a patch injector. The overall dose and protein concentration may be quite high impacting drug stability and viscosity, drug processing and injection forces.

For example, the protein concentration of blockbuster biologic drugs such as adalimumab and trastuzumab is in the 50-150 mg/mL range and total payloads

"Ideally, the less frequently used patch injector should be as easy to use as a disposable two-step autoinjector."

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> "Whereas the drug in the prefilled syringe is directly connected to the fluid path, within the YpsoDose Needle Unit the fluid path is completed only on injection. The cartridge does not interact with the rest of the YpsoDose injector until the actual time of injection."

for a single dose may be high as 600 mg or greater. A positive development trend is also the general move from other routes of administration such as IV infusions to subcutaneous administration, in order to reduce the higher proximal and physical administration costs.[2]

Whatever the type of subcutaneous therapy, there are a number of established therapies, which confirm that the overall injection flow rates for such drugs are in the 0.33-1.00 mL/min range. Examples include: immunoglobulins that are injected at 20-30 mL/h or 1 mL/2-3 min; 3 mL of evolocumab is injected in nine minutes; and 5 mL of trastuzumab containing hyaluronidase is injected at approximately 1 mL/min.

OVERVIEW OF THE YPSODOSE PATCH INJECTOR

Ideally, the less frequently used patch injector should be as easy to use as a disposable two-step autoinjector. The key technical features and benefits incorporated into the prefilled YpsoDose (Figure 1) format are shown in Box 1. They are enabled by YpsoDose's proprietary electromechanical systems.

Simplifying Drug Filling & Final Assembly

The ability to prefill the drug reservoir and maintain the sterility of the drug reservoir and fluid path during the lifetime of the device is a notable crucial characteristic. YpsoDose achieves this by incorporating a bespoke sterile fluid path enclosed within the Needle Unit. (The Needle Unit can be compared to the staked needle and rigid needle shield of a prefilled syringe.)

Whereas the drug in the prefilled syringe is directly connected to the fluid path, within the YpsoDose Needle Unit the fluid path is completed only on injection. The cartridge, being a well characterised container closure system, does not interact with the rest of the YpsoDose injector until the actual time of injection.

The standardised interface between the 10 mL cartridge and Needle Unit has been designed to allow the cartridge to be filled on conventional filling equipment using ready-to-fill tub formats. Ypsomed is working closely with partners to ensure that standard components and processes are compatible with the YpsoDose device:

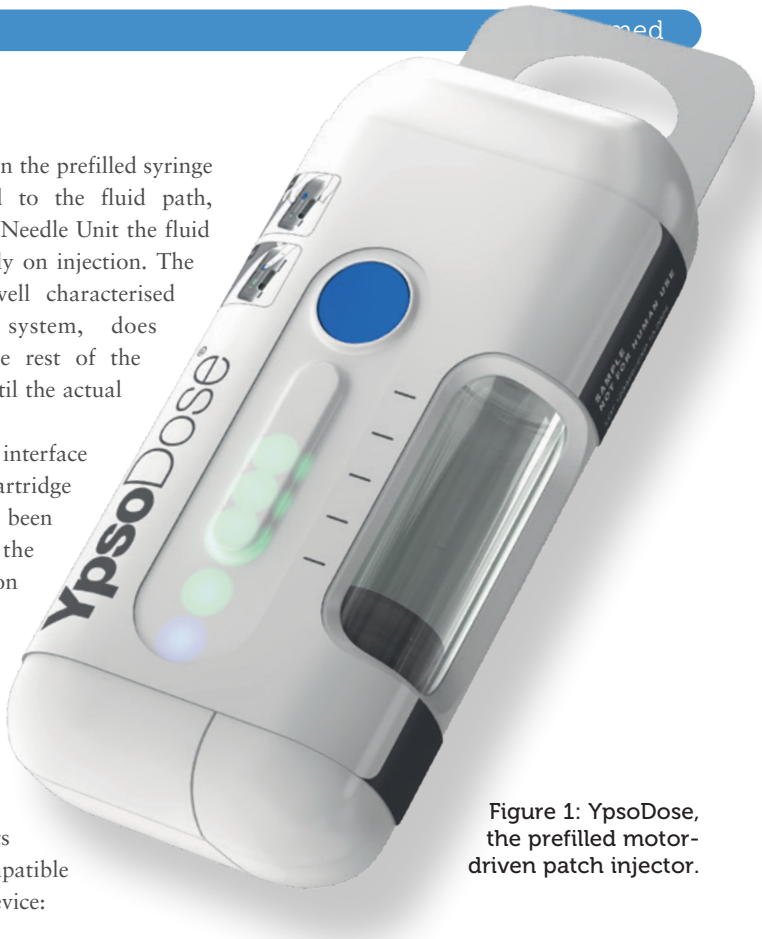

Figure 1: YpsoDose, the prefilled motor-driven patch injector.

- The 10 mL glass cartridge is compatible with standard 13 mm coated vial stoppers and 20 mm coated plungers.
- The pre-crimped cartridges are supplied in a standard three-inch tub format compatible with established filling processes.
- Cartridge characterisation and filling work is ongoing with customers and contract partners.

YPSODOSE USABILITY UPDATE

Current patch injectors are generally HCP or patient filled or assembled; and no prefilled, ready-to-use wearable devices are currently approved for use by patients. Ultimately, to ensure that patch injector therapies are going to be adopted widely for biological therapies, usability is the most important aspect that needs to be successfully tested with patients.

Continuing human factors work with YpsoDose is proving and optimising the patch system and user interface (Figure 2). The skin sensor system is key to ensure that the injection can only be initiated once YpsoDose is correctly attached to the skin, and to minimise the number of steps required to perform the injection.

BOX 1: YPSODOSE KEY TECHNICAL FEATURES AND BENEFITS

- Prefilled and fully disposable to remove any need to assemble the drug reservoir and device.
- Adheres well to the skin during injection and is easy to remove after injection.
- A capacitive sensing patch which only allows initiation of the injection after the skin sensor has been activated.
- Onboard electronics provide audible and visual signals to clearly communicate with the user before, during and after the injection.
- Automatic insertion of the injection needle at the start and retraction at the end of the injection process. The needle is also retracted if the device is removed from the skin before the end of injection.
- An electromechanical drive accommodates a range of fill volumes and viscosities and provides a programmable and reproducible injection time for each drug.
- The electronics also allow wireless connectivity as required.

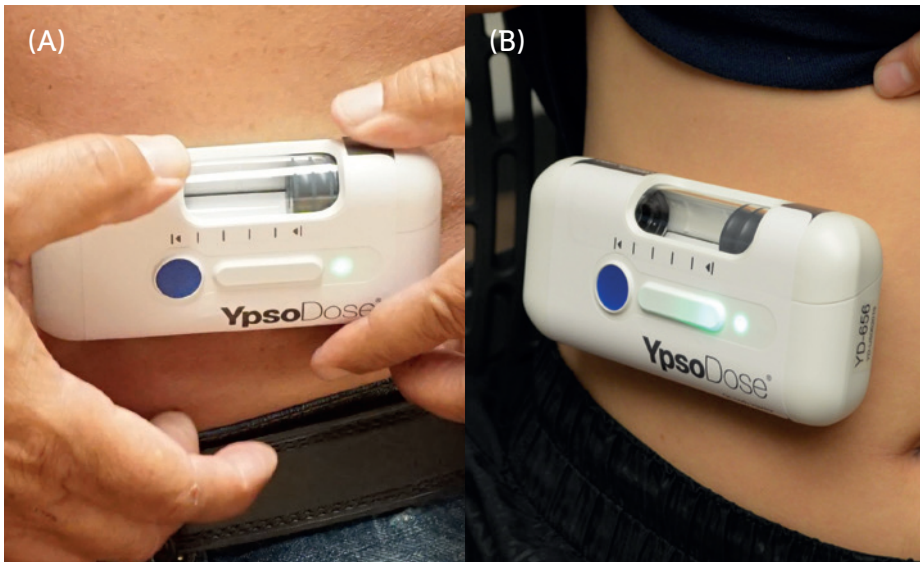

Figure 2: YsoDose being applied (A) and injecting (B).

All-in-all, YpsoDose's handling steps are like a two-step autoinjector: **remove the cap** and **inject**. For YpsoDose this is simply **patch** and **inject**. All other steps are controlled by YpsoDose, which guides the patient when to push the injection button and provide feedback throughout the injection process. At the end of injection the needle is retracted and YpsoDose is ready for disposal or specialist recycling.

In July 2019, YpsoDose 10 mL was tested in the latest formative usability evaluation in the US, to explore the overall handling and safe and effective use in a simulated use scenario, as well to determine the acceptability of the device size and weight. The study included 17 patients from a broad range of disease states, and six HCPs who work with oncology patients.

	Question	Average Score
Usability	I felt confident using this device	4.76
	It was easy to keep track of what step I was on with this device	4.65
Wearability	It was easy to place the device on my body	5.00
	It was easy to check the device while it was on my body	4.94
After use	It was easy to detect when the device had finished the injection	4.94
	It was difficult to remove the device from my skin	1.94

Table 1: YpsoDose patient ratings for Usability, Wearability and After Use. Participants (N=17, adult, adolescent and elderly patients) rated their level of agreement with the statements from 1 (strongly disagree) to 5 (strongly agree).

The results (Table 1) and feedback were positive, and included that:

1. All participants completed successful injections following initial training.
2. From the HCP perspective, using YpsoDose was seen as a simple and easy way for patients to receive injections or self-inject.
3. The user interface is simple and easy to understand, and the orientation of the device was intuitive while placing it on the body.
4. Participants were comfortable with YpsoDose's size and weight, especially with the understanding that it is a single-dose, infrequent injection. Participants were positively surprised by how well YpsoDose could be worn on the body to deliver the dose and throughout the study activities.
5. Participants viewed YpsoDose favourably in terms of overall design. It was simple to use, communicated how it was to be used, and it was not perceived to be "medical".

In summary, the latest 2019 usability evaluation confirms earlier testing performed with previous functional prototypes.

The 10 mL YpsoDose fully functional prototypes are now being tested by pharma customers and contract partners. Ypsomed is committed to the successful development and commercialisation of YpsoDose as a new state-of-the-art patch injector.

ABOUT THE COMPANY

Ypsomed is the leading independent developer and manufacturer of both innovative mechanical and connected autoinjector and pen injector systems for self-administration. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and

1.5 mL cartridges, reusable pens that include automated injection mechanisms and ready-to-use pre-filled 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. Ypsomed provides its partners with excellent technological expertise and full regulatory support for the device relevant aspects of the registration process.

The injection systems are developed in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities in Switzerland, and a new facility in Germany, are regularly inspected by both pharma customers and regulatory agencies and supply devices for global markets including US, Europe, Japan, China and India. Ypsomed has more than 35 years' experience and well-established working relationships with numerous leading pharma and biotech companies.

REFERENCES

1. *Mathaes R et al, "Subcutaneous Injection Volume of Biopharmaceuticals-Pushing the Boundaries". J Pharm Sci, Aug 2016, Vol 105(8), pp 2255–2259.*
2. *Tetteh EK, Morris S, "Evaluating the administration costs of biologic drugs: development of a cost algorithm". Health Econ Rev, Dec 2014, Vol 4(1), p 26.*
3. *Knight JF, Baber C, "A tool to assess the comfort of wearable computers". Human Factors, 2005, Vol 47(1), pp 77–91.*

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Ian Thompson has been with Ypsomed since 1995 in a number of roles in key account management and business development working with pharma companies to develop and bring to market innovative self-injection systems. He studied biochemistry and biotechnology in the UK and has worked in medical device companies since moving to Switzerland in 1990. Since 2003 his main focus has been business development and new product innovation leading to the successful development and launch of a range of new pen and autoinjector Custom Products. Ypsomed Delivery Systems continues to focus on the development and manufacture of next generation pen, autoinjector, wearable and connected injector technologies.

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