WEARABLE INJECTORS

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EDITORIAL:

Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

James Arnold, Assistant Editor
T: +44 1273 47 28 28
E: james.arnold@ondrugdelivery.com

SUBSCRIPTIONS:

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ADVERTISING:

Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

Frederick Furness Publishing Ltd
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Contact Europe

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2014 TO 2018: AN UPDATE ON THE STATE OF WEARABLE INJECTORS

Looking back on the developments in large volume injectors since his article in ONdrugDelivery's 2014 issue on wearable injectors, Paul Jansen, Professional Engineer, Board Member of both Haselmeier and Subcuject, reflects on the state of this technology space today, how it has progressed and the value it is likely to offer.

Four years ago, I had the privilege of writing the introduction to the first edition of ONdrugDelivery Magazine's "Wearable Injectors" issue. In preparing to write this introduction I went back and reread what I wrote in 2014. While much of it remains relevant and still stands, I did see that several changes have taken place. In this editorial I will share my views on those changes and trends.

It was my belief at the time, and it remains so today, that the adoption of wearable large volume injectors (LVIs) would accelerate in the coming years. What has surprised me, as I look back, is the glacial acceptance of the technology over the past four years. There are more products than ever to evaluate and to consider but relatively few actually approved and in use; a close look at the market shows that there are some approved applications for the delivery of insulin and a couple for biologics. Pharma and biotech companies appear to have maintained their traditional risk-averse stance and seem to be waiting to see large volume delivery become "real" before making their move. It seems that everyone wants to be second.

This is amidst a continued, and growing, requirement for subcutaneous delivery of larger volumes of drug product. Healthcare today is changing rapidly and there are several resulting key trends that are continuing to drive the market opportunities for LVIs. These trends are:

- The continued increase in the development of biologics
- Lifecycle management of older biologics products
- Cost containment pressure
- Reduced frequency of injection
- Data/connectivity being integrated into healthcare.

> "It was my belief at the time, and it remains so today, that the adoption of wearable on-body injectors or large volume injectors would accelerate in the coming years. What has surprised me, as I look back, is the glacial acceptance of the technology over the past four years."

In the past four years the number of injectable drugs approved and in development has grown. The number of products in development is two to three times higher than it was in 2014. There are currently more than 3000 injectable drugs in development. Of those, more than 2000 are biologics. Not only are there more products in development, but the biologics are becoming more complex and are increasing in size as bi-specific antibodies become more prevalent.

Biologics are viscous by their very nature, thus it is generally accepted that concentrating them to more than 150–200 mg/mL is difficult, if not impossible, without causing unwanted drug precipitation. There is also a trend towards fewer injections with weekly, bi-weekly and monthly applications being developed. The resulting math is simple. The required drug cannot be formulated to fit into a 1 mL prefilled syringe, nor into a 2.25 mL prefilled syringe. Furthermore, in those instances where the drug can be formulated into these volumes, it is typically too viscous to inject in a reasonable amount of time and simply will not meet patient usability requirements for the injection in either a safety syringe system or an autoinjector. Thus, LVIs come to the rescue. The 2–3 mL volume continues to be seen as a grey zone, with many companies trying to push the boundaries and find ways with innovative

Paul Jansen
Professional Engineer
T: +1 857 203 1740
E: paulejansen@gmail.com

Haselmeier
Board Member & Senior Advisor

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"Companies are working to extend the life of their drug franchises, and as such are looking for new drug delivery systems to provide continued sales to compete with biosimilar products."

formulation solutions to allow them to adopt a prefilled syringe or autoinjector delivery system. However, should they not be successful an LVI can be used to meet the need.

Regardless of the volume, the design challenge for LVIs is making them size appropriate, convenient to wear, simple and intuitive to use and to make them operate free of noise and vibration. The volume ranges that will prevail are still not well defined, however the development pipelines continue to support the idea that a majority will be in the 3–5 mL range. Nonetheless, there are applications being looked at with volumes all the way up to 50 mL. The question I have with these very large volumes is how to attach and wear a 50 mL LVI. We will see how this works out as I am not sure I understand how one designs a system containing 50 mL of drug product that can be attached to the body long enough to deliver the entire volume of drug product. In the end, I foresee the market focusing on the 3–10 mL volume product.

Many very successful biologics have reached, or will soon reach, patent expiry. Companies are working to extend the life of their drug franchises, and as such are looking for new drug delivery systems to provide continued sales to compete with biosimilar products. As these drugs are older, they naturally use older drug delivery systems, developed some years ago. There have been a significant number of technology advancements since these systems were first designed. A wish to use modern technology that can be administered more easily by the patient naturally leads to LVIs. There are many opportunities for different form factors, volumes and improved patient convenience.

There continue to be developments of both prefilled and patient-filled LVI devices. The arguments for both are compelling but I believe that the convenience and safety aspects related to prefilled LVI devices will win out in most cases. There are of course exceptions, as demonstrated by those already approved devices, which are, in several instances, patient-filled devices.

There is a growing push to save cost and move treatment from hospitals and clinics into the home. Patients often travel long distances and spend several hours getting their treatment in a healthcare facility. There is also a burden for the healthcare professionals, who must prepare the medications properly and administer them correctly. Reformulating these intravenous (IV) drugs to be injected subcutaneously allows treatment to move into the home. The result is a lower cost for the healthcare institutions and much more convenience for patients. For example, oncology products, such as Herceptin (trastuzumab), are being reformulated from IV infusion delivery to subcutaneous delivery. These new formulations fit well in the LVI segment, based on their required volumes and delivery time. Patients have responded to this, as one would expect, with a resounding thumbs up.

The addition of digital health technologies and big data analytics will further provide patients, physicians and healthcare companies with the information to fine-tune individual therapies to optimise therapeutic outcomes. Another important benefit of connected devices is the ability to increase patient safety; medical errors are a leading cause of death and having timely data and feedback can help reduce those deaths. In the not too distant future, you can imagine a fully connected healthcare system capturing data that, in collaboration with artificial intelligence (AI) and machine learning, alongside clinical support decision algorithms, will result in improved patient outcomes. Luckily, the required technology can easily be incorporated into LVIs.

However, cost of the LVI devices is still a challenge for adoption in many therapeutic areas. The majority of the LVIs in development are electromechanical (60–70%), although there are new concepts emerging using purely mechanical or other advanced technologies (e.g. chemical, electrochemical) to power the LVI. Current electromechanical systems are quite pricey, so when purely mechanical LVIs, or those made with the other advanced technologies, make it to market they will have a significant cost advantage. Broader adoption of LVIs will require a step reduction in the cost of disposable devices or the use of reusable devices.

I do not believe that there will be widespread conversion to reusable devices given the downsides of more use-steps and increased risk of misuse. Furthermore, in order to really penetrate the market with connected LVIs, the cost of electronics and power will need to come down. I am anticipating that the next generations of sensors will come down in price, industry estimates are that from 2015 to 2020 the cost of sensors will decrease by 50%. Provided this reduction in cost is realised, sensors will become affordable for disposable LVIs and will be designed into the devices. Research is also underway to provide low cost power using technologies outside of batteries. Low power and sensor costs will allow cost competitive designs for disposable LVIs, which will facilitate market utilisation.

An important difference with LVI devices is that delivery is typically not rate dependent. The focus is on accurate delivery of total volume rather than accurate delivery time, the same being true for prefilled syringe and autoinjector systems. The primary packaging for some of these LVI technologies is being developed with novel materials and shapes, which provides significant form-factor flexibility and advantages. The disadvantage is the additional development work required by the pharma or biotech company to qualify these primary packaging containers. While this is a burden, more companies are biting the bullet and moving to rigid polymer containers, as well as flexible bags. This may be driven by the drug properties but, regardless of why it is happening, it is helping to drive further adoption of new primary packaging materials.

Regulatory requirements continue to evolve. The requirement of using "to be marketed" devices for Phase III clinical trials is still murky and not completely clear. The issuance of an ISO standard for LVIs ("on-body wearable injectors" in the ISO world) still appears to be some time away. It has taken longer than anticipated for the ISO experts to gain clarity on requirements. The US FDA has also taken the position in discussions around the ISO standard that LVIs will be subject to infusion pump tests. This means adherence to the infusion pump standard requirements is a must, although an exemption from tests is possible provided an explanation is given. There also continues to be a debate on the need for testing beyond bioequivalence testing when converting an existing drug to an LVI from an already approved drug delivery system. There may be situations where additional

testing is required for a conversion. However when the same formulation is moved from one device to another, the drug company should not require anything more than a bioequivalence test in their submission dossier. Anything beyond this would not add any value.

Most companies are looking for an LVI platform. The use of a platform LVI will reduce costs and reduce time to market. The platform route means that there is a need for only one LVI development, followed by specific and relatively minor variations for each new drug. That said, the platform needs to be flexible enough to meet the needs of the company's portfolio without major changes for each drug. In an attempt to gain a competitive advantage, companies continue to compete aggressively for access to technology that can provide a platform for many of the portfolio drugs that they have. This is not without risk, as there is a significant body of granted IP to be aware of. However, I have been impressed over the past four years with the ingenuity that has been shown in finding new ways to do the same thing. For example, I once thought that there were very few new ways to have a unique automatic needle cannula insertion device, yet I have recently seen several very nice designs. It seems that innovation can still solve any of the IP-related challenges that may come up.

In summary, while much of what I described in my 2014 article still stands (*ONdrugDelivery Magazine* Issue 51, July 2014, available online), and while adoption of LVIs is slower than I had anticipated, much has changed and the future for LVIs looks bright. As you read through all of the articles in this issue I am sure that this is the conclusion that you will also reach.

> "The platform route means that there is a need for only one LVI development, followed by specific and relatively minor variations for each new drug."

ABOUT THE AUTHOR

Paul Jansen is currently a board member and senior adviser with Haselmeier. He also sits on the board of Subcuject. He was formerly associate vice-president, medical device development, Sanofi. Mr Jansen is a professional engineer with more than 30 years of experience in medical devices. He completed his degree in mechanical engineering and has completed graduate work in biomedical engineering at the University of Toronto (Toronto, Canada).

Mr Jansen has extensive experience in the design, development, manufacturing and lifecycle management of medical devices. He has multiple patents to his name and has deep experience in the creation and management of IP portfolios. He has successfully led teams that have developed and launched several devices, including Lantus SoloStar®.

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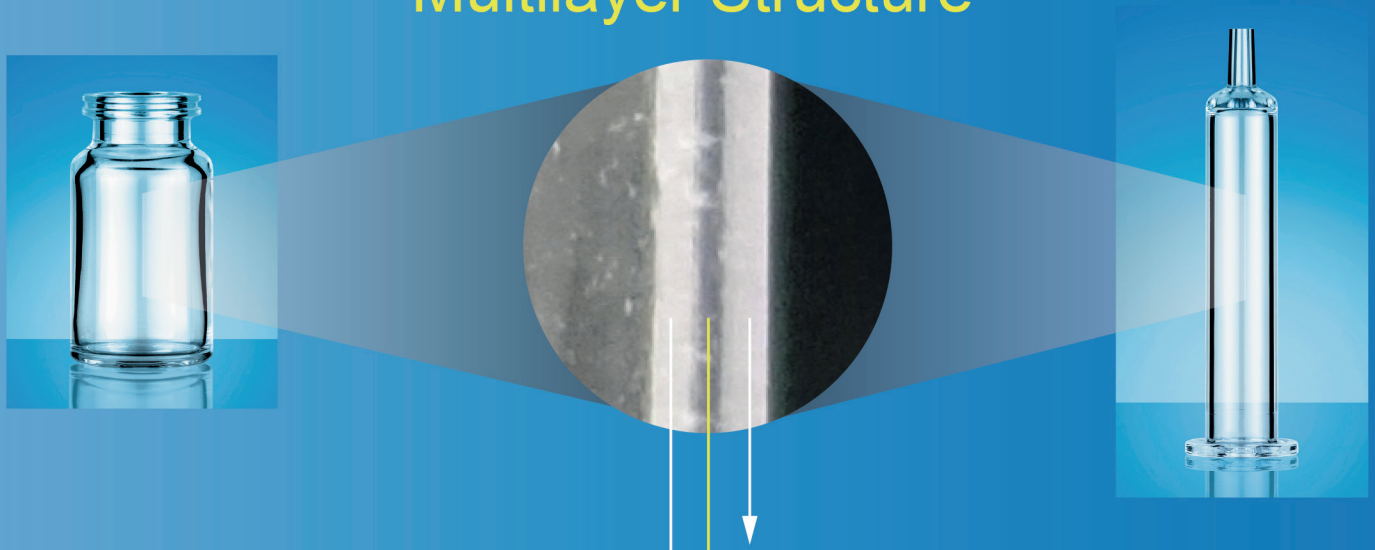

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BIOLOGIC DRUGS AND THEIR DELIVERY SYSTEMS: A SYMBIOSIS KEY TO COMMERCIAL SUCCESS

Here, Jeannie Joughin, PhD, Executive Vice-President, Enable Injections, discusses the ever-growing importance of the delivery system in the biologic combination product area, highlighting how it is the delivery system, not the drug, that defines the patient experience.

There's a new wind in the healthcare industry. Pharma industry meetings are focusing heavily on it. Regulatory authorities are establishing new departments and guidelines to review and approve it. Companies developing biologic drugs are streaming in for site visits and signing development deals to attain it. Patients in focus groups and participants in human factors trials say they prefer it. What is this new wind that pharma companies, regulatory authorities, patients and healthcare providers are turning their focus to? It's the "combination product", specifically the full integration of biologic drugs with their delivery system in the form of wearable injectors. These biologic-delivery combination products are becoming mainstream, and the addition of higher delivery volume combination products will greatly benefit users, as well as help to control healthcare costs.

But that is not what the paradigm shift is about. Rather, it's the realisation that biologic drugs and their delivery mechanism share a symbiotic relationship as closely aligned as the one between a bow and arrow. There is little value in one without the other.

SYMBIOSIS: BOW AND ARROW

The distinctions between a drug and its delivery system have been falling away for years, just as predicted by Deloitte.[1] As the life sciences consultancy discerned some time ago, the integration of technology and pharma products has indeed gained traction and accelerated. Why? Because the drug itself represents a diminishing portion of the whole that comes together to deliver an overall outcome. Outcome is the key metric for today's healthcare systems and is increasingly being assessed with big data and artificial intelligence (AI).

> "The distinctions between a drug and its delivery system have been falling away for years, just as predicted by Deloitte."

To achieve the desired outcomes, patients first have to take the drugs. Therefore, what's good for patients – easy, painless, less costly, more convenient biologic drug administration – is very good for business. Take Amgen's Neulasta® (pegfilgrastim): despite its loss of patent protection in 2015, the addition of an on-body injector has been effective at extending Neulasta's lifecycle. Because Neulasta must be given the day after chemotherapy, the wearable injector allows patients to administer the dose at home without having to return to a healthcare provider. Tony Hooper, Amgen's Executive Vice-President of Global Commercial Operations, told investors during a recent call that, with regard to Neulasta, "We continue to drive

Dr Jeannie Joughin
Executive Vice-President and
Chief Commercial Officer
T: +1 513 326 2800
E: jjoughin@enableinjections.com

Enable Injections, Inc
2863 East Sharon Road
Cincinnati
OH 45241
United States

www.enableinjections.com

increasing adoption and [the combination product] now represents over 50% share of all Neulasta purchases. This has been a great example of a very successful lifecycle management strategy."[2]

A WINNING PATIENT ENGAGEMENT STRATEGY

Amgen has found a key to patient engagement with a winning combination product. Without the integration of their drug with a delivery system that patients found far more convenient, would Neulasta be as commercially successful in the face of biosimilar approvals? It's doubtful.

Other pharma executives are thinking about patient engagement as well, more than the general news or trade press would have one believe. For example, most interviews with GSK's new head of R&D, Hal Barron, result primarily in reports about the drug pipeline and its implications for the company's business. But apparently there's more on his mind. In a television interview on business channel CNBC, discussing GSK's investment in 23andMe, Barron had the opportunity to slip in that, in addition to obtaining access to 23andMe's vast trove of data, GSK would have the benefit of access to engaged patients, those who have given permission for their genetic information to be used in research. That cohort of accessible patients could be invaluable to GSK.

"Patient value has now become synonymous with business value," said Josh Bramwell, Director of industry group eyeforpharma. "Companies listening to the growing patient voice and incorporating those insights into the design of products, trials and strategy are being rewarded with higher uptake and better outcomes."

DELIVERY, NOT BIOLOGIC, DEFINES THE PATIENT EXPERIENCE

From the patient perspective, the delivery device is the element that defines the treatment experience more than any other. Delivery is especially challenging for large-volume biologic drugs, which in most cases

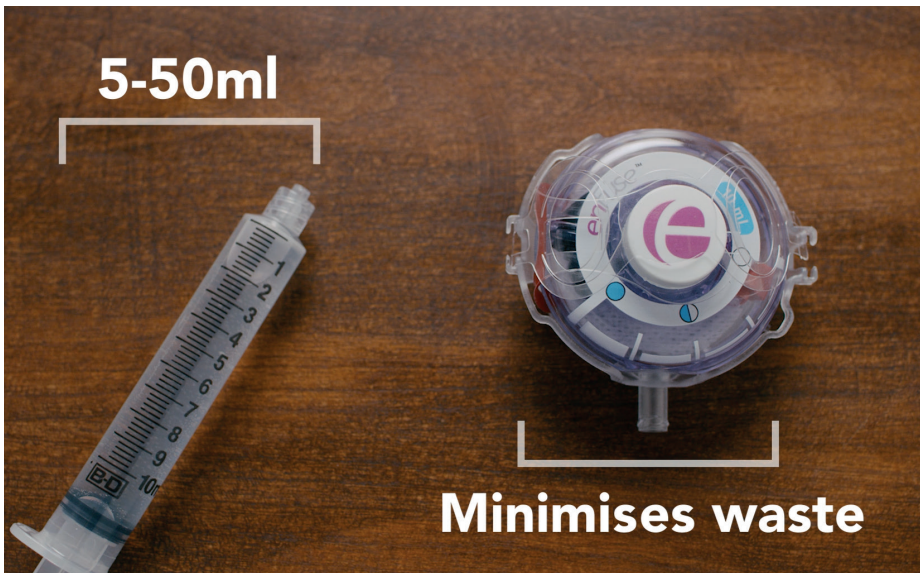

Figure 1: The EnFuse™ patient-loaded wearable injector.

are still being administered intravenously (IV). In addition to adding significant costs, IV administration is unpopular with patients. It is inconvenient. It can be painful. It is not a promising path for pharmaceutical companies racing to improve outcomes and be recognised as patient centric.

Subcutaneous injection is faster and more convenient, thus tends to be preferred by patients over IV. A time-and-motion study undertaken in eight countries reported significant time-savings for both healthcare professionals and patients through use of subcutaneous rituximab versus IV rituximab. The findings suggest potential for reduced waiting times, greater appointment availability and improved efficiency of oncology units with the subcutaneous formulation. Compared with IV drugs, the majority of participants in the study considered subcutaneous drugs clinically safer and more cost-effective, resulting in higher patient satisfaction.[3]

And now, as with Neulasta, subcutaneous injections can be administered by the patient at home or work by employing new, user-friendly delivery technology. Such injections are not generally painful and carry a reduced risk of infection, needlestick injuries and other complications. These wearable large volume injectors, with no needle in sight, make it even easier and less fearful for patients to administer their own treatment. It's of benefit not only to patients but to the caregivers tasked with giving injections.

Indeed, Accenture Life Sciences found that 69% of patients said product benefits were a top factor in their treatment decisions and suggested that pharma companies should be thinking about promoting benefits that appeal to patients. Many patients would welcome an alternative to an IV infusion that doesn't require a time-consuming, inconvenient trip to a health facility. It could burnish the brand, just as Neulasta's combination product has done for Amgen.

> "For preloaded injectors needing refrigeration, the patient has to wait for 30 minutes or more for the drug/device to warm to room temperature."

> "There are questions delivery device companies ask that pharmaceutical companies may not, and they are relevant to actualising the patient-centric approach that speeds patient adoption."

ADDITIONAL PATIENT PREFERENCES TO CONSIDER FOR SPEEDIER ADOPTION

Patient concerns are another reason for the must-have partnership between biologic drugs and their delivery device. There are questions delivery device companies ask that pharmaceutical companies may not, questions relevant to actualising the patient-centric approach that speeds patient adoption.

For example, across dozens of human factors studies, Enable Injections has found that, surprisingly, patients receiving high volume (up to 50 mL) preferred

patient-loaded to pre-loaded devices. It's counterintuitive. Almost anyone's initial reaction when presented with the choice "preloaded" or "patient-loaded" would be to assume that a preloaded device is preferable. In the case of non-refrigerated, small-volume (<5 mL) drugs, they may be right. But in the case of a large-volume, refrigerated drug, most patients preferred the Enable Injections enFuse™ patient-loaded system (Figure 1). Why? They no longer had to wait. For preloaded injectors needing refrigeration, the patient has to wait for a long period, typically 30 minutes or more, for the drug/device to warm to room temperature. At colder temperatures the drug viscosity increases significantly, causing a painful injection.

When using the enFuse device, the patient stores the vial or syringe in the refrigerator but not the delivery mechanism. When ready, the patient removes the container from the fridge and inserts it into the enFuse system, which automatically and passively warms the drug during the transfer to the injector. The injector is ready to use immediately after it is filled, a total wait of about a minute or so.

Other reasons patients gave for their preference for patient-filled devices were:

- The vial doesn't take up much room in the refrigerator.
- The vial is childproof, an injector isn't.
- Once I start something I want to finish it.
- If I have to leave it out I might forget about it.

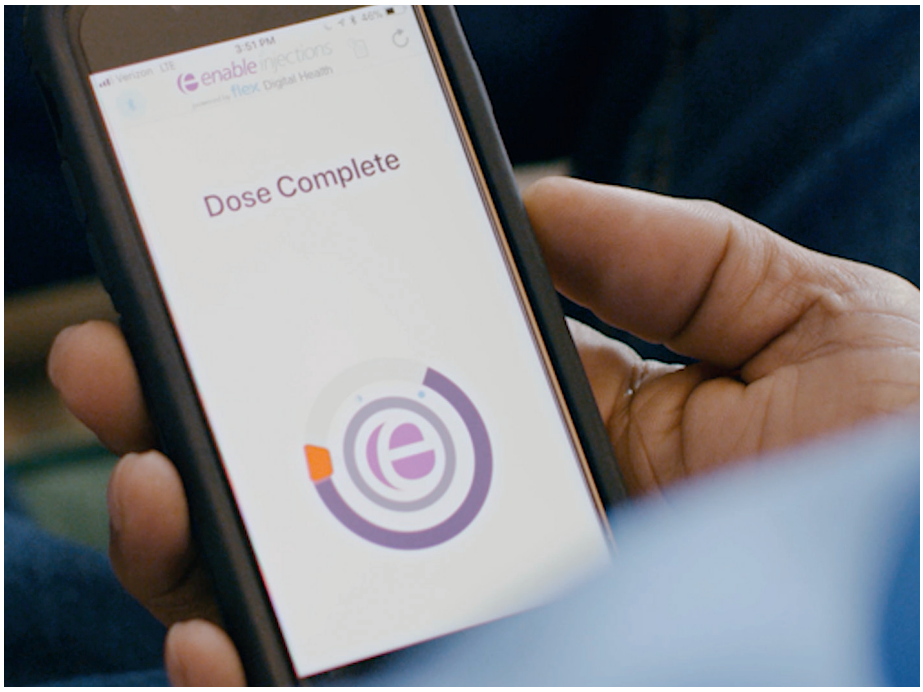

Figure 2: The Smart enFuse™ companion app.

Since patient acceptance is a top priority, not only are needles never visible, but the most advanced on-body delivery systems (OBDS) also incorporate pause control for optimum personalised comfort, and connectivity to monitor adherence (Figure 2). They can deliver doses as large as 50 mL. Their small profile allows them to be easily concealed under clothing, leaving patients free to ambulate and go about their daily routine during treatment (Figure 3). There are other things on patients' minds as well. "The opportunities in wearable devices are vast," says Ashley Whitney at Cambridge Consultants. "As drugs evolve to improve patient care, however, device designs must evolve in parallel. Patients with chronic diseases do not want to be defined by their disease; wearable devices offer a brief reprieve from the reminder that they are living with an illness."[4]

Figure 3: enFuse™ has a small profile, minimising its intrusion into patients' daily lives.

FEEDBACK FROM CLINICAL TRIAL PATIENTS

Finally, the importance of the patient perspective extends to today's clinical trials, where the patient's role is pivotal. It has become much more important in trials to have a representative person experience and comment on the treatment. Physiological, safety and efficacy data are of course gathered, but patients are now reporting back on how the treatment experience feels, how it could be made easier, what they liked and disliked about it. In pharmaceutical company patient panels, Enable Injections' enFuse technology was preferred to other delivery methods, providing some assurance that patients would report a positive experience.

EVEN THE FDA IS "LEANING IN" ON COMBINATION PRODUCTS

Gone are the days of the US FDA approving drugs based on their clinical trial data alone. The regulatory agency has established an Office of Combination Products to meet

the demand for advanced treatments that combine drugs and delivery.[5] Can there be any further doubt that in categories in which existing injection technology is inadequate for administration, biologic drugs and their delivery technology are, like a bow and arrow, essentially inseparable?

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ABOUT THE AUTHOR

Jeannie Joughin has held various scientific positions including Senior Research Scientist, Post-Doctorate and Senior Post-Doctorate positions in Australia at The Alfred Hospital, The Walter & Eliza Hall Institute, as well as internationally in Austria (University Clinic, Innsbruck) and Switzerland (Ludwig Institute for Cancer Research, Lausanne). Dr Joughin began her career in the pharmaceutical industry in 1992 as a Clinical Research Manager with Bristol-Myers Squibb. After managing local trials in oncology and cardiology, she moved into new product commercialisation as the interface between the medical and marketing departments. From there, Dr Joughin worked in brand management. After successfully completing several marketing roles in the National Stroke Foundation, MediMark International and Mayne Pharma, Dr Joughin joined CSL Biotherapies in 2005 as Director, Pharmaceuticals Marketing and In-licensing. She assumed responsibility for a portfolio of pharmaceutical products from several licensing partners in various therapeutic areas. Her responsibilities included extending distribution agreements with current partners when appropriate and securing various new product distribution agreements. As Vice-President, Business Development at CSL Behring, Dr Joughin was responsible for managing business licensing arrangements and relationships. This involved close liaison with CSL Behring's Commercial Development Team in the US, Germany and Switzerland. Dr Joughin joined Enable Injections as Vice-President of Corporate Development in 2015 and now, as Executive Vice-President and Chief Commercial Officer, she supports the CEO and Board with investment strategy and remains responsible for business development, strategic pharma partnerships, alliance management, as well as aiding in selection and prioritisation of Enable Injections' global portfolio.

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THE CHANGING LANDSCAPE OF WEARABLE DRUG CONTAINMENT AND DELIVERY

Biologics and biosimilars are set to make waves in the pharmaceutical arena, but these drugs can be very difficult to deliver in a patient-centric way. Wearable injectors offer a solution to the large, infrequent dosing regimens these drugs often demand. Here, Graham Reynolds, Vice-President, Strategic Partnerships and Business Development, West Pharmaceutical Services, explains more.

As innovations in medicine enable the introduction of new therapies for the treatment of chronic conditions that impact patients around the globe, safely containing and delivering these therapies is a top priority for both pharmaceutical companies and their manufacturing partners. For many new injectable medicines, the patient's first experience is often with the delivery system rather than the drug itself.

A patient- and therapy-centric drug delivery system can open the door to at-home self-injection for medicines that might previously have only been available through multiple injections or intravenous (IV) administration. While a good injection system cannot improve the drug product itself, there is a recognition that an inadequate system, meaning one that a patient struggles to use effectively and in compliance with the appropriate regimen, may have an impact on both the experience and therapeutic outcome for that patient.

> "With the commercialisation of Amgen's Repatha® (evolocumab), available as a once-monthly dose via the Pushtronex® system, the landscape of injectable medication has changed."

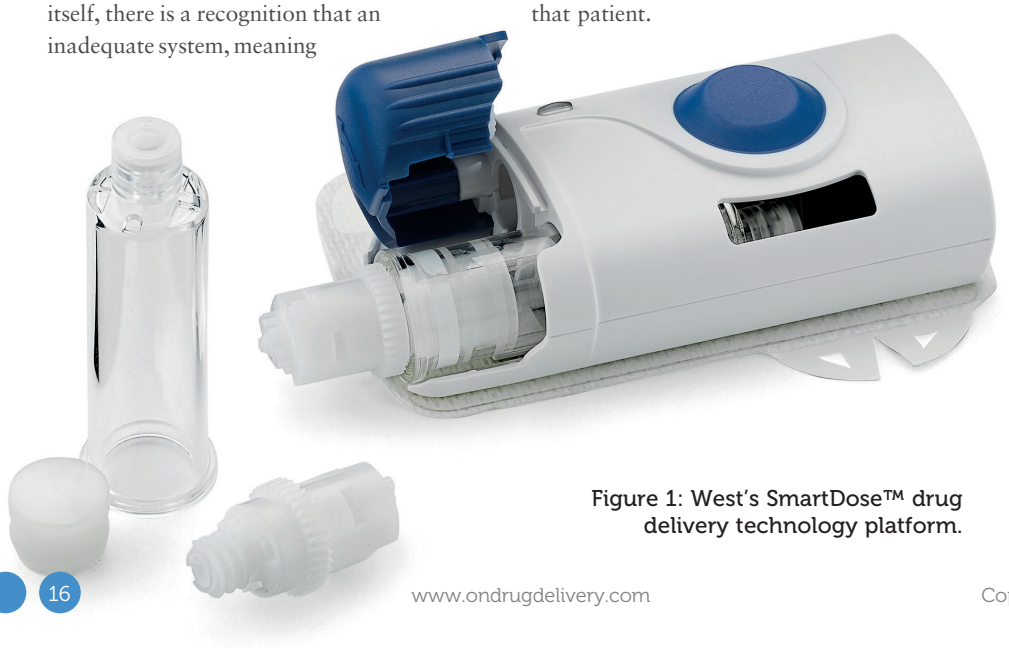

Figure 1: West's SmartDose™ drug delivery technology platform.

Graham Reynolds
Vice-President, Strategic Partnerships and Business Development
T: +1 610 594 2900
E: graham.reynolds@westpharma.com

West Pharmaceutical Services, Inc
530 Herman O. West Drive Exton
PA 19341
United States

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"When creating a drug delivery system, the primary goal is to ensure ease of use for the patient, best achieved via minimal use steps and a convenient device format."

With the commercialisation of Amgen's Repatha® (evolocumab), available as a once-monthly dose via the Pushtronex® system, the landscape of injectable medication has changed. The wearable self-injection system, which is the first-generation device from West's SmartDose™ drug delivery technology platform (Figure 1), was many years in the making. Through an ongoing innovation process, improvements have been made to the platform, including a greater variety of dose delivery options. While potentially impacting time-to-market, taking the time to qualify how a new delivery system works, not only with the drug but also with the end user, can help to improve patient adherence and compliance to therapeutic regimens.

By partnering with a device or delivery system manufacturer early in the drug development journey, and working closely with them to make the most of their expertise, pharmaceutical companies can not only move to market with an approved, commercially viable drug delivery system, but also gain valuable insight into the drug product along the way.

PUTTING PATIENTS FIRST

In many cases, being diagnosed with a chronic condition is a life-changing event. With diseases such as diabetes, haemophilia, rheumatoid arthritis, multiple sclerosis and other chronic conditions, a patient is often beginning a constantly evolving journey of care. After the initial shock of diagnosis has worn off, patients may experience a sense of relief that the cause of their health issues has been found. On the other hand, many will respond with more negative emotions, such as anger or depression. The need to adhere to a regimen of treatment may be met with denial, fear or anxiety.

While adjusting to a new normal, patients with chronic diseases are also seeking freedom from frequent visits to the clinic or hospital, sometimes opting instead to self-administer their prescribed medications at home, when the opportunity exists. This trend is emerging alongside an increase in new biologic and biosimilar medicines for the treatment of many autoimmune diseases.

With a steady pipeline of biologics and biosimilars poised to come onto the market as self-injectable treatments for several chronic conditions – often in autoinjectors or wearable injector systems – the pharmaceutical industry is experiencing the very beginning of a potential new wave of drug delivery. Patients who must regularly self-administer medication have eagerly awaited this shift to more user-friendly drug delivery systems, which better align with how they live their everyday lives.

However, as the use of biologic therapies is on the rise, it can be challenging for patients tasked with injecting these therapies to do so consistently and effectively, as many are delivered as large doses of highly viscous medicines. This is compounded by the fact that biologics are often dosed less frequently, meaning that just as a patient is adjusting to a new diagnosis and how to use a self-administered therapy and new drug delivery system, the time between doses gets longer and potential loss of device familiarity looms larger.

MAKING A GOOD FIRST IMPRESSION

When creating a drug delivery system, the primary goal is to ensure ease of use for the patient, best achieved via minimal use steps and a convenient device format. As more biologic drugs enter the market, delivery systems need to be able to accommodate a range of dose volumes and injection times or rates, while still accommodating the patient's desire for a small, simple system. Additionally, biopharmaceutical manufacturers are seeking to bring drugs to market quickly and optimise patient outcomes whilst also ensuring a robust and reliable supply chain for their product. Once on the market, the drug must demonstrate the ability to positively impact patient outcomes in order to support the higher cost of some newer therapies. Therefore, patient adherence and the ability to demonstrate outcomes through data are also important factors.

"Simple systems with excellent training and onboarding systems, easy access to help and educational information, and a professional look can complement the drug product and encourage compliance."

When injecting a drug, the first thing a patient or caregiver sees is the delivery system – not the drug itself. A complex delivery system can create initial patient frustration and confusion, which may lead to an ongoing unwillingness to comply with therapeutic regimens if the process of injection is seen as too complicated. On the other hand, simple systems with excellent training and onboarding systems, easy access to help and educational information, and a professional look can complement the drug product and encourage compliance. If a pharmaceutical manufacturer begins to think of the system as an extension of the drug itself, it is clear that making a good first impression will be of paramount importance.

Because bringing a drug delivery system from concept to market can take several years, it's imperative that drug product manufacturers think about delivery options as early as possible in the development process. This process may start with an early evaluation of the container system, supported by analytical testing, which is used to help ensure that the primary drug packaging is a viable option for the drug product. Additionally, the selection of container and delivery system have often been disconnected in this process, however, the most successful approach requires consideration of both the container and device as an integrated system early in the process. Testing that supports such an evaluation can provide valuable insight into the drug product and how it reacts with its primary packaging, and how the product and its delivery system are perceived and used by the patient.

INSIGHT ALONG THE DEVELOPMENT JOURNEY

Innovation doesn't take place overnight in the pharmaceutical and biopharmaceutical packaging and delivery industries. An idea may spring to life today but take several years before it is fully realised and ready to be introduced to the market.

With an early-stage molecule, it can be difficult to determine the product's strength or final dose frequency. Different analytical studies can help determine the proper primary containment selection, including the need for barrier film-coated elastomers or a cyclic olefin polymer (COP) container instead of glass. The final selection of materials may help to map out delivery options. COPs, such as the Daikyo Crystal Zenith® cartridge used in the SmartDose drug delivery technology platform, can offer design flexibility, as they can be moulded into a variety of shapes and sizes, and are highly break resistant when compared with glass.

As the molecule moves through the clinical phases and delivery becomes more structured, there is a need for speed, flexibility and expertise in the development of a delivery system. For example, Phase I may require multiple injections from a vial containment system, but, by Phase II, dose volume and frequency, as well as patient considerations, may drive the need for a delivery system such as prefilled syringe, autoinjector or wearable injector. The ability to fill the container at different stages must also be considered. Working with a partner with in-house small-quantity filling capabilities can provide samples during early phase development. Considering whether to use a contract manufacturing partner or leverage internal capabilities can also help to support fill-finish operations during scale up. Biopharmaceutical manufacturers should seek out a partner with a range of different filling options, from clinical to commercial, and those that can easily adapt to handle unique containment systems.

As the drug manufacturer prepares to commercialise the product, patient adherence, onboarding and compliance must be considered with respect to drug delivery. Furthermore, it will be critical to consider what information is required to support product registration, such as stability studies, human factors testing, device studies, etc. In preparation for commercialisation, it is also critical to consider the overall supply chain and provide a robust solution including containers, drug, filling, device manufacture and assembly, secondary assembly of the device and drug container, patient services (training and adherence solutions) and a variety of other factors. West has increased its capabilities in these areas to be able to partner with customers through the journey from the early molecule all the way to the patient. Traveling the development pathway together can help reach these patient-preferred options much sooner, as well as prevent a move to market with a drug product that may cause adherence and compliance concerns due to the delivery system technology.

Figure 2: Wearable injectors are a route to maximising patient convenience and comfort by delivering large volumes over a period of minutes or hours.

BUILDING ON WEARABLE INNOVATION

Modern biologics are large molecules that may need high dose volumes to ensure the proper concentration, but too-frequent or too-rapid dosing may cause pain to patients and therefore hinder adherence. Typical dose volumes have been in the 1 mL range, however, with more complex molecules and the desire for less-frequent dosing, volumes of up to 10 mL can be required. Based on patient preference, and the effectiveness of the drug, this type of volume requires either multiple injections of 1–2 mL, or a single injection of a higher volume that should be administered over a longer period of time. Typically, it is desirable that a hand-held device, such as an autoinjector, should deliver its dose within 10 seconds, whereas a device attached to the body, commonly referred to as a "wearable injector", can deliver slowly over a period of minutes or even hours, to help optimise drug absorption and patient comfort (Figure 2).

As the next generation of wearables moves through development, options for higher dose volumes, preloaded systems and the inclusion of findings around human factors and connectivity have helped to ensure that upcoming delivery systems offer a sophisticated, yet simple, solution to drug delivery.

OPTIMISING WITH PATIENTS IN MIND

The typical drug development cycle can take several years. Optimising drug containment

and delivery systems – from primary containment to commercialisation – during that time can help ensure that, when pharmaceutical manufacturers are ready to move to market, the delivery system will make a great first impression on the patient. By understanding the requirements of the drug product as well as the patient, continued innovation in wearable injectors will help move products to market with minimal risk and maximum benefit.

By partnering with experienced drug containment and delivery system manufacturers, companies may be able to shorten the drug development cycle by potentially avoiding unnecessary delays. As the next generation of wearables continue to build on the success of West's SmartDose drug delivery technology platform, pharmaceutical and biopharmaceutical companies and their drug delivery system partners can ensure that the patient remains at the forefront of development innovations. A strong partnership from the onset will help influence a needed positive first impression and a lasting impact on adherence and compliance so the drug product can do what it was designed to do – help patients.

ABOUT THE COMPANY

West Pharmaceutical Services Inc. is a leading manufacturer of packaging components and delivery systems for injectable drugs and healthcare products. Working by the side of its customers from concept to patient, West creates products that promote the efficiency, reliability and safety of the world's pharmaceutical drug supply. West is headquartered in Exton, PA, US, and supports its customers from locations in North and South America, Europe, Asia and Australia. West's 2017 net sales of US$1.6 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.

ON drugDELIVERY

2018/19 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Oct 2018	Prefilled Syringes & Injection Devices	Sep 6th 2018
Nov 2018	Pulmonary & Nasal Drug Delivery	Oct 4th 2018
Dec 2018	Connecting Drug Delivery	Nov 1st 2018
Jan 2019	Ophthalmic Drug Delivery	Dec 6th 2018
Feb 2019	Prefilled Syringes & Injection Devices	Jan 3rd 2019
Mar 2019	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 7th 2019
Apr 2019	Pulmonary & Nasal Delivery	Mar 7th 2019
May 2019	Injectable Drug Delivery	Apr 4th 2019
Jun 2019	Connecting Drug Delivery	May 2nd 2019
Jul 2019	Novel Oral Delivery Systems	Jun 6th 2019
Aug 2019	Industrialising Drug Delivery Systems	Jul 4th 2019
Sep 2019	Wearable Injectors	Aug 1st 2019
Oct 2019	Prefilled Syringes & Injection Devices	Sep 5th 2019
Nov 2019	Pulmonary & Nasal Drug Delivery	Oct 3rd 2019
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MOBILE DEVICES AND USE-RELATED RISK – TIME TO REINSTATE DETECTABILITY?

In this article, Richard Featherstone, Managing Director, Medical Device Usability, makes the case for designing detectability into the user interfaces of wearable devices, enabling the user to be an active part of ensuring the device operates safely, as intended.

Wearable medical devices can free a patient to live a more normal life, but they bring with them a high degree of responsibility on the part of manufacturers to make sure that the device can be worn and used safely whilst the patient is mobile. When a patient wears a medical device, the bond between user and device is very close. Users rely on the device to keep them safe, to keep the medicine flowing and, crucially, to alert them when something goes wrong.

> "However, when we consider use-related risk assessments we need to focus on the user. The patient is not a passive component – if they become aware of a problem early enough, they may be able to take corrective action and thus stay safe."

Risk assessments are at the heart of design for safety. When writing a risk assessment for a medical device, risk is commonly calculated as a function of the probability of a failure mode occurring combined with the severity of harm that would ensue. So, for example, if the infusion line on a portable syringe driver gets kinked, drug flow is impeded and the patient's condition may rapidly deteriorate. Multiplying the probability that the line gets kinked by the severity of the harm that would be caused by impeded drug flow gives an overall estimate of risk.

However, when we consider use-related risk assessments we need to focus on the user. The patient is not a passive component – if they become aware of a problem early enough, they may be able to take corrective action and thus stay safe. Therefore, a wearable device that provides feedback is inherently safer than one that does not.

> "Detectability means that if a user of a wearable device performs a use error, the error state is rapidly, and clearly, communicated back to the user."

So "detectability" – the extent to which a problem is detectable by its user – is surely a critical component of risk. Detectability essentially means that the user can become aware that a failure has occurred, or is about to occur, and is therefore able to take corrective action. However, recent trends in risk assessment have removed this third component. Arguments have been made that the inclusion of detectability redirects attention away from the underlying causes of failure towards improving detectability.[1] Whilst this may be an appropriate concern for failure modes, detectability may be of more relevance when evaluating risk associated with usability of a mobile wearable device.

In the world of human factors, we are interested in identifying the potential use errors. Detectability means that if a user of a wearable device performs a use error, the error state is rapidly, and clearly, communicated back to the user. So, to continue with the example of a portable syringe driver, if the line does get kinked, the risk of harm is greatly reduced if the user is aware that drug flow is impeded. If the user cannot detect that there is something wrong they are in a much more hazardous situation than if they had detected the problem early.

Richard Featherstone
Managing Director
T: +44 1223 214 044
E: richard@medical-device-usability.com

Medical Device Usability Ltd
150, Cambridge Science Park
Milton Road
Cambridge
CB4 0GN
United Kingdom

www.medical-device-usability.com

Feature	High detectability	Low detectability
Unambiguous	Distinct, has only one possible meaning	Multiple possible meanings
Understandable	The method of signalling is easily understood by the user	Signal not easily understood by user
Binary	Either condition A or condition B has occurred	Poor signalling – more than one possible state may have occurred
Repeatable	The same signal from the same state, every time	One signal used from multiple possible states
Decision-focused	Supports the user when making the decision – Is this right? Have I done this correctly? Is there a problem, and if so, what is it? How do I resolve it?	Poor feedback to user, does not guide the user to safety
Timely	Provides feedback to the user in real time, giving them sufficient time to make a safe response	Delay in signalling

Table 1: Features of a user interface with high detectability.

UI with high detectability	Why	UI with poor detectability	Why
 Traffic lights	Unambiguous, the states (stop, get ready and go) are obvious and clear. The sequence of moving from red to amber to green is repeatable every time, and corresponds to the actions required of drivers. Drivers can predict the sequence and can take corrective action as required	 Black watch face	Presents information in an unfamiliar way. Poor visibility of the current time. Forces the user to work hard to understand the information being presented.

Table 2: Examples of user interfaces with high and low detectability.

> "A good user interface should provide clear feedback to users. It should provide a clear, unambiguous and repeatable signal of its status. It should be binary – either the mechanism has worked, or it has not."

A good user interface should provide clear feedback to users (Table 1). It should provide a clear, unambiguous and repeatable signal of its status. It should be binary – either the mechanism has worked, or it has not. Furthermore, to focus on usability, the binary state should be that either the task has been completed correctly or it has not. The user must be left in no doubt as to whether or not they have completed the task in the way the manufacturer intends. The designer of a device's user interface obviously wants to design something that is safe and that supports the user.

Indeed, system visibility is one of the key heuristic principles of good medical device design.[2] A "visible" system should inform users about what is going on with the device through appropriate feedback and display of information. It should inform the user about what actions are available, and the interface should change after an action is made. Why is this of particular importance for wearable devices? Because the user is carrying the device with them into their world. The wider world is unpredictable and the user is very intimately reliant on the device to keep them safe.

To illustrate this concept clearly, let's take some hypothetical examples of high and low detectability user interfaces (UIs) from the wider world (Table 2).

We want product designers to be designing detectability into the user interface of wearable devices, to give clear status signals to the user. A user interface with high detectability is inherently safer. So, perhaps it is time for detectability to be included as a component when calculating use-related risk.

ABOUT THE COMPANY

Medical Device Usability is one of the world's leading consultancies specialising in usability and human factors for medical devices. Based on the Cambridge Science Park, MDU performs formative and summative human factors studies for global pharmaceutical, medical device and diagnostics clients.

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ABOUT THE AUTHOR

Richard Featherstone is Founder and Managing Director of Medical Device Usability. Mr Featherstone leads the team of human factors specialists at MDU. With 15 years' experience of usability consultancy for medical devices, he speaks internationally on human factors, and advises some of the world's leading companies on their human factors strategies.

- CCIT
- ISO 8009
- ISO 11040
- ISO 11608
- Glide Force
- Connectivity
- Trigger Force
- Needle Testing
- Dose Accuracy
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- Break Loose Force
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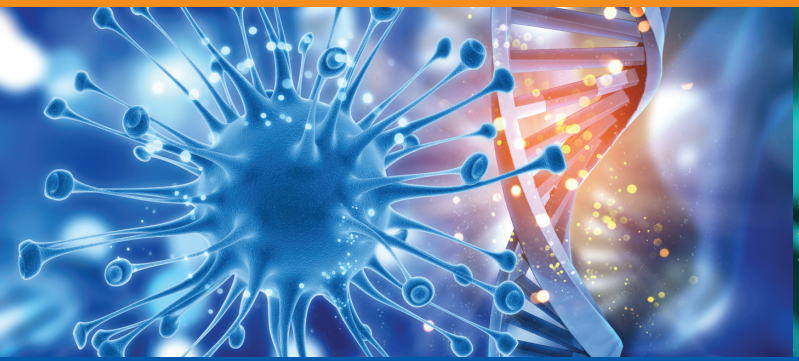

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MEDICAL ENGINEERING TECHNOLOGIES

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DRUG DELIVERY MEETS AUTOMOTIVE ENGINEERING

Here, Thomas Mayer, Business Development Manager, Sonceboz Medical, discusses Sonceboz's activity in the world of wearable injectors and how the company's experiences in the automotive industry and its in-house development of high-quality motors provide significant advantages for the design and production of wearable devices.

Whilst at a first glance the pharma and automotive sectors have nothing obvious in common, a more detailed look under the hood reveals quite important shared requirements and challenges, such as a rigorous need for quality, reliability and safety of supply. Failing drive elements in patch-pumps can potentially cause life-threatening situations, just as failing brake systems in cars can.

To further the comparison, in both cases designs need to be user-friendly such that patient or driver errors are prevented in the first place. One way of achieving this goal is to reduce user steps and enable intuitive interaction. In addition, both industries are governed by strong norms and regulations which must be obeyed in order to maintain market access and customer trust. Last but not least, in both pharma and automotive there is strong pressure for cost efficiency. One possible avenue towards this is found in highly integrated platform designs. By reducing parts whenever and wherever possible and by utilising proven, identical design elements for different use-case specific devices, one can reduce cost while still maintaining the highest level of quality.

As a leading provider in mechatronic systems, with over 25 years of experience in medical technology and having the top 10 car makers among its customer base, Sonceboz adds value to pharmaceutical companies by enabling them to cover a broad range of injection-based therapies while leveraging a true device platform architecture. For each and every device Sonceboz designs, whether a motor with gearbox or a large volume injector, it stringently follows design-for-manufacture and design-to-cost principles, ensuring Swiss quality at world-market prices. Each year over 70 million mechatronic systems are manufactured at the company's sites in Switzerland and shipped across the globe, working reliably in cars, trucks, and dialysis machines alike.

A PLATFORM APPROACH FOR BIOLOGICS

Today's pharmaceutical landscape is characterised by an increasing number of biologic drugs being introduced into the marketplace.[1,2] These often come with challenges not only regarding the fill and finish, but also administration to the most important stakeholder – the patient. High viscosity formulations for subcutaneous administration can be difficult to inject using traditional tools, such as prefilled syringes.[3] In turn, formulations designed to mitigate increasing viscosities by diluting the same molecule payload over a higher volume of drug provide challenges as well – especially

> "With biologics – often stored in a lyophilised form to enhance long-term stability – it is even more challenging for patients to carry out the complex steps required when preparing the drug for injection."

Mr Thomas Mayer
Business Development Manager
T: +41 79 545 46 12
E: thomas.mayer@sonceboz.com

Sonceboz SA
Rue Rosselet-Challandes 5
2605 Sonceboz
Switzerland

www.medical.sonceboz.com

when using rapidly injecting delivery systems such as autoinjectors where the typical volume limit is 2.25 mL. This is mostly because of injection pain and discomfort due to either the compression caused by the injected volume or the drug's own characteristics.

Furthermore, ever increasing healthcare expenditures are a strong driver to at-home self-injection of medications previously administered in-clinic or at a doctor's office. Wearable systems enable the patient to inject the drug slowly and comfortably in a controlled fashion, thereby providing increased personal freedom and quality of life. Sonceboz's large volume injector (LVI), displayed in Figure 1 is designed to hold a prefilled and preloaded 6 mL glass cartridge with the ability to facilitate both bolus injection and complex delivery profiles that have been programmed into the device.

With biologics – often stored in a lyophilised form to enhance long-term stability – it is even more challenging for patients to carry out the complex steps required when preparing the drug for injection. The manual reconstitution of lyophilised drugs requires substantial training and care in order to avoid user errors, such as potential contamination of the drug product[4] or incomplete mixing of the drug powder and its diluent. By creating a device which automatically reconstitutes from prefilled and preloaded containers, such as a vial and a glass cartridge, prior to placement on the body, one clearly reduces the risk for user error and enhances safety and simplicity.

"By utilising a small piston pump to apply a vacuum to the drugs' primary containers, Sonceboz is able to provide a device which is able to pump from two primary drug containers independently."

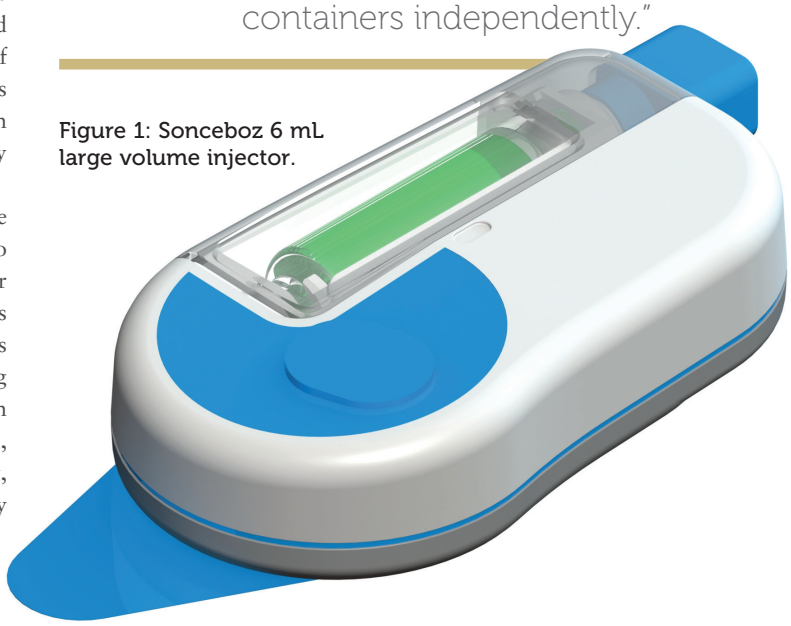

Figure 1: Sonceboz 6 mL large volume injector.

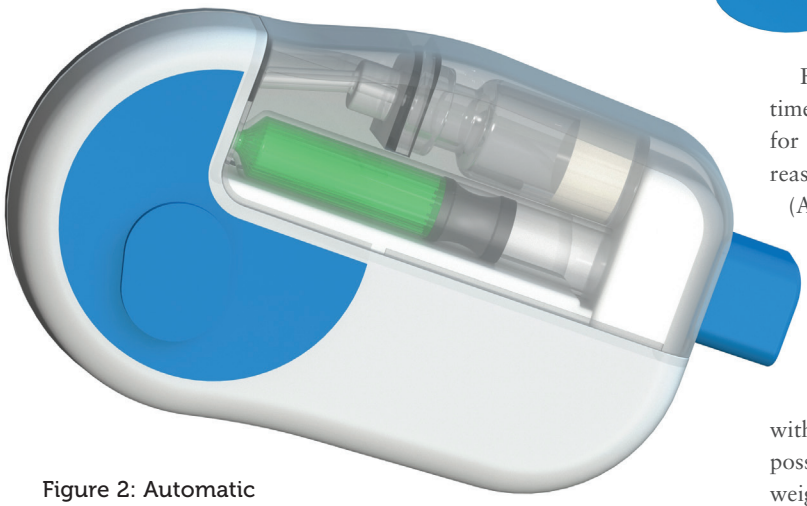

Figure 2: Automatic reconstitution injector.

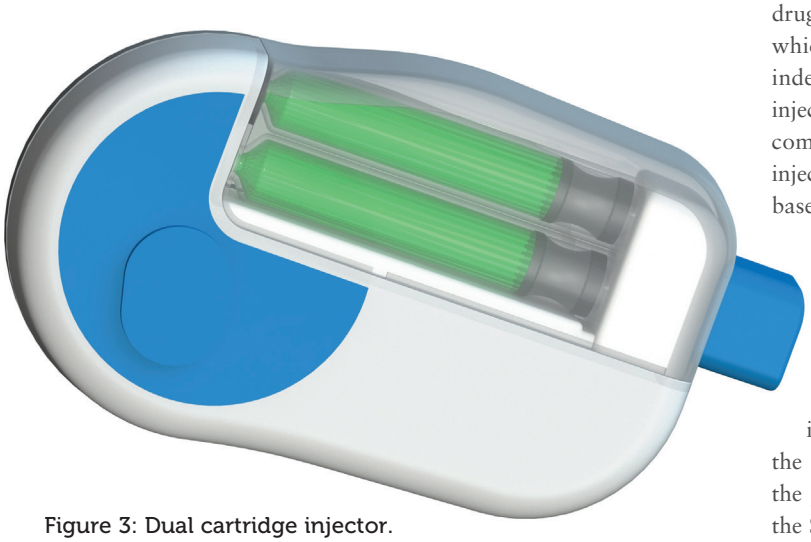

Figure 3: Dual cartridge injector.

Furthermore, such technology enables pharma to achieve a faster time-to-market, due to avoidance of lengthy stability studies with, for example, novel drug containers or liquid formulations. For this reason, Sonceboz is working on an automatic reconstitution injector (ARI), which is designed to make drug reconstitution easy, and therefore safe, for a broad spectrum of patients (Figure 2).

Also, recent trends in combining multiple biologic drugs, so called drug-combination therapies, are becoming increasingly important – especially in immuno-oncology.[5] Although today these drugs are often injected intravenously in a hospital setting, novel formulation options and better tolerability in combination with modern devices could make subcutaneous administration possible. In addition, personalised medicine with individual and weight-based dosing and drug combination is becoming more prominently discussed in literature.[6]

By utilising a small piston pump to apply a vacuum to the drugs' primary containers, Sonceboz is able to provide a device which is able to pump from two primary drug containers independently. This technology is called a dual cartridge injector (DCI) and will empower patients to administer complex combination therapies in their own home by conveniently injecting two drugs sequentially in a bolus or programmed fashion based on their individual needs. Also, this technology can be helpful when an injection site needs to be prepared using hyaluronidase in cases where a co-formulation of the enzyme and the drug aren't possible or such is undesirable for other reasons. Last but not least, a wearable device holding two containers can be an asset if a drug is already approved on the market in, for example, 3 mL cartridges and a new indication or lifecycle management update requires doubling the drug volume (Figure 3). In such cases, one could keep using the proven container and its filling equipment and place them into the Sonceboz DCI.

HUMAN FACTORS, STANDARD CONTAINERS AND A MOLECULE-FRIENDLY PUMP

The unique pump architecture allows for omnidirectional flow of the pumped liquid depending on the programmed parameters, for example from vial to cartridge or from cartridge to cartridge. The pump is made of three different parts:

- a pump piston
- a valve piston
- a pump cylinder.

The valve piston has the function of selecting one of the three ports to enable pumping from one port and injecting from the other. Simply put, it creates a vacuum in the primary drug containers and is thereby actively drawing the liquid in a non-turbulent and gentle fashion, like filling and emptying a syringe. This is of particular importance when considering drug integrity with sensitive large molecule biologics. First data suggests the compatibility of this pump design with large molecule drugs. Test results with TNFα monoclonal antibodies revealed both molecule integrity as well as activity – showing no signs of shear damage. In addition, our material selection and manufacturing processes are designed to be compatible with biologic drugs.

The independent pump plungers are driven using proprietary low-noise slimline-stepper motors, which are placed directly on the circuit board in a solderless fashion, helping to reduce cost and potential weak points of the system. Patients prefer devices which seamlessly integrate into their daily routine, which is why low-noise emission is as important as a compact footprint. Due to the flat shape of the motors, the device thickness can be kept low.

Using closed-loop controlled motors enables load monitoring and helps achieve extraordinary flow accuracy of about ±2%. Since Sonceboz is in the advantageous position of manufacturing its own quality motors (200,000 per day in case of the slimline-stepper), it is not required to build its platform around low-cost motors, often running at high revolutions per minute, contributing to noise (Figure 4).

The common brain of all the platform devices is found in the smart electronics on the circuit board, which helps patients in receiving their required dose of medication the way they need it. From bolus injection to patient-specific profiles, many different dosing regimens are possible thanks to a dedicated microprocessor. For data transfer and user feedback, Sonceboz integrated a Bluetooth Low-Energy chip on the board designed for digital health applications.

In order to enhance patient comfort and help prevent needlestick injuries, the dynamic needle-insertion system (DNIS) uses a solid needle in combination with a soft-cannula made from PTFE. Once the device is triggered by the user and satisfactory skin contact is established, the DNIS releases the needle and directly retracts leaving behind only the soft-cannula.

In order to minimise the burden of validating novel types of drug containers, Sonceboz focused on designing its device around existing and proven containers, such as glass cartridges of different sizes. In general, it was able to adapt its drug container interface to the container a pharma company intended to use. The only requirement is that the device needs to be able to actively draw liquid from the container using vacuum. If required, the platform integrates containers in a prefilled and preassembled fashion, which is important in avoiding potential user errors during drug handling, insertion and filling. In collaboration with its partners, Sonceboz will provide an assembly process that seamlessly integrates into current fill-finish infrastructure.

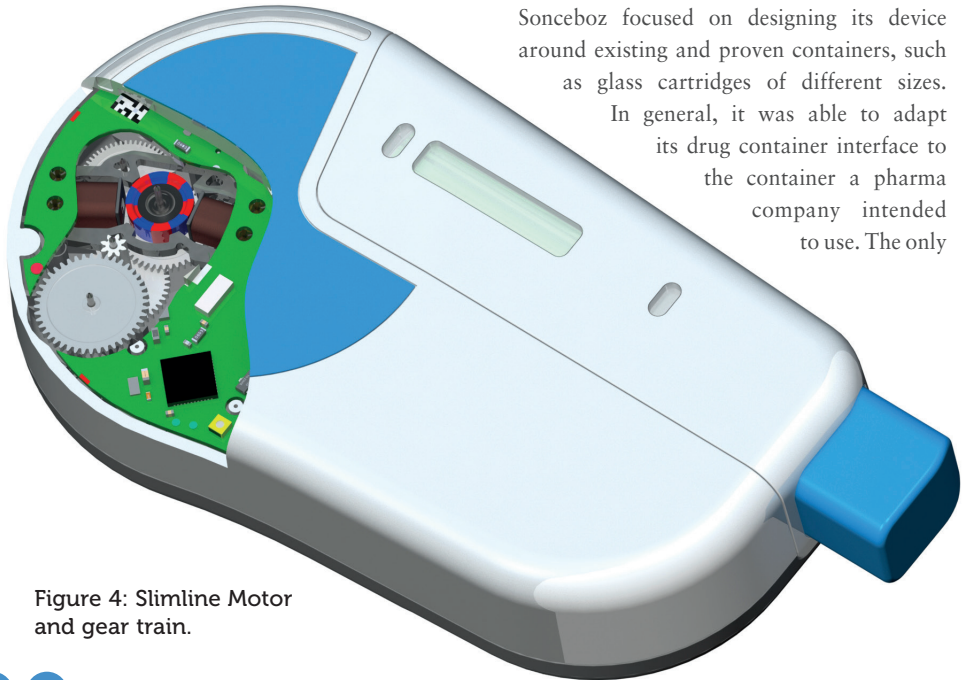

Figure 4: Slimline Motor and gear train.

> "From the very beginning, the platform was designed with user friendliness in mind, which means that user steps should be intuitive and reduced wherever possible."

From the very beginning, the platform was designed with user friendliness in mind, which means that user steps should be intuitive and reduced wherever possible. This is one of the main drivers to enable a prefilled and preassembled device configuration. Also, size, weight and feedback are important to achieve patient acceptance. In order to have a platform which can be adapted to different use-cases, Sonceboz decided to design for one of the most challenging applications – self-injection in rheumatoid arthritis (RA). Patients suffering from RA often have difficulties with dexterity and extreme pain in their joints.[7] The design is continuously tested and iterated upon with patients suffering from RA by performing formative studies. The use steps for the device are:

- Take the device out of the package
- Activate the patch-pump by pushing the activation button inwards
- Remove the adhesive tape
- Place the device on the skin
- Start the injection by pushing the inject button on the top of the device (see Figure 5).

SUMMARY

Sonceboz is working on a wearable device platform aimed to cover the most challenging applications for large volume self-injection systems, with the intention of empowering patients in self-injection

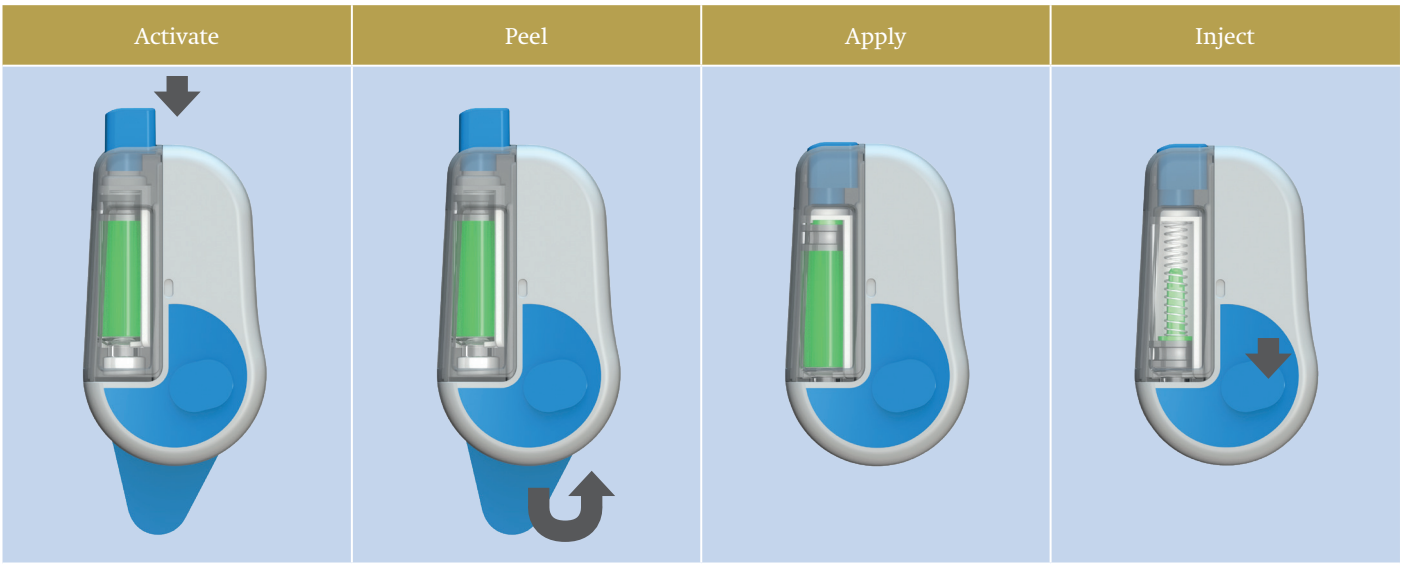

Figure 5: User steps to injection.

applications that weren't possible before. Figure 6 illustrates the Sonceboz platform architecture with its different device arms and the associated stakeholders influencing and contributing to the design.

Sonceboz differentiates itself by its versatile platform built around a piston pump which provides omnidirectional, highly precise flow and connects multiple containers at once. This technology allows for novel device designs such the DCI and ARI. Thanks to a programmable microcontroller, Sonceboz offers a device platform that truly adapts to a drug's intended therapy profile. There is also the option to have a prefilled/preloaded device design without the need to change to a special container type, shape or material, which substantially reduces time to market, risk and ultimately cost. By using proven high-quality components and leveraging high-volume automotive production, Sonceboz provides the highly integrated, cost efficient and low noise drug delivery devices of tomorrow.

Figure 6: Sonceboz device platform architecture.

ABOUT THE COMPANY

Sonceboz's core competencies consist of design, development and production of mechatronic drive systems. Since 1936, the company's focus has been on innovation, and best-in-class quality and service, which is key to success for worldwide OEM customers. Sonceboz is ISO 13485 certified and active in wearable drug delivery, medical devices and laboratory industry.

Pharma companies looking for large volume injectors for high viscosity drugs, dual cartridge or auto-reconstitution injectors will find interesting solutions in Sonceboz's new drug delivery device platform. Customised technology modules like motor-drives, electronics, pumps and needle insertion systems are available for medical device manufacturers.

Sonceboz's activity in medical devices is based on a long experience in automotive where top quality, reliability and cost effectiveness is key.

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ABOUT THE AUTHOR

Thomas Mayer is responsible for Business Development at Sonceboz Medical. Prior joining Sonceboz in 2016, Mr Mayer held various management positions at Boston Scientific's cardiac rhythm management division. His first interactions with the pharmaceutical industry came early during his apprenticeship at Uhlmann Pac-Systeme in Laupheim, Germany. Mr Mayer holds a Diploma degree in Medical Engineering from Furtwangen University (Germany) and an MBA with honours from FOM University in Munich.

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DUAL CARTRIDGE INJECTION

AUTOMATIC RECONSTITUTION INJECTION

YPSOMED
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YPSODOSE: SIMPLIFYING LARGE-VOLUME PATCH INJECTION FOR PHARMA COMPANIES AND PATIENTS

In this article, Ian Thompson, Vice-President Business Development, Delivery Systems, Ypsomed, provides an update on YpsoDose, a new prefilled large-volume patch injector platform, and how it is designed to simplify the approach to wearable patch injectors for both pharma companies and patients.

MARKET REQUIREMENTS FOR PATCH INJECTORS

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

General expectations for these drugs are that they will be dosed subcutaneously every two weeks, monthly or even less frequently; that the dosage will be in the 3–10 mL range; and that the injection will require 5–30 minutes.[1] The large injection volume and longer injection time compared with autoinjectors mean that the injection system needs to be worn on the skin during administration. A skin worn patch injector requires a new drug reservoir compared with a prefilled syringe-based autoinjector, which is held against the skin for around 10–20 seconds.

The possible selection of a wearable patch injector continues to compete against more frequent dosing regimes using standard prefilled syringe-based autoinjector therapies. If pharma companies want 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 preferences. Fulfilling these requirements will allow the patch injector market to grow significantly over the coming years and establish itself as a third self-injection device class to complement the well developed markets for pens and autoinjectors.

> "Developing and designing a wearable patch injector is demanding and requires a broad range of technology and medical device know-how."

LARGE-VOLUME SUBCUTANEOUS INJECTION CHARACTERISTICS

Biologics and mAb-based therapeutics have a large therapeutic window and allow the use of a large fixed-dose drug payload, making them 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 for a single dose may be as high as 600 mg or greater. Additionally, a positive development trend is the general move from other routes of administration, such as intravenous (IV)

Ian Thompson
Vice-President Business Development, Delivery Systems
T: +41 34 424 32 23
E: ian.thompson@ypsomed.com

Ypsomed AG
Brunnmattstrasse 6
CH-3401 Burgdorf
Switzerland

www.ypsomed.com/yds

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 confirming that the overall injection flow rates for such drugs are best suited to the 0.33–1.00 mL/minute range. Examples include:

- Immunoglobulins that are injected in the 20–30 mL/h range
- 3 mL dose of evolocumab that is injected over nine minutes
- 5 mL dose of trastuzumab (containing hyaluronidase) that is injected at approximately 1 mL/minute.

YPSODOSE PATCH INJECTOR OVERVIEW

Developing and designing a wearable patch injector is a demanding task that requires a broad range of technology and medical device know-how. Ideally, the less frequently used patch injector should be as easy to use as a disposable two-step autoinjector, therefore the 3–10 mL prefilled YpsoDose format (Figure 1) incorporates the following key technical features:

- Prefilled and fully disposable to remove any need to assemble the drug reservoir and device, thus eliminating potential handling errors by the patient.
- Adheres well to the skin during injection, is easy to remove after injection and the sensing patch only allows initiation of the injection after contact with the skin, to eliminate an accidental or premature start of injection.
- YpsoDose automatically inserts the injection needle at the start and retracts the needle at the end of the injection process. The needle is also retracted if YpsoDose is removed from the skin before the end of injection.
- A stepper-motor drive, which accommodates a range of fill volumes and viscosities, drives the injection, providing a reproducible injection time for each drug.
- The onboard electronics incorporate wireless connectivity and provide audible and visual signals to clearly communicate with the patient before, during and after the injection.

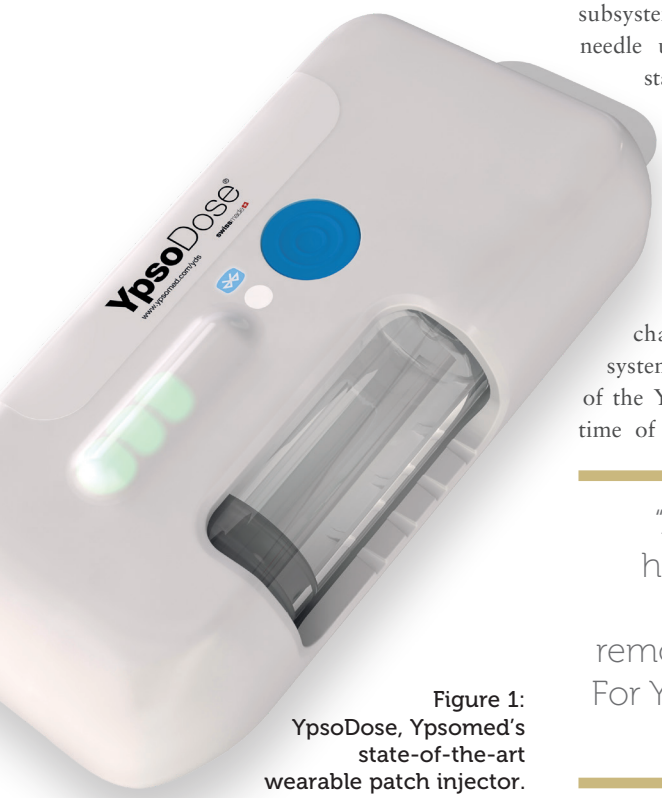

Figure 1: YpsoDose, Ypsomed's state-of-the-art wearable patch injector.

SIMPLIFYING DRUG FILLING AND FINAL ASSEMBLY

These wearable patch injector features and aspects are covered by YpsoDose's electromechanical systems. However, one key aspect is the ability to prefill the device and maintain the sterility of the drug reservoir and fluid path during its lifetime. YpsoDose achieves this by incorporating a bespoke sterile fluid path enclosed within an encapsulated, sterile subsystem, called the needle unit. The needle unit can be compared with 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 interface between the cartridge and needle unit has been designed to allow the cartridge to be filled on conventional filling equipment, either in bulk or ready-to-fill tub formats. Ypsomed is continuing to work closely with pharma partners, cartridge component manufacturers and filling equipment and contract filling specialists to ensure that standard components and filling processes can be utilised.

"All in all, the YpsoDose handling steps are like a two-step autoinjector: remove the cap and inject. For YpsoDose this is simply patch and inject."

"Ultimately, if patch injector therapies are going to be adopted widely for biologic therapies, usability is the most important aspect that needs to be successfully tested with patients."

YPSODOSE USABILITY UPDATE

Ultimately, if patch injector therapies are going to be adopted widely for biologic therapies, usability is the most important aspect that needs to be successfully tested with patients. Current systems are generally healthcare provider (HCP) or patient filled or assembled; no prefilled, ready-to-use wearable devices are currently approved for use by patients. Human factors work with YpsoDose is ongoing to prove and optimise the patch system and user interface. The skin sensor system is key to ensure that the injection can only be initiated once YpsoDose is correctly attached to the skin, as well as to minimise the number of steps required to perform the injection (Figure 2).

All in all, the YpsoDose handling steps are like a two-step autoinjector: remove the cap and inject. For YpsoDose this is simply patch and inject. All other steps

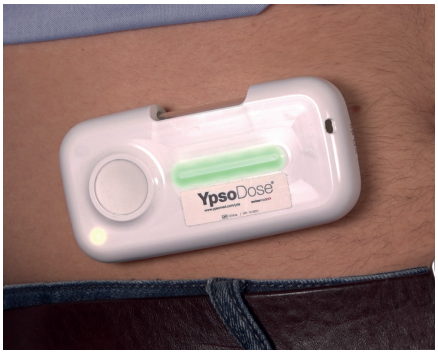

Figure 2: YpsoDose worn on the body.

are controlled by YpsoDose, guiding the patient when to push the injection button and providing feedback throughout the injection process. At the end of injection the needle is retracted and YpsoDose is ready for disposal or specialist recycling.

The most recent human factor studies in the US, performed with the first generation 5 mL YpsoDose format across a wide range of different user groups, have confirmed that:

1. All participants completed successful injections on the first attempt.
2. The user interface is simple and easy to understand, with the orientation of the device proving intuitive when placing it on the body.
3. Participants were comfortable with YpsoDose's size and weight, especially with the understanding that it is a single-dose, infrequent injection.
4. Participants were generally comfortable and not worried when wearing the device. The injector did not prevent them from completing daily activities.
5. The look and feel of the device were acceptable because participants would generally administer this injection in the comfort of their home.

Based on the feedback from the latest studies, the functional prototype design has been finalised for use in pharma customer feasibility studies. As shown in Table 1, based on the comfort rating scale[3] scores, participants rated the most critical dimensions of YpsoDose's wearability the lowest (i.e. Harm, Emotion and Anxiety) confirming that the participants do not negatively score these dimensions. The overall CRS score of 4.3 means that participants generally felt that YpsoDose was comfortable to wear for the duration of the injection.

In summary, Ypsomed is committed to the successful development and commercialisation of YpsoDose as a new state-of-the-art wearable patch injector. Achieving this requires Ypsomed to drive collaboration with key partners, including pharmaceutical companies and drug reservoir and filling specialists, in addition to needing to understand patient characteristics and needs completely.

Dimension	Statements	Mean
Emotion	I am worried about how I look when I wear this device. I feel tense and on edge because I am wearing the device.	2
Attachment	I can feel the device on my body. I can feel the device moving.	9
Harm	The device is causing me some harm. The device is painful to wear.	1
Perceived change	Wearing the device makes me physically different. I feel strange when wearing the device.	5
Movement	The device affects the way I move. The device inhibits or restricts my movement.	6
Anxiety	I do not feel secure wearing the device.	3

Table 1: YpsoDose's wearability rating as a summary of comfort rating scale results. Participants (N=17, adult, adolescent and elderly patients) rated their level of agreement with the following statements from 0 (Disagree) to 20 (Agree).

ABOUT THE COMPANY

Ypsomed is the leading independent developer and manufacturer of innovative self-injection and insulin pump systems for self-administration. Within the Delivery Systems business unit 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 and easy-to-use injection devices for lyophilised drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complete the broad self-injection systems product portfolio. The 3–10 mL YpsoDose patch injector draws on Ypsomed's depth of expertise in diabetes care with fully connected insulin pump systems. 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 and manufactured 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 are regularly inspected by both pharma customers and regulatory agencies and supply devices for global markets including the US, Europe, Japan, China and India. Ypsomed has more than 30 years' experience and well-established working relationships with numerous leading pharma and biotech companies.

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ABOUT THE AUTHOR

Ian Thompson has been with Ypsomed AG, formerly Disetronic AG, 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 for Ypsomed Delivery Systems.

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CUSTOMISED SOLUTIONS FOR LARGE VOLUME INJECTORS

In this article, Paul Senn, PhD, Vice-President of Business Development, Sensile Medical, discusses the products and philosophy of Sensile Medical, a developer of large volume injection devices utilising a patented micro pump technology.

When it comes to wearable injectors, customisation is key. Since every patient group and therapy has its own specific needs, the device must correspond to match. It has to be flexible and fulfil 100% of the specific requirements of the target patient group. Sensile Medical's products show that pump devices are very flexible by design and work in a safe, efficient and simple way (Figure 1). Characterised by modularity and flexibility, Sensile's new range of devices seeks to deliver patient safety and comfort through reliable drug delivery products.

> "Sensile's on-body wearable devices have a mechanism that enables automated needle insertion and retraction before and after administration of the drug."

A drug delivery device is mainly defined by the drug to be administered, the treatment regime and the patient. Opinions of patient groups and healthcare providers, the patient's physical condition, the place of administration and other similar factors are taken into account during early handling studies in order to address all stakeholder needs. No matter which patient group receives the device – paediatrics, adults or geriatrics; mobile or immobile patients – Sensile Medical's

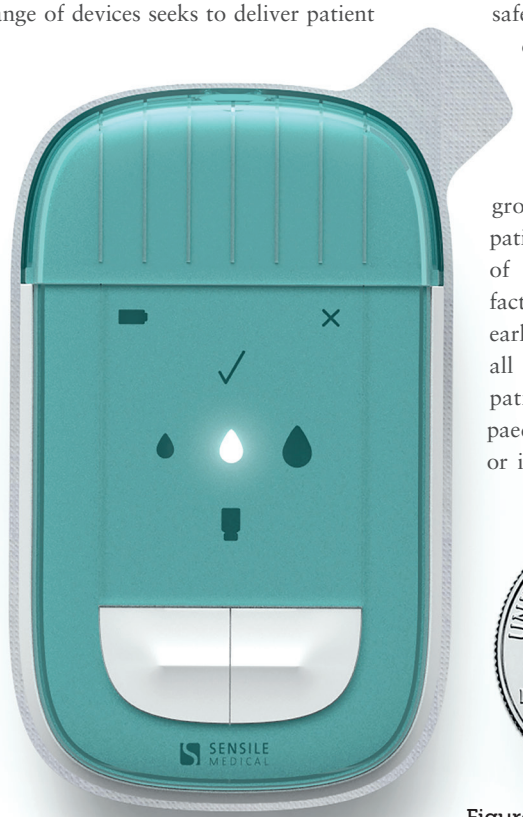

Figure 1: Sensile's small volume, on-body patch pump.

Dr Paul Senn
Vice-President of
Business Development
T: +41 68 209 71 08
E: paul.senn@sensile-medical.com

Sensile Medical
Solothurnerstrasse 235
4600 Olten
Switzerland

www.sensile-medical.com

Figure 2: Sensile's belt-worn infusion pump.

"The patient interface can also be varied, for example it can be controlled by an easy user interface with a start/stop button and a limited number of LEDs that indicate the status of the device."

devices are tailored and customised for the individual patient group. Sensile also addresses the increasing demand for technologies for eHealth applications and is working on connectivity solutions and sensor technologies as an additional option for device flexibility.

SAFETY FIRST

Sensile's on-body wearable devices have a mechanism that enables automated needle insertion before, and retraction after, administration of the drug. This feature greatly reduces the risk of needlestick injuries and contamination before or after administration. Sensile also offers a number of other technologies and sensors to actively monitor the status of the device and the administration of the drug. The core design at the heart of all Sensile devices – a micro piston pump – is used to monitor if an occlusion is present in the system which might inhibit the delivery of the drug to the patient. If an occlusion is detected, the patient is alerted and can take appropriate measures and actions depending on the indication and treatment regime.

"All Sensile devices consist of a reusable and a disposable part, which are connected prior to use ."

FLEXIBILITY FOR SPECIFIC NEEDS

In addition to wearable patch pumps, Sensile also offers a large volume injector that is worn off-body, for example attached to a belt (Figure 2). The device has a standard Luer Lock connection for use with most commercially available infusion sets. The patient interface can also be varied, for example it can be controlled by an easy user interface with a start/stop button and a limited number of LEDs that indicate the status of the device. Alternatively, the device may be controlled by a more sophisticated user interface, using control buttons and a screen to display the status of the device, as well as further functionalities. These additional functions can include independent infusion rates or various bolus options.

COST EFFICIENT AND ENVIRONMENTALLY FRIENDLY

All Sensile devices consist of a reusable and a disposable part, which are connected prior to use. The reusable unit contains a rechargeable battery, a motor, a gear drive and the electronics with the control software. Depending on the treatment regime, the reusable unit can be recharged and re-used hundreds of times. The sterile disposable part, containing the entire fluidic path with the drug reservoir, the pump and the needle, is only used once and can be safely disposed of after the delivery of the drug. The disposable unit is locked after use in order to prevent multiple uses. This design reduces waste and protects the environment.

ACCURATE DOSE DELIVERY

SenseCore, Sensile's proprietary two-part micro rotary-piston pump is flexible in delivery volume and in flow rates, ranging from below 1 µL up to 6 mL per minute. It can pump up to 50 mL from an external primary container into an internal reservoir. The micro piston pump is able to pump and dose water-like liquids or viscous solutions accurately, in increments down to 1 µL. Thanks to Sensile's flexible solutions, it is not necessary for customers to modify the primary packaging, regardless of whether the drug solution is in a 1.5 mL or 3 mL cartridge, a syringe with 5–10 mL or a standard vial with up to 50 mL of content. Since the drug is transferred from the existing primary container to the device prior to injection, the drug does not have to be reformulated in a new specific container, reducing the risk and cost of development. Also, there is no need to invest in new dedicated filling lines.

DIVERSITY AND CONVENIENCE

Based on the same micro rotary-piston pump technology, Sensile also offers a drug reconstitution device that enables fully automated reconstitution of lyophilised drugs with an aqueous solution, as well as transfer to a container for subsequent injection.

Another form of administration is the pen bolus injector, which can inject multiple drug products simultaneously or sequentially, with independently programmable delivery rates and injection times. This may replace the use of multiple conventional syringes and therefore reduce the number of injections necessary for patients with complex, multi-drug regimes.

All Sensile's devices – both small and large volume – are indication independent and tailored to the specific needs of the target therapy. Sensile's products can be used for a wide variety of treatments, including those where drug infusion must be done by a healthcare provider or for an application where the patient can self-inject the drug at home.

ABOUT THE COMPANY

Sensile Medical Ltd is a globally-active Swiss-based medical technology company in the field of large volume injectors. In close corporation with pharma and biotech companies, Sensile develops devices for liquid drug delivery. The core of its system is the patented SenseCore technology, a micro pump that is cost-efficient to produce and provides very accurate dosage. Sensile's designs are characterised by modularity and flexibility to meet patient needs in the best way possible. Sensile Medical employs about 120 employees at its the headquarter in Olten, Switzerland.

ABOUT THE AUTHOR

Paul Senn has been VP Business Development of Sensile Medical AG since January 2017. Prior to Sensile, Dr Senn held several management positions with increasing responsibilities in pharmaceutical and medical device companies in business development, marketing and development of drug products and design of medical devices. He holds a Master's degree in Chemistry and a PhD in Physical Chemistry from the University of Basel (Basel, Switzerland) and received a management education at the International Institute for Management Development (Lausanne, Switzerland).

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Subcuject

WEARABLE INJECTORS: THE PERCEPTION OF INHERENT EXPENSE AND COMPLEXITY

There is a widespread belief that wearable injectors are too expensive and complex to really take off as a commercially viable method of drug delivery. Here, Jesper Roested, Chief Executive Officer of Subcuject, tackles the causes of this belief, and explains why it is not truly the case.

Any discussion on wearable injectors is almost inevitably going to start with the rise of biopharmaceuticals. It is these novel therapies, both with huge potential therapeutic benefits and significant practical challenges that will, when formulated for subcutaneous delivery, drive the growth of the wearable injector market. A number of biologic therapies will, by their nature, have high volumes and viscosities, making it increasingly apparent that a standard pen or autoinjector device is not a suitable administration system for these drugs. At the same time, the pharmaceutical industry's shift towards a patient-centric – and more cost-effective – model means that many of the biologics in development are targeting subcutaneous at-home self-administration rather than intravenous (IV) administration in a clinical or hospital setting. Thus, wearable injectors are the natural home for these novel medicines.

At-home delivery is a priority for the modern-day pharma industry, not only because it is easier and more convenient for patients, but because professional healthcare systems are straining under the weight of a growing and ageing population. Reducing the burden on healthcare systems, both in terms of patients needing clinical-setting treatment and financial expense, is therefore a focus. Wearable injectors facilitate this aim by moving treatment into the home and being a relatively inexpensive way to administer large volumes.

At present, there are many wearable injector delivery systems in development, but very few actually approved and marketed. It is a significant challenge to design and develop a system that meets the necessary criteria:

"At-home delivery is a priority for the modern-day pharma industry, not only because it is easier and more convenient for patients, but because professional healthcare systems are straining under the weight of a growing and ageing population."

- Worn on the body
- High delivery force
- Low and controlled delivery speed.

Many of the wearable injectors in development use electromechanical drive

"A key factor in the cost and logistical difficulties of several proposed wearable injectors is the electronics."

Jesper Roested
Chief Executive Officer
T: +45 2122 7772
E: jr@subcuject.com

Subcuject
Nordre Strandvej 119, F1
3150 Hellebaek
Denmark

www.subcuject.com

> "The success of the autoinjector is in large part due to the fact that, for the patient, its use is an incredibly easy concept to grasp. A wearable injector should therefore aim to be as simple."

systems and electronics. In some cases, because the electronics are already in place, device developers have elected to add programmability and connectivity into their devices. For some drugs and indications this will prove valuable, however in many others the patient may be better served by keeping the device as simple, and as inexpensive, as possible, simply delivering higher volumes of drug over a longer period of time than is possible with a pen injector or autoinjector.

ARE WEARABLE INJECTORS COMPLEX AND EXPENSIVE?

There is a notion in the industry that wearable injectors are inherently complex devices. This is certainly the case for some devices currently in development, possible reasons being that:

- The patients may have to load the drug into the device themselves.
- The patients may have to assemble the device themselves.
- The patients may have to set the injection program or settings themselves.

Furthermore, the more complexity is added into a device, the more the device becomes difficult to use, expensive and/or bulky. As such, complexity and extra features constantly need to be weighed up as a trade-off against these other factors. Often as not, solving one of these problems exacerbates another.

A key factor in the cost and logistical difficulties of several proposed wearable injectors is the electronics. Electronics and batteries are a poor match for the cold storage required by many biologics and also pose environmental concerns around disposal.

In practice, many of the wearable injectors currently in development will have a contract manufacturing organisation (CMO) price of US$20–30 (£16–24) at volume production. At this level, the unit cost to pharma companies is simply too high for many drugs, even when considering those needing only bi-weekly or monthly administration. This complexity, either for the patient or in manufacturing, and anticipated high cost is leading some to the belief that wearable injectors may not be viable for many drugs, causing pharma companies to prefer working with established pen injector and autoinjector systems, despite them being naturally less-suitable.

CAN A WEARABLE INJECTOR BE AS SIMPLE AND INEXPENSIVE AS AN AUTOINJECTOR?

Even in the face of opposition, there is no doubt that some biologic therapies will require complex and expensive advanced delivery systems. However, this is not a universal truth. For many applications, a simple-to-manufacture, simple-to-use wearable injector that is, in essence, nothing more than a prefilled syringe and drive system adhered to the skin that is capable of high-volume, low-speed injection will perfectly serve the needs of both drug and patient. Such a device, provided at a low cost threshold, will therefore be a highly competitive offering in this up-and-coming market.

> "Subcuject's solution is purely based on the powerful, and very inexpensive, natural process of forward osmosis, not using any electromechanical or electronic parts at all."

A "simple-to-use" device is key. The success of the autoinjector is in large part due to the fact that, for the patient, its use is an incredibly easy concept to grasp. A wearable injector should therefore aim to be just as simple. This means that, ideally, a patient should have to do nothing more than unpack the wearable injector, stick it on their body and press a single button. All other functions, such as needle insertion, injection and needle retraction, should be handled by the device itself.

In many cases, in order for it to be seen as advantageous for the pharma or biotech company to adopt a wearable injector solution in the first place, the device should have a unit cost to pharma roughly equal to that of a standard autoinjector. Similarly, the wearable injector should use familiar materials for its primary packaging, ideally standard components if at all possible so that it can use standard filling lines. Furthermore, it needs to take into account the need for cold-storage and its ultimate disposal after use.

Subcuject is developing such a device and is currently in the process of maturing the concept (Figure 1). Subcuject's solution is purely based on the powerful, and very inexpensive, natural process of forward osmosis, not using any electromechanical or electronic parts at all. Whilst the core of the

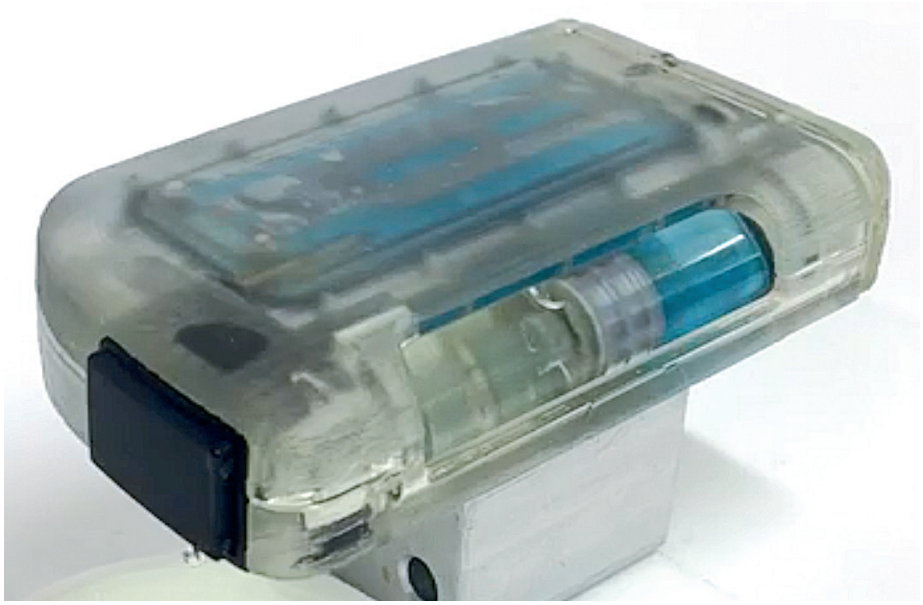

Figure 1: Functional model of the Subcuject device.

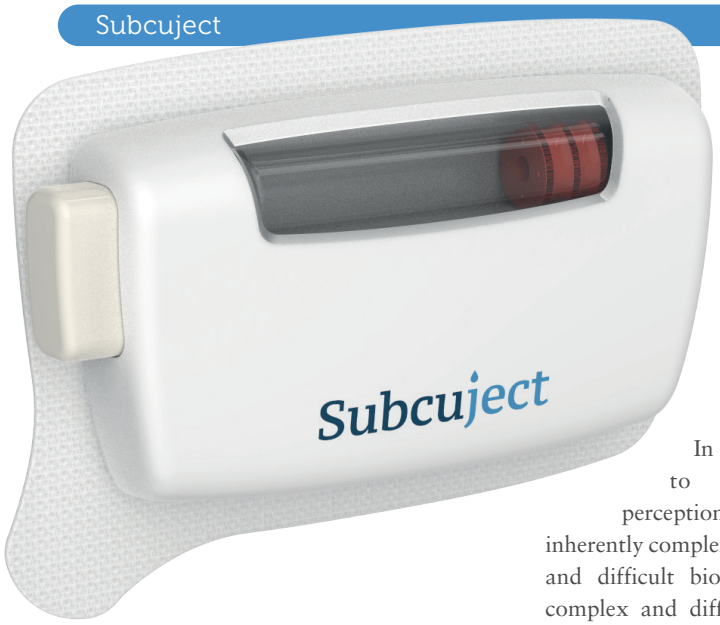

Figure 2: Rendered image of a potential final device.

system is completely without electronics, electronics for e.g. connectivity could be added in a later generation.

The near future therefore holds the promise of prefilled, disposable, low-cost, small, simple-to-manufacture, simple-to-use wearable injectors for the delivery of biologics (Figure 2). Such devices will be suitable for at-home administration, make sound financial sense to both payers and pharma, and will be an attractive option for patients and healthcare providers.

CONCLUSION

In conclusion, it is necessary to modify the existing perception of wearable injectors as inherently complex and expensive. Complex and difficult biologics may well require complex and difficult devices, but this is not a universal truth. It is entirely possible for a wearable injector to be simple, both in terms of use and manufacture, and inexpensive, with unit costs to pharma reaching down towards $5, similar to an autoinjector, rather than the present $20–30. Subcuject is working towards such a device and is looking forward to revealing further details as the concept matures.

ABOUT THE COMPANY

Subcuject develops an innovative and proprietary wearable device platform for 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 collective experience and a long track-record working in medical devices, pharma and drug delivey. Subcuject is a privately held company located north of Copenhagen, Denmark.

ABOUT THE AUTHOR

Jesper Roested, Chief Executive Officer of Subcuject, holds an MSc in Medical Electronics and Physics and has 25 years of business experience. Mr Roested has primarily held business development and management roles in the life science industries, including seven years as a partner in a venture capital fund, specialised in medtech.

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DEVICE TRAINING AND ONBOARDING CONSIDERATIONS FOR ON-BODY DELIVERY SYSTEMS

In this article, Joe Reynolds, Research Manager at Noble, explains how on-body injection devices have arisen from the need to develop viscous, large-volume biopharmaceutical therapies, and how Noble's on-body training devices can help patients learn how to use their devices correctly, reliably and safely.

INTRODUCTION

While still a younger segment in the broader scope of healthcare and medicine, the market for biopharmaceuticals and complex chemical entities has revolutionised the practice of modern medicine and significantly improved the quality of life of millions of patients worldwide. Since biopharma's early origins in the 1980s and the US FDA's approval of Humulin (insulin), the first recombinant pharmaceutical product marketed in the US, advancements in science and our understanding of disease mechanisms and pathways have supported the discovery and development of a broad portfolio of currently marketed biotherapies and a robust pipeline of future innovative medicines.[1] According to statistics from The Pharmaceutical Research and Manufacturers of America (PhRMA), there are currently over 6300 biological compounds in clinical development globally, the majority of which (≈74%) are described as having novel clinical profiles that could provide first-in-class pharmacological and therapeutic benefits to patients.[2] In addition to serving as a strong base for future therapies, many of these products leverage innovative scientific approaches, such as gene/cell therapy, conjugated antibodies, nanotechnology and other pioneering techniques seeking to advance the field of medicine and address unmet patient, clinical and economic needs. While these medications have the potential to augment and enhance the prognosis of rare and debilitating conditions, novel approaches to drug delivery are often required to ensure that patients realise the full therapeutic benefits of these innovative compounds.

DELIVERING BIOLOGICS

Due to the structure and clinical properties of biologics and other large molecule compounds, many of these substances are administered through parenteral routes, including intravenous (IV), intramuscular (IM), subcutaneous (SC), intradermal (ID) or other injectable methods for localised or systematic effect. While numerous factors influence the final dosing route and delivery method of a therapy, subcutaneous injections – many of which are marketed for at-home administration by patients – are usually administered using prefilled syringes, injection pens, autoinjectors or other conventional device platforms.

> "While the duration and key onboarding considerations may vary across therapies, research suggests that the strength and retention of training and treatment information increases through experience and repetition over time."

Joe Reynolds
Research Manager
T: +1 888 933 5646 Ext 147
E: jreynolds@gonoble.com

Noble
121 South Orange Avenue
Suite 1070
North Orlando, FL 32801
United States

www.gonoble.com

Over the years, these delivery devices have significantly improved in terms of user experiences and safety. However, they also present technical constraints and limitations for drug developers, particularly associated to dosing characteristics such as volume, concentration and viscosity.

To address the limitations of conventional delivery systems, a new segment of the device delivery market was established for larger volume and more viscous medications, many of which are not suitable or feasible for use with traditional delivery technologies. Commonly referred to as on-body, wearable or bolus injectors, these new delivery systems are typically adhered to a patient's body, where they are intended to remain until a prescribed dose has been successfully administered. In addition to adhering to patients' bodies, these new delivery devices also introduce new behaviours and protocols into the patient experience that increase the need for and importance of patient training and onboarding.

ONBOARDING

Within healthcare and drug delivery, the onboarding process is commonly viewed as a patient's first 30, 60 or 90 days of therapy, where their initial treatment attitudes and behaviours are established. While the duration and key onboarding considerations may vary across therapies, research suggests that the strength and retention of training and treatment information increases through experience and repetition over time. Inversely, patients that receive suboptimal training and onboarding may be more likely to misuse drug delivery devices or experience lapses in treatment. According to this research, it is estimated that after one day of training, patients retain, and are able to recall, only 33% of the information they successfully perceived and encoded. After six days, recall decreases to 25%, where it continues to erode and decay over time (Figure 1).[3]

To address these adherence barriers and support the proper use of on-body systems, Noble applies a number of complimentary learning theories and methodologies to develop the most optimal training devices and onboarding experiences for patients using on-body and other forms of drug delivery. Ultimately, the goal of Noble's on-body training devices and other onboarding solutions is to provide patients with the skills and knowledge required to confidently manage their treatments, successfully use their delivery systems and achieve an improved quality of life. To support this goal, Noble applies a number of best practice design, development and manufacturing methodologies throughout its process to ensure that every patient receives a consistent and meaningful onboarding experience.

> "To be most effective, training devices must replicate the complete user experience and delivery process, with exception of containing a real needle or liquid, to ensure that patients understand the operating requirements of their delivery systems and are properly onboarded."

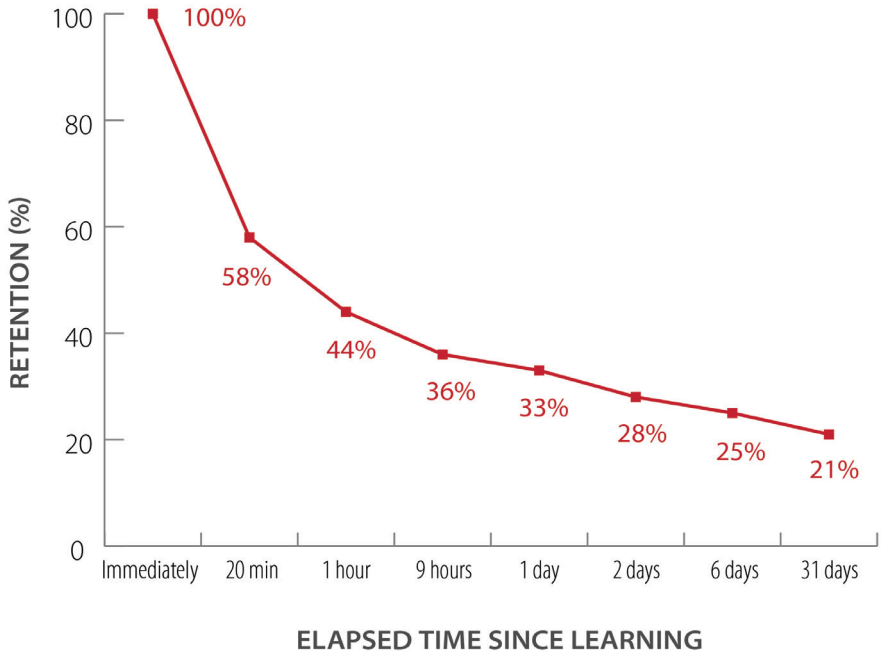

Figure 1: "Forgetting Curve" theory illustrating the decay in training and treatment information over time.

ON-BODY TRAINING SOLUTIONS

Similar to developing training solutions for other forms of drug delivery, engineering large volume and wearable trainers for manufacturability and repeatability is a delicate balance. Fully understanding device development, mechanical design and other technical disciplines is one of the first steps in engineering robust training device solutions for on-body devices.

To be most effective, training devices must replicate the complete user experience and delivery process, with the exception of containing a real needle or liquid, to ensure that patients understand the operating requirements of their delivery systems and are properly onboarded. As such, the exterior of a trainer should emulate the commercial injection device so that patients become familiar with key features and physical characteristics such as the look, feel and weight of their device.

For on-body trainers this commonly includes unique features such as adhesive patches and multisensory user feedback, which are less prevalent in conventional delivery devices. Characteristics of the injection system, such as the dimensions, viewing window, actuation method, surface finish and other external features, are all accurately matched so that patients can familiarise themselves with the complete user interface and task flow.

In addition to external details, internal mechanics are also crucial to the design and engineering process. To incorporate all of these necessary components, the interior design of training devices needs to be meticulously engineered in order to provide a proper training experience. To accomplish this, human factors are taken

Figure 2: West Pharmaceutical Services and Noble have worked together to offer a multisensory-based educational and training solution for the SmartDose technology platform to pharmaceutical and biotechnology customers.[4]

into consideration throughout the design process to ensure that training devices align with the physical, cognitive and emotional needs of users. In addition to understanding user needs, Noble leverages numerous design inputs to prioritise design requirements for training devices and maximise training value for targeted user populations. Though in some cases mechanisms similar to commercial devices are used, ground-up mechanical design is usually employed to integrate all necessary functions in a resettable and reusable training device. This means that the trainer will look the same on the outside but will be vastly different internally (Figure 2).

USER EXPERIENCE

From a user experience standpoint, one of the most distinguishable differences between on-body systems and conventional injectors is that they are adhered to a patient's body using adhesives.

Incorporating this aspect of on-body systems into reusable training devices requires careful consideration for sanitation, biocompatibility and other design trade-offs that must be evaluated when determining and prioritising requirements for on-body trainers. To assist manufacturers through this process, Noble has developed a number of 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 experience the sensation of how long it takes the medication to deploy and be fully delivered.

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 may ramp-up slowly while others have a fast on-set 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. Other considerations include representing the audible and haptic feedback levels that are present and integrating tactile feel elements, such as subtle internal vibrations associated to drive elements. In addition to these items, along with the fact that it needs to be easily resettable rather than just a single-use product, the trainer must also maintain a 1:1 size ratio, i.e. it cannot get any larger than the real drug delivery device.

CONCLUSION

To address the demand for this emerging market, Noble has developed a broad portfolio of on-body training solutions and platform technologies that can be leveraged by manufacturers to address the onboarding needs of patients and other stakeholders. While designing the optimal training device comes down to the unique needs of patients and other user populations, Noble's development process and proprietary portfolio of technologies, including multisensory, error detecting, wireless, smart and others, support manufacturers in prioritising requirements and developing solutions that maximise training value for patients and other stakeholders. As innovative on-body therapies continue launching and diffusing in the market, onboarding and training will continue influencing patient acceptance, confidence, satisfaction and outcomes with therapy.

ABOUT THE COMPANY

Noble is a full-service, user-centric advanced drug delivery training device and patient onboarding company. Noble works closely with the world's leading drug delivery device original equipment manufacturers and pharmaceutical companies to develop educational and training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes.

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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. His experiences include commercial, managed care and product development initiatives with leading medical device, pharmaceutical and biopharmaceutical manufacturers. 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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