WEARABLE INJECTORS

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WEARABLE INJECTORS

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2017/18 EDITORIAL CALENDAR

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Nov	Pulmonary & Nasal Delivery
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WEARABLE INJECTOR PLATFORM: THE CASE FOR EARLY PARTNERING

In this article, Jeannie Joughin, PhD, Vice-President, Corporate Development, Enable Injections, describes how significant factors and developments, in society, in science and in the industry, have converged leading to the rise of patient-centric healthcare, and with it self-administration, with the wearable injector now emerging at the cutting edge. She goes on to show that early clinical partnership with a platform wearable device company is beneficial across numerous criteria, and how suitability for early partnership through to commercial launch was a key design consideration for Enable's wearable technology.

Those with experience in the many areas of pharma that involve partnering, such as drug delivery, might have become numb to the calls for early partnering from would-be partners. However, whilst there is a lot of noise on this, it is important to be able to distinguish instances where the case for early partnership is in fact robust, evidence based and compelling. In this article we will make just such a case for early clinical partnership in the context of pharmaceutical product development involving the Enable wearable injector device platform.

> "The ever closer integration of devices and therapeutic candidates was inevitable. The key to success for pharmaceutical companies embarking on new development projects today is to integrate the device early in development."

A NEW ERA IN BIOLOGIC DRUG DEVELOPMENT

Before focusing on Enable's platform, it is useful to look at how we arrived at this point where patients, without special skills or professional training, are now able not only to receive valuable, highly advanced, complex and previously very difficult-to-deliver (sometimes impossible-to-deliver) biotherapeutics, but also to take these treatments home and administer them to themselves easily, hassle- and worry-free, and without disruption to their everyday lives.

In the 1990s, new science, in particular genomics, began bringing to light new means of treating and curing disease. The prospect of such innovative medicines spurred a period of intensive research into disease modifying therapies and treatments for chronic diseases that continues today.

It has been fruitful, giving us a new generation of effective biotech compounds such as monoclonal antibodies, multivalent vaccines and recombinant peptides. Yet today, developing innovative biotech compounds into marketed drugs is increasingly challenging in terms of the burden of cost, time, risk all arising from factors such as the tough regulatory environment and the sheer complexity of the task – the complex compounds, complex therapeutic mechanisms, and the increasing number of ever rarer diseases to be treated.

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Over the same period that the biotech industry has been born and grown, the wider world, including patient populations, has undergone huge change too. Patients have evolved, rapidly becoming more educated and aware, in part due to the internet. The healthcare sector has changed too – placing the patient at the centre of the value equation with an emphasis on value-based care and patient outcomes rather than just the treatment alone.

PUTTING PATIENTS AT THE CENTER BENEFITS ALL

The marketplace has thus been transforming from a provider-dominated marketplace (pharma) to a consumer-centred system. On a simple level the consumer (the patient) can be seen to demand products that are more responsive and reflect their needs. But people are highly complicated and so the question then becomes, what are their needs?

Hope, control, freedom, independence, burden-free treatment, and treatment liberation are some of the things we might seek after being diagnosed with a serious, chronic disease. It is when considering these sorts of patient desires and demands that the value of self-administration becomes apparent - bringing biotech therapies out of the clinical setting and offering more of what the patient wants and needs.

Self-injection, and its ability to take quite advanced treatment out of the clinical setting, is favourable not least because in many circumstances it is ultimately more successful. Patient adherence benefits are clear, as are cost reduction benefits to the entire healthcare system. Shifting patients out of the clinical setting without compromising safety or efficacy frees up more resources to be used on those patients who absolutely need a clinical setting and the presence of healthcare professionals for drug administration (e.g. combination oncology therapies) and other treatments.

In response to these major changes that have taken place over the past few decades – the emergence of biotherapeutics, the associated cost, time, risk and complexity, the increasing focus on the patient, and in particular allowing them to self-administer at home – delivery solutions have begun to emerge that enable a new pharmaceutical product both to meet the patient's demands and desires from the outset and accommodate means to overcome the inherent obstacles that would otherwise ultimately affect the time, costs and risk involved in moving through clinical trial phases to commercial production.

> "The patient is now at the centre of the value equation and the delivery device is now the element that, from the patient perspective, often defines the treatment experience more than any other."

With hindsight, it is easy to see that the ever closer integration of devices and therapeutic candidates was inevitable. The key to success for pharmaceutical companies embarking on new development projects today is to integrate the device early in development.

Crucially the patient's role in clinical trials has also changed dramatically over time. In the past, human volunteers, in terms of their value to the trial, were almost just an organic substrate into which product candidates were infused and the physiological effects monitored and recorded. In contrast, the patient's role in clinical trials today is much more that of a whole person experiencing the treatment. The physiological data is gathered of course but patients are now reporting back on how the treatment experience felt, how it could be made easier, what they liked and disliked about it.

Bringing the device in at the early clinical stage provides an opportunity to engage associated patient populations early in product development. It improves the ability of the product to meet the patient needs and thus to align better with the reward for outcomes that governments and payers insist upon. It enables the pharma company to answer contextual questions regarding the patient sooner and therefore decrease cycle time for new product development

In this environment – with self-evident significant benefits to the product development process of these additional insights from the patient as a whole person experiencing the complete product, drug and device, the potential for greater product differentiation, better acceptance, and better uptake at the time of launch to achieve better outcomes – the case for including the drug delivery device from early in the clinical stage becomes ever stronger. Conversely, a pharma company leaving the inclusion of the delivery device as an afterthought, after the clinical trial stage, risks a huge missed opportunity, an inexcusable omission, and a substantial competitive disadvantage.

The patient is now at the centre of the value equation and the delivery device is now the element that, from the patient perspective, often defines the treatment experience more than any other. The drug itself will remain a most important factor, but inevitably it will represent a diminishing share of what comes together to deliver an overall outcome for the patient.

FLEXIBLE DEVICE PLATFORM: A SUITABLE SOLUTION

Whilst early clinical-stage partnering and integration of a patient-centric device for self-administration is desirable, not all devices out there are necessary suited for clinical stage partnering. What then are the characteristics that describe a valuable and convenient delivery solution that is attractive for early partnership in the clinical environment?

Clearly, any solution must be affordable and flexible for pharma to accept at this stage of development. These are prerequisites, and point towards a technology platform. The platform approach embraces the fact that one size does not fit all and thus offers multiple "sizes" to a pharma partner (for example, the ability to use different types of standard drug container, or deliver a range of dose volumes) to accommodate various scenarios and patient populations.

> "A pharma company leaving the inclusion of the delivery device as an afterthought, after the clinical trial stage, risks a huge missed opportunity, an inexcusable omission, and a substantial competitive disadvantage."

Modern drug development is risk heavy already and so pharma companies want the device solution to be a de-risking influence ideally, and definitely not a source of additional risk.

With a robust, versatile device platform integrated into the development process, if one drug candidate fails, the delivery device remains and is ready, both technically and in terms of budget spend, to take the next candidate forward. This allows the development project more "shots on goal" with drug candidates, increasing the chances (decreasing the cost and time) of finding the one that will be taken through full product development. Device flexibility, for example the capacity to deliver a large range of dose volumes up to very high volumes, increases the number of possible drug candidates and thus, again, increases "shots on goal" and de-risks the entire development program.

In addition, the solution should accommodate and utilise the existing infrastructure the pharma partner has already established to avoid risk, decrease costs and reduce timelines. The requirement for change should be minimal. A suitable device platform should avoid, and certainly not exacerbate, the challenges of filling complex compounds, and avoid the longer timelines, and increased risk and cost associated with bringing in a new container (e.g. testing). Utilising standard primary container closures minimises change, and the ability to use various forms (i.e. both syringes and vials, of the kind already used in clinic) adds the flexibility to accommodate a wide variety of drugs and user populations.

TRANSITIONING FROM CLINIC TO MARKET

To be a viable proposition, a low risk clinical-stage drug delivery solution must also easily transition into a commercial solution. In the same way that both the delivery technology and the strategic partnership relating to it must be flexible and responsive for clinical trials, they must both be responsive to the needs of the commercial environment.

This goes beyond merely being suited to application in lifecycle management. Things change fast in the commercial environment. Market drivers change, concepts within biotech evolve. Patents expire and mature products are suddenly faced with new competition. Innovative delivery solutions that add value and convenience will prolong a branded drug's premium pricing and define its market share against competitive entrants with similar indications and patient profiles.

As pharma companies increasingly put patients at the centre of the value equation, and view them as their customers, with specific wants, needs and expectations, it becomes clear that the right delivery device platform offers many of the capabilities and features needed to accommodate current and future patient requirements, fulfilling the demand for better treatment outcomes, but going further, digging deeper. For example, patients are attracted to the idea of self-administration, and want greater convenience related to the services they are receiving, and the right device platform enables the pharma company to fulfil that customer desire completely. Likewise, the right device platform meets the patient-customer's wish for: comfortable drug administration (e.g. minimally invasive solutions); an administration means that allows them to control their chronic illnesses without compromising their daily activities; minimal anxiety and intimidation; and perhaps for a product that has an attractive appearance with environmentally responsible packaging.

Figure 1: Enable Injections' syringe transfer systems are favourable for variable fill volumes and provide the flexibility of accommodating any syringe or vial primary container.

Figure 2: Enable Injections' vial transfer systems will transfer entire or partial contents from the vial and can accommodate single or multiple vials.

Figure 3: Enable Injections' mixing systems can automatically or manually mix/reconstitute two vials of liquid or liquid/powder.

ENABLE PLATFORM – OPTIMISED FOR CLINICAL-STAGE INTEGRATION

Enable Injections has long understood that the wearable injector would not be a mere afterthought in pharmaceutical product development. Whilst there are of course beneficial applications in lifecycle management later in development, the Enable wearable platform, and indeed the structure and culture of Enable Injections the company, is designed and built to fulfil their principle role – to play an integral part of pharma partners' overall development pipelines from the early clinical phase through to launch and beyond.

The Enable wearable injector is the core technology that can adapted to deliver a defined or variable dose, at a pre-determined flow rate, based on viscosity and patient comfort. Once the key attributes and the design are determined, the same injector may be used to deliver multiple clinical compounds. In early-phase clinical studies, when dose has yet to be determined, the injector may be filled with variable volumes using a syringe-transfer system (see Figure 1). Once the dosing regimen is established the same injector may be filled with the entire/partial contents of a vial (vial-transfer system, see Figure 2). If mixing is required – lyophilised product + diluent or two products in solution – the filling mechanism can transition to a simple, convenient means of pre-mixing and filling that same injector (see Figure 3).

Enable Injections actively encourages clinical collaborations with partners with a strong pipeline of products and/or additional lifecycle management – for example, new indications – since the platform technology offers the partner a fast-track to clinical trial. This form of collaboration provides a cost-effective, milestone-based means of supporting subsequent validation/verification for additional combination therapies in the partner's pipeline and mitigates development risk and cost for the pharma partner.

SUMMARY

The last decade has seen remarkable breakthroughs in biotech, transformational changes in healthcare, and more broadly in society too. The patient is now at the heart of the pharmaceutical industry value equation, viewed as a person with feelings and desires and as a customer with demands and requirements.

A parenteral delivery device is required for the administration of the vast majority of new biologics, and this is increasingly integrated into the pharmaceutical product. The delivery system is often the aspect of the treatment that is most tangible to the patient and most able to meet their specific wants and needs. For drugs that require high volumes and longer delivery times, a wearable injector is a game changer, freeing patients from the healthcare setting and enabling them to take their medicine themselves, at home – self administration.

The value of the delivery device does not end there though. If the delivery system is brought in at the early clinical stage, the patients' feelings and opinions about the real treatment experience can be taken into account to improve the product at the right time, during development and not after launch when it is too late. Furthermore, the technical challenges complex biological molecules present can and do slow or halt product development. Utilising a delivery solution that accommodates variable dosing and can be readily switched to other pipeline products in the event of product failure significantly helps mitigate this risk.

Biotech/pharma companies are thus increasingly looking for a device partner whose business structure, culture and strategy is configured to work with them from the early clinical stage onwards, and which offers a technology platform that can accommodate a wide variety of drugs and user populations. We believe that Enable Injections the company, and the Enable on-body delivery platform, represent that partner.

In today's pharma industry, a delivery solution cannot just be "kept in mind" during clinical development. A drug delivery device platform must be brought in and implemented during clinical development as part of any optimised and streamlined biopharmaceutical development pipeline.

ABOUT THE COMPANY

Enable Injections is a late-stage start-up company that has developed a disposable on-body injector to deliver high volume (up to 50 mL), high-viscosity drug/biological products to the subcutaneous tissue. The system utilises standard container closures (syringes or vials) and can automatically mix solutions or solubilise lyophilised product. It is designed to be simple to use and discreet promoting convenience and comfort for a preferred injection experience for the user. Enable's technology provides many differentiating advantages to both the user and bio-pharmaceutical company. Founded by medical device veterans the company has R&D, operations and manufacturing facilities in Cincinnati, OH, US. *For investigational use only.*

ABOUT THE AUTHOR

Jeannie Joughin, PhD, Vice-President of Corporate Development at Enable Injections, is responsible for business development, strategic alliances, alliance management, marketing and clinical activities. She previously 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).

ON drugDELIVERY

2017/18 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Oct 2017	Prefilled Syringes	DEADLINE PASSED
Nov 2017	Pulmonary & Nasal Drug Delivery	DEADLINE EXTENDED
Dec 2017	Connecting Drug Delivery	Oct 23rd 2017
Jan 2018	Opthalmic Drug Delivery	Nov 20th 2017
Feb 2018	Prefilled Syringes	Dec 22nd 2017
Mar 2018	Skin Drug Delivery: Dermal, Transdermal Microneedles	Jan 20th 2018
Apr 2018	Pulmonary & Nasal Drug Delivery	Feb 19th 2018
May 2018	Injectable Drug Delivery: Devices Focus	Mar 19th 2018
June 2018	Connecting Drug Delivery	April 23rd 2018
July 2018	Novel Oral Delivery Systems	May 21st 2018
Sept 2018	Wearable Injectors	July 23rd 2018
Oct 2018	Prefilled Syringes & Injection Devices	Aug 27th 2018
Nov 2018	Pulmonary & Nasal Drug Delivery	Sept 24th 2018
Dec 2018	Connecting Drug Delivery	Oct 29th 2018

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In 2004 Sensile Medical started developing its micro pump, and patented the SenseCore technology (Figure 1) that powers it. Compatible with many different types of medicines, SenseCore is small, precise, flexible and, since it is composed of just two plastic parts, affordable. SenseCore provides the core functionality for other pump platforms like SenseFlex (belt-worn pump) and SensePatch (body-worn patch pump).

SensePatch (Figure 2), complete with its own adhesive, has an integrated auto needle inserter, which makes its subcutaneous needle not only simple to use but also discrete – a big help for those patients who are afraid of needles. SensePatch is suitable for volumes up to 20 mL. The SenseLyo (Figure 3) is an automated reconstitution device, compatible with a variety of reservoirs.

In 2007, the company moved to Haegendorf in Switzerland's Solothurn canton. Lying in the centre of German-speaking Switzerland, Haegendorf is not only accessible for more clients, but also for new employees. In 2015, the SenseCore technology won the Swiss Technology Award – the most important award of its kind in Switzerland.

The company has recently moved again, to a new facility (pictured on Page 11) offering more space for larger laboratories and more employees, since much more will be done in-house. In Autumn 2016, Sensile had 65 employees. One year later, it has more than 100, and by the end of 2017, the company is expected to employ 120 people. Multiple projects are under development. Sensile is confident that with the further development of biotech the demand for devices like the ones Sensile produces will rise.

That's as good a reason as any to look back at the last ten years of Sensile Medical. Chief Executive Officer Derek Brandt and three of his colleagues – Christoph Lüdi, Head of Systems Engineering, Alex Perrier, Senior Technology Manager, and Marco Drüssel, Mechanical Engineering Manager – have all been a part of the company for the past ten years, so are in a good position to reflect on the company's past and discuss the future.

Q Which position did you start in at Sensile?

DB: I came to Sensile in 2007 and started as Chief Executive Officer.

CL: In the summer of 2007, I came to Sensile Medical as Head of Software with the goal of building up the software department for our pumps. At that point, there was no development for the device available. Even though I had experience, the beginning, and especially the build-up phase, went very slowly.

> "Finding a device for a therapy and then bringing them together is almost like marriage, in the sense that you are constantly dependent on the other."

AP: I started as Project Leader at Sensile Medical. I was especially interested in development work.

MD: Right after I got my degree, I began to work at Sensile as a testing engineer.

Q Has your job changed over the past ten years?

DB: Back then, three to four people worked in our offices at Baar, Switzerland. Pretty soon we moved, and our employee count rose quickly. At that point, everyone was involved in everything, from the creation of quality processes to picking out furniture. In the meantime, I needed to learn how to delegate some of my responsibilities to new coworkers – it was a mutual learning experience.

CL: For the past three years, I've been the Head Systems Engineer. Systems engineering is fundamentally different from software engineering, but we use similar approaches to solving problems. Our job is to develop the architecture for the device, keeping in mind all the components that comprise the whole. Without considering the whole, each part functions less efficiently – especially the software. As a systems engineer you become a sort of middleman, in the sense that you're in constant contact with other departments. The entire project needs to work together if it wants to implement its solutions efficiently.

AP: I quickly and unofficially began leading mechanical engineering. It was important to me that we work in a structured manner. So I

Sensile Medical's new facility it Olten, Switzerland offers more space for larger laboratories and more employees, enabling much more work will be done in-house.

made checklists, established a clear drawing number definition, and set up tolerance analyses. I focused about 60% of my attention on being Project Leader and then devoted the rest to the fundamental development of our organisational structure. For a while, I separated myself from the materials (plastics). Since mid-2014, I've worked solely as Project Leader, but I'm still heavily involved in the mechanical side of development, especially with our pump. For this reason, I joined the Technology group in September 2016.

MD: After a few years in the workshop and after university, I transferred into mechanical development. As of the beginning of this year, I'm still a partial Project Leader. Structurally, we needed to adapt to the number of new employees coming each month—the company is growing rapidly. My job has changed in the sense that I'm not doing hands-on development anymore, but instead I'm focusing on documentation, requests and analyses.

Q Which milestones has Sensile reached in the last ten years?

DB: Ten years ago, we were still a start-up. I wouldn't call us that today, because we survived the critical portion of a start-up's life – 80% of start-ups go out of business in the first ten years. We managed to beat the trend, thanks to Sensile's fantastic employees and thanks to our investors, who stood by us through every setback.

Q How have the demands of customers and the industry changed?

DB: The regulatory aspect of doing business in the medical devices industry has become fundamentally stricter. Of course, in this industry, this is normal. What is also changing is the quality expectations from our pharma clients. Quality audits are today more comprehensive than ever before. Finding a device for a therapy and then bringing them together is almost like marriage, in the sense that you are constantly dependent on the other. Given the demands of the industry, companies on both ends want to make sure that the marriage is solid before anything is signed.

CL: New technologies like the iPhone also bring with them new expectations. For example, connectivity is a huge challenge for a small business like Sensile: naturally, a client would prefer it if our device connected with a smartphone. Building in functionality like that means a lot of time spent in the development phase, reworking parts of the device.

Figure 1: The SenseCore pump technology.

"I generally believe that the demand for pumps that patients can use easily by themselves will rise quickly. The therapies that make this possible are also growing quickly. The old kinds of pumps, that aren't reusable or disposable, have become far less lucrative for manufacturers to produce."

AP: For me, in principle nothing has changed. The environment built itself up. There is one difference: today, there is an insulin patch pump on the market that stands as a benchmark. Ten years ago, that was not the case.

MD: The biggest change occurred in the organisation overall, when we began to focus more on developing a product rather than developing a technology. There are always new technologies we could implement in our project. The question then becomes to which degree and for which reason do we implement them.

Q Has digitalisation made things simpler?

CL: In my area digitalisation has a lot to do with the theme of "requirement management", which really started coming up around 10 to 15 years ago, and today is "state of the art". In 2012, we introduced a tool to answer this. Without this programme, our work wouldn't be efficient; each component and interface needs to develop and follow its own requirements. It also means, though, more time spent, since traversing this extensive database isn't trivial. Maintenance is needed and people need to be trained to use it – it demands a different way of working.

Figure 2: The SensePatch body worn pump is suitable for volumes up to 20 mL.

AP: These changes are visible in many different areas. You always have access to the workplace, even from home. It makes work both faster and easier. I see the cost more in insecurity than in documentation, in the sense that, to do everything correctly, you have to fundamentally alter existing processes. Also, our paper filing system couldn't to keep pace with our digital one. Today, you can send a manufacturer an electronic CAD model, which might be correct only in the sense that it could be manufactured, and you can get a finished part back – that's a big advantage.

MD: In the medical technologies sector, we have always had to deal with lots of documentation. There are new tools that do so much and open up so many opportunities. For example, now it's not just physical models, but also simulations. Today, work goes faster. On the other hand, doing everything on the computer generates massive amounts of data, and that brings with it its own questions – for example, how to handle the data and make it easily accessible.

Q How has your field changed in the past few years?

CL: At Sensile Medical, systems engineering is a new development. This work demanded a change in the previous development process. Originally, our approach stemmed from one used in the aerospace sector, but it works well

Figure 3: The SenseLyo automated reconstitution device is compatible with a variety of reservoirs.

for our devices, too – fundamentally because both approaches try to create synergy in a system with an incredibly diverse set of interdependencies. It also helps strengthen workplace synergy – each coworker helps in the development of our device architecture. It's a joint effort, but with this system, everyone knows exactly what he or she is responsible for.

AP: In my opinion, leading a project focuses more on co-ordinating jobs. The project leader lets teams work independently for the most part, since teams should have the ability and experience to do so. As far as my experience goes, this isn't always the case – often, the project leaders are more experienced than their coworkers. I think this is because five years ago employers demanded more expertise from their project leaders.

"One clear trend is the move towards digital health or smart devices that can transmit information to the patient and/or the patient's doctor so that the correct medicine can be given."

MD: Fundamental research was the first thing we did. The technology itself stood in the foreground, and we really only produced sample pieces of our technology until we got our first project. Then, all of a sudden, with the first project the focus changed from technology to adaptation of the technology in terms of how it applies to a device. Now as Sensile receives even more projects, this transformation – from a company that produces a technology to a company that produces a product – affects Sensile at all levels.

Q In which direction do you see your industry moving in the future?

DB: One clear trend is the move towards digital health or smart devices that can transmit information to the patient and/or the patient's doctor so that the correct medicine can be given. The theme of connectivity will develop further, and we need to make certain that we keep up with it.

AP: I generally believe that the demand for pumps that patients can use easily by themselves will rise quickly. The therapies that make this possible are also growing quickly. The old kinds of pumps, that aren't reusable or disposable, have become far less lucrative for manufacturers to produce. I'm convinced that we have a great concept for our pump – both our reusable and disposable unit.

MD: The medical technologies sector doesn't change quickly, since in a highly regulated industry everything takes so much time. There is a trend, though, that devices need to meet a certain set of requirements: that they get smaller and that they look more stylish, so that they stop being recognised as a medical device and start being seen more as a gadget or lifestyle product. Of course, the influences on the industry are myriad. What would happen if someone invented an insulin pill? Would we still need a pump? And what if ObamaCare is repealed?

Q What has kept you at Sensile for ten years?

DB: My motivation comes in principle from improving the lives of patients. To create the right product for a therapy and then to bring that product to the patients – all of that motivates me. The road from start to finish is such an interesting one. My coworkers at Sensile are also great; each one is really an integral part of the entire process.

CL: I saw the chance to build something here, and I accepted that that would be a longer-term project. Looking back, the development has been very positive, especially considering that we started at nothing and have already achieved so much. The best part – nothing has been boring at Sensile. And the experience I've had here is not something I could have got anywhere else.

MD: I like my job. There are always new challenges and new opportunities. Sometimes, you have to develop something new and then, looking back, you realise you should have done it that way all along. Processes always need to be adapted, which can be a little tiresome. Still, I find it positive, the sort of insight I've got here and the lessons I've learned. Not just in my sector, either – I've also had the chance to apply that to other branches of the company when I support their efforts.

AP: There are few undertakings that combine so many disciplines and technologies in one product. We have the opportunity to be a pioneer in our field and to build a product from the ground up. We are a very agile company; whatever the customers need, we can adapt to meet their demands. In my case, I appreciate the scope of our business a lot. I'm very involved in development but am also in constant contact with manufacturers, suppliers and clients. It's a rich environment with inexhaustible possibility, and in a field like that, there is never a dull day.

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THE CHANGING DRUG DELIVERY PARADIGM

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

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

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

LIMITATIONS OF CONVENTIONAL DELIVERY SYSTEMS

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

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

This trend poses a fundamental problem with two possible

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

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

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

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

WEARABLE INJECTORS PRESENT A SOLUTION

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

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

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

THE VALUE OF EXPERIENCE

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

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

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

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

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

BD LIBERTAS™, THE NEXT GENERATION OF WEARABLE INJECTORS

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

Simplicity in Design

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

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

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

Pioneering Injection Research

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

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

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

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

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

Integrating Trusted Components

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

Benefits of Mechanical Systems

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

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

Customisation Options

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

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

Flexibility to Become "Smart"

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

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

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

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

SUMMARY

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

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

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

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

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

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BD Libertas™ wearable injector

BD Libertas™ wearable injector with Smart option

Learn more at bd.com/Discover-BD1

BD Libertas™ wearable injector, BD Libertas™ wearable injector with Smart option and BD Intevia™ autoinjector are products in development; some statements made are subject to a variety of risks and uncertainty.

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REDUCING THE COMPLEXITY OF LARGE-VOLUME SELF-INJECTION FOR PHARMA COMPANIES & PATIENTS

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

MARKET REQUIREMENTS FOR WEARABLE INJECTORS

Larger-volume injectable drugs are in pharmaceutical development and being considered for the treatment of auto-immune diseases such as rheumatoid arthritis, psoriasis and IBD/Crohn's disease. Looking into the future their demand will be further increased by new drugs for treating diseases like migraine, asthma and dermatitis, and immuno-oncology drugs as maintenance therapies for treated cancers.

General expectations for these drugs is that they will be dosed subcutaneously every two weeks, monthly or even less frequently; that they will be in the range 2-10 mL; and that the injection will require 5-15 minutes.[1] The longer time of injection compared with auto-injectors means that injection systems need to be worn on the skin during administration. And, a skin-worn wearable injector requires a different drug reservoir compared with an auto-injector. The need to maintain a flexible sterile fluid path and needle system between the drug reservoir and the skin means that a cartridge is the drug container of choice. Cartridges have known container closure integrity characteristics and utilise existing filling processes and infrastructure.

Wearable injector therapies will ultimately be competing against more frequent dosing based on standard prefilled syringe-based therapies. For pharma companies to consider and invest in wearable 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 wearable injector market to grow significantly over the coming years and establish itself as a third self-injection device class to complement the already well developed markets for pens and auto-injectors.

VOLUMES & VISCOSITIES: IMPACT ON THE WEARABLE INJECTOR

Biologics and antibody-based therapeutics have a large therapeutic window and allow the use of a fixed dose payload. This means, though, that often the overall dose and thus protein concentration is quite high, which influences drug stability and viscosity, drug processing and device injection forces.

The typical protein concentration of blockbuster biologic drugs is in the 50-150 mg/mL range and total payloads for a single dose may be high as 600 mg or greater. Examples of biotherapeutics with their concentrations and dose volumes are provided in Table 1.

There is also significant experience for therapies that require large payloads for systemic release such as the use of immunoglobulins for the treatment of immunodeficiency, and here up to 50 mL of antibody is infused using re-usable pumps and multiple infusion sets. Also, there is a general move to subcutaneous (SC) administration in order to reduce the higher proximal and

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Drug	Indication	Pharma Company	Dose / Volume	Concentration (mg/mL)
Adalimumab	Autoimmune diseases	AbbVie	40 mg / 0.4 mL	100
Etanercept	Autoimmune diseases	Amgen / Pfizer	50 mg / 1 mL	50
Trastuzumab	Oncology	Roche	600 mg / 5 mL	120
Evolocumab	Hyperlipidaemia	Amgen	420 mg / 3 mL	140

Table 1: Examples of biologic drugs, with their doses and concentrations.

> "Being able to accommodate different flowrates and viscosities within a wearable injector platform requires a reliable and flexible drive mechanism."

physical administration costs associated with other routes of administration such as intravenous infusions.[2]

Our recent interactions with big pharma companies active in the auto-immune and oncology therapeutic areas confirm that the 2-10 mL SC injection is the most likely volume range for wearable injectors. Whatever the type of SC therapy, there are a number of references confirming the overall injection flow rates are in the 0.33-1.00 mL/min range. Examples include: immunoglobulins that are injected in the 20-30 mL/hr range or 1 mL / 2-3 min; 3 mL of evolocumab is injected in 9 min; and 5 mL of trastuzumab containing hyaluronidase is injected at approximately 1 mL/min.

Being able to accommodate different flowrates and viscosities within a wearable injector platform requires a reliable and flexible drive mechanism. This is why YpsoDose (see Figure 1) incorporates a standard electromechanical drive that provides the necessary forces capable of achieving the maximum flowrates of 1 mL/min at high protein concentrations.

WEARABLE INJECTOR NEEDS

Developing and designing a wearable patch injector is demanding and requires a broad range of technology and medical device know-how. Ideally, the wearable injector, which is used less frequently, should be as easy to use as a disposable two-step auto-injector, which means it needs to incorporate the following key technical features:

- Prefilled and fully disposable to remove any need to assemble the drug reservoir and device
- Easily adhere to the skin during injection; and be easy to remove after injection
- Automatically insert the injection needle at the start and retract or shield the needle at the end of the injection process.

In order to be truly versatile and easy to use, the device also needs to be able to deal with the following aspects:

- Cover a range of fill volumes and viscosities and provide a reproducible injection time per drug
- Recognise that the device is only ready to inject when attached to the skin
- Communicate clearly with the patient via advanced audio and visual signals before, during and after the injection
- Offer wireless connectivity for additional services.

REDUCING COMPLEXITY FOR PHARMA WITH A READY-TO-FILL FORMAT

The wearable patch injector features and aspects just listed are covered by YpsoDose's electromechanical systems. But particularly important is the ability to prefill the drug reservoir and incorporate the sterile unit into the device in a simple and robust way.

Being prefilled and fully disposable, and to remove any need for the patient to assemble the drug reservoir, the device requires a bespoke fluid path which, in the case of YpsoDose, is provided by the Needle Unit. The Needle Unit can be compared with the staked needle and rigid needle shield of a prefilled syringe. But, 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 Needle Unit and cartridge are pre-assembled in a terminally sterilised tub format (Figure 2, next page) to provide an intrinsically stable ready-to-fill unit which is compatible with existing filling equipment.

Ypsomed is working closely with cartridge component manufacturers, filling equipment and contract filling specialists to make sure that generally available and standardised cartridge components are utilised in this bespoke ready-to-fill format. The cartridge, being a well characterised container closure system, does not interact with the rest of the injector until the actual time of injection.

USABILITY ASPECTS: PATIENT INTERFACE, 2-STEP WEARABLE, PATCH AND INJECT

Ultimately, if wearable injector therapies are going to be adopted widely for biological therapies, usability is the most important aspect that needs to be successfully tested with patients. Current systems are generally filled or assembled by the healthcare

Figure 1: The YpsoDose prefilled large-volume patch injector platform.

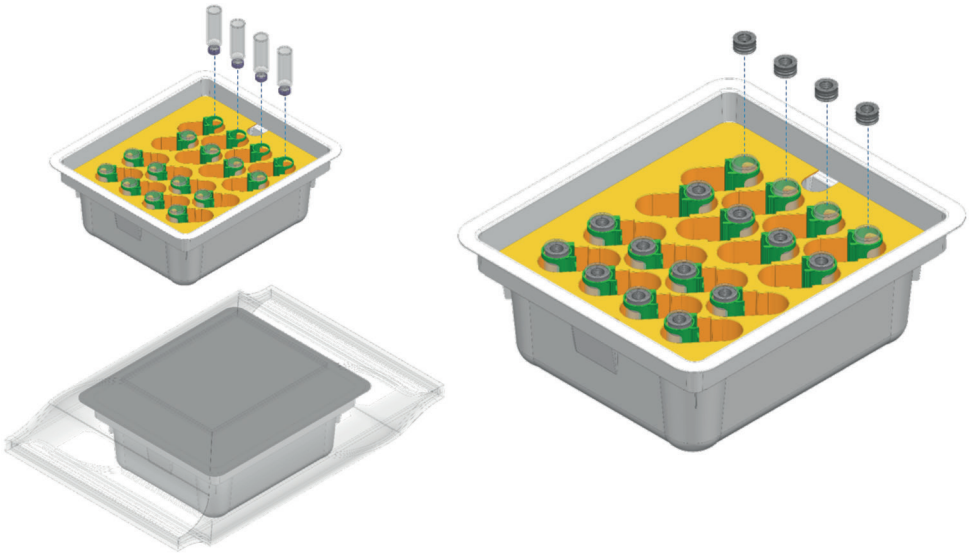

Figure 2: Cartridge and Needle Unit in the ready-to-fill tub format. Left: Cartridge-Needle Unit assembly prior to EtO sterilisation. Right: Cartridge filling in ready-to-fill format.

"All-in-all the YpsoDose handling steps are like a two-step auto-injector: remove the cap and inject. For YpsoDose this is simply: patch and inject. All other steps are controlled by YpsoDose."

professional or patient. 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, and to minimise the number of steps required to perform the injection.

All-in-all the YpsoDose handling steps are like a two-step auto-injector: remove the cap and inject. For YpsoDose this is simply: patch and inject. All other steps 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 made safe and YpsoDose is ready for disposal or specialist recycling.

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

ABOUT THE COMPANY

Ypsomed is the leading independent developer and manufacturer of innovative auto-injector and pen injector systems for self-administration. The customisable product platforms cover auto-injectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pens that include automated injection mechanisms and easy-to-use injection devices for drugs in dual-chamber cartridges such as lyophilised drugs. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio. Ypsomed provides its partners with excellent technological expertise and full regulatory support for the device relevant aspects of the registration process.

"The skin sensor system is key to ensure that the injection can only be initiated once YpsoDose is correctly attached to the skin, and to minimise the number of steps required to perform the injection."

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 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 from 1979 to 1983, working initially in commercial roles for fermentation technology. He 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 auto-injector Custom Products for Ypsomed Delivery Systems.

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- Unique electromechanical drive system offers flexibility for a range of viscosities and fill volumes

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PUTTING PATIENTS FIRST: INNOVATING DRUG CONTAINMENT AND DELIVERY

Innovations in self-administered drug delivery systems are supporting care for a variety of medical conditions transitioning out of hospitals and clinical settings into the home. To ensure patient compliance with treatment is maintained, an easy-to-use self-administration system can be key. Chris Henshall, Senior Director, Strategic Marketing – Biologics, West Pharmaceutical Services, discusses the factors manufacturers should consider to ensure self-injected therapies meet patients' needs and therefore improve patient outcomes.

Increasingly, the biopharma industry is moving towards precision medicine, and a patient-centric approach to treatment along with a shift in healthcare costs being shared more evenly with the end user. Innovations in drug delivery are supporting care for a variety of medical conditions transitioning out of the hospital and clinical setting and into the home. This is good news for many patients with chronic conditions such as diabetes, multiple sclerosis, rheumatoid arthritis and haemophilia, who are now able to self-administer injections safely at home away from the traditional healthcare setting, and take a more active role in their treatment.

> "... the makers of injectable medicines must fully understand and incorporate the needs of end users when bringing a self-injected therapy to market."

While it is convenient for patients to self-administer medication, it can also be quite difficult to accomplish effectively. As a result, drug delivery systems that can support home use and aid in patient compliance, adherence and safety have rapidly evolved using new developments in technology such as wearable drug delivery injectors.

While wearable injectors offer a safe, reliable and effective method for at-home administration and improving potential patient outcomes, developing these new systems can pose a significant challenge for pharmaceutical manufacturers, i.e. how to design a wearable injector that patients not only can use, but also want to use.

To meet this challenge the makers of injectable medicines must fully understand and incorporate the needs of end users when bringing a self-injected therapy to market. This requires careful thought about how a medication will be administered by patients. As such, the design of an injectable medicine's delivery system is fast becoming an essential aspect of the manufacturer's go-to-market strategy. To be successful, however, it is important that pharmaceutical manufacturers consider several factors.

KEY FACTORS IN THE DESIGN OF SELF-INJECTION SYSTEMS

User Experience

The user experience is an extremely important element when designing a

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Figure 1: West's SmartDose® platform includes a Daikyo Crystal Zenith® cartridge with elastomer components using FluroTec® barrier film.

drug delivery system. With many chronic conditions on the rise, it is critical that the healthcare industry find ways to improve patients' ability and desire to maintain an appropriate self-care treatment regimen. The WHO reports that adherence rates for patients with chronic conditions are only approximately 50% in developed countries, and much lower in developing countries.[1]

While many products do provide systems that aid compliance reasonably well, a truly successful combination product must also consider the needs of the end user at a variety of stages during the patient journey. A diabetes patient, for instance, may transition through a variety of injection systems: from a syringe to an auto-injector and, ultimately, to a wearable pump.

Human Factors

When creating a delivery system, pharmaceutical companies and their drug delivery system partners must consider patient needs in conjunction with functionality along all stages of the patient journey. Drug makers stand a better chance of satisfying the needs of users if they bring the relationship between the delivery system design and the patient experience into the centre of the development process.

Human factors research, testing and analysis can provide a deeper view of the emotional needs and desires of users, and provide valuable perspective on features and visual cues. It can help manufacturers understand the nuances of where a delivery system is used and who is using it. This research can yield valuable insight into users' preferences and emotional requirements, which can then translate into feature sets and design elements of the drug delivery system before it goes on the market.

Additionally, while it is best to think about delivery systems during the initial development process, it is never too late to employ human factors analysis for drugs that have already cleared regulatory approval. Improved usability can be retrofitted into manual drug delivery systems that might not be faring as well on the market as they should – for example, adding ergonomic features for a self-injector to aid patients with dexterity issues – and help support product differentiation.

Figure 2: SmartDose® platform incorporates human factors and usability testing to deliver a truly patient-centric approach.

Figure 3: West's SmartDose® injector adheres to the patient's body, usually on the abdomen.

"The overall patient experience can be improved by careful consideration of patient-centric device design, human factors, the integration between a delivery system and its components, and effective education and onboarding."

Component Compatibility

The compatibility of a drug and its integrated delivery system is of utmost concern for all injectable drugs and particularly with biologics. Wearable drug delivery systems that effectively manage the interrelationship of a drug, its primary container and its administration system can help ensure the system functions accurately, effectively and reliably every time.

Many modern biologic formulations may be sensitive to silicone oil – used as a lubricant in glass syringes – or tungsten and, therefore, may require alternative packaging component materials such as cyclic olefin polymers. These can be attractive alternatives as they offer solutions to several drug delivery challenges, including break resistance, dimensional precision, consistent gliding forces, reduced extractables and leachables. They also minimise the risk of drug-container incompatibility due to the impact of silicone oil and tungsten on drug stability and protein aggregation. Additionally, polymer-based syringes can provide dimensional precision and strength, which can be significant factors when combining a syringe with a spring-based auto-injector.

Wearable Drug Delivery Systems

While prefilled syringes have been common drug delivery systems for many injectable medicines for years, some patients either don't want to inject themselves with medications in prefilled syringes, or their conditions make it difficult for them to do so. Additionally, for some injectable medicines with higher-volume doses, it can be hard to administer the drug consistently via a prefilled syringe. Furthermore, some drugs – including many new biologics – might require large volumes of viscous solutions, making a single-dose option either difficult or impossible.

Wearable auto-injectors are quickly becoming popular choices for delivering therapies for chronic conditions. They are convenient and easy to use, can eliminate the need for patients to measure dosages and can help prevent the risk of needlestick injuries. One example is West's SmartDose® platform (Figures 1 & 2) – a wearable, subcutaneous injector with an integrated drug delivery system that incorporates human factors and usability testing to deliver a truly patient-centric approach to self-administration.

The single-use SmartDose® injector adheres to the patient's body, usually on the abdomen (Figure 3), and is pre-programmed to deliver high volumes of viscous or sensitive drug products. The SmartDose® platform includes a Daikyo Crystal Zenith® cartridge with elastomer components using FluroTec® barrier film. It is ideal for silicone-sensitive biologic formulations. Additionally, it offers connectivity to a variety of software platforms.

Onboarding

Another critical consideration for self-administration is how the patient will learn to use the self-injection system. New patients with self-injectors often make errors in administration. One reason

> "Multisensory, comprehensive, human factors-based educational and training programmes for drug delivery systems can reduce patients' anxiety and the risk of administration errors."

for this is that many patients do not thoroughly read the steps outlined in the Instructions for Use document prior to beginning drug treatment. This can potentially lead to administration errors and may impact a patient's compliance with a prescribed therapy.

Pharmaceutical and drug delivery companies should therefore consider and plan for patient education and onboarding in the development phase. Multisensory, comprehensive, human factors-based educational and training programmes for drug delivery systems can reduce patients' anxiety and the risk of administration errors.

Encouraging Adherence

Even with proper education and onboarding it can be difficult for many patients to stay motivated to stick with their prescribed treatment regimen. To address this issue, West has collaborated with HealthPrize Technologies (Norwalk, CT, US) on a connected health offering that rewards medication adherence using unique gamification technologies.

HealthPrize's Software-as-a-Service (SaaS) medication adherence and patient engagement platform is integrated within West's injectable drug delivery systems, providing an end-to-end connected health solution for pharmaceutical companies and patients. The combined offering provides electronically-connected drug delivery systems that track when patients take their medication, educates and engages patients to increase their medical literacy and foster adherence, and rewards them for compliance with their prescribed regimen. By offering education and rewards-based self-injection systems, West and HealthPrize aim to motivate patients, boost medication adherence and help improve patient outcomes.

Partnering for Success

While there are numerous self-injection systems on the market, pharmaceutical companies need forward-thinking drug packaging and delivery system partners that anticipate and address the needs of end users and the requirements of new sophisticated therapies for chronic conditions and can help develop the right system for their injectable drug product.

It is important for drug makers and their partners to have conversations at all stages of the development process about how to impact patient outcomes positively.

CONCLUSION

The overall patient experience can be improved by careful consideration of patient-centric device design, human factors, the integration between a delivery system and its components, and effective education and onboarding. Advanced self-administration systems that incorporate these essential elements can help improve the overall value and effectiveness of a drug product, and may drive down healthcare costs by helping to keep patients on their medication plans and avoiding health problems associated with non-compliance.

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 2016 sales of US$1.5 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.

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ABOUT THE AUTHOR

Chris Henshall leads the strategic marketing efforts in global biologics for West. In this role, he is responsible for the development and delivery of strategic and operational commercialisation plans across the biologics portfolio. Working in partnership with the sales and customer-facing teams and other functional leadership, Mr Henshall drives performance, ensuring the success of West biologics is optimised for both the short and long term, securing organisational alignment from strategy through execution.

Mr Henshall has a wealth of pharma and biotech experience across his 20 plus years in the industry. He has led and launched multiple brands in his career both domestically and globally. He is an entrepreneur at heart who brings a new dimension to the team with his diverse background and unique blend of professional experience.

Mr Henshall is a native of South Africa where he received his undergraduate degree. He now lives permanently in the US, where he also received his MBA.

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TriboFilm Research, Inc.

HOW LUBRICANT CHOICE AFFECTS DOSE ACCURACY IN INSULIN PUMPS

The development of fully automated, closed-loop glucose monitoring and insulin delivery systems can significantly improve patients' quality of life by closely mimicking a real pancreas. However, since the patient is not directly involved in administering the dose, these devices depend on one key factor - dosing accuracy. One wrong dose can be fatal. Here, Jackson Thornton, Associate Director of Research, and Vinay Sakhrani, Vice-President, Technology, both of TriboFilm Research, examine how lubricant selection in the insulin cartridge, which is typically an afterthought, can make the delivery device more accurate. They also look at how lubricant choice affects dosing accuracy using a "real-patient simulation" test method.

Insulin pump therapy is considered the gold standard of care for insulin-requiring diabetic patients. An insulin pump provides glucose control by subcutaneously delivering fast-acting insulin to the patient in a programmed sequence that mimics the pancreas. In addition to the clinical benefits of glucose control, insulin pumps can improve the quality of life for patients with diabetes by eliminating the need for multiple daily insulin injections.

The US FDA recently approved the first "artificial pancreas" for diabetes treatment, which wirelessly links an insulin pump to a glucose monitor using a closed-loop control system. To achieve closed-loop control, the insulin pump must accurately deliver the dose requested by the control unit on short timescales.

Accurate dose delivery becomes problematic when the device flow rate changes throughout the day – such as when mimicking a healthy pancreas that reacts rapidly and precisely to changing amounts of glucose in the blood stream. Rapid infusion start-up and precise delivery at low infusion rates are critical to ensure patient safety and maintain the integrity of the feedback control.

This publication examines how improving the frictional properties of pump components, particularly the lubricant in the insulin container closure system, impacts infusion pump response time and leads to superior pump operation.

The current insulin reservoir lubrication methods and testing standards used to evaluate pump operation are insufficient for the new artifical pancreas devices. Thus a next-generation lubricant coating and test set-up were used to evaluate the dose accuracy of a pump using a realistic insulin delivery profile.

"Lubrication is usually an afterthought when drug delivery systems are designed. However, the lubricant is an integral system component that facilitates the movement of the plunger through the barrel of an insulin reservoir."

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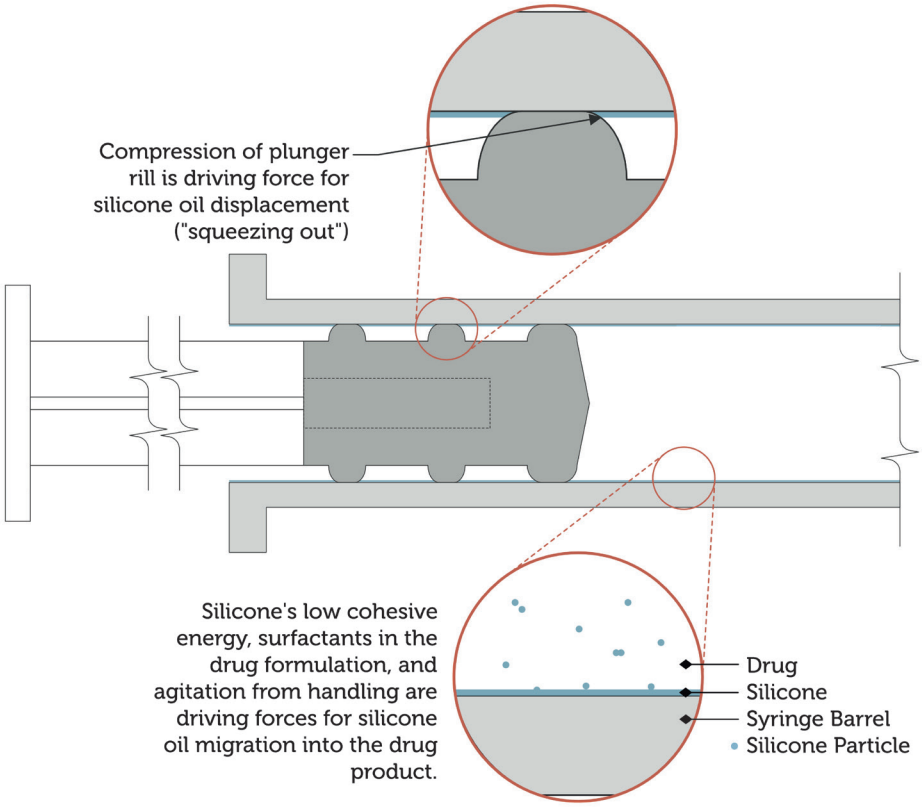

Figure 1: Silicone oil, the most commonly used pharmaceutical container lubricant, can easily be displaced by the plunger, leading to stick-slip.

LUBRICATION IN INSULIN INFUSION PUMPS

Most insulin infusion pumps use a container closure system, which consists of a 3 mL plastic or glass cartridge that is filled with insulin and sealed using an elastomer plunger. The pump drive mechanism pushes the plunger to deliver insulin to the patient through a subcutaneous cannula. Insulin is delivered in small, discrete pulses, where the volume of each pulse and the time between pulses dictates the time-averaged insulin infusion rate. The container closure system must be lubricated to ensure proper movement of the plunger through the cartridge.

Lubrication is usually an afterthought when drug delivery systems are designed. However, the lubricant is an integral system component that facilitates the movement of the plunger through the barrel of an insulin reservoir. Silicone oil, the most commonly used lubricant, can easily be displaced under the compressive loads exerted by the slow-moving plunger. The displacement of silicone oil leads to "stick-slip" plunger movement, dosage inaccuracies due to plunger compression and sub-visible lubricant particles in the drug medium (see Figure 1).

TriboFilm Research has developed a unique atmospheric gas plasma technology that immobilises a lubricant onto the surface of a drug container. This immobilisation prevents the lubricant layer from being displaced by the plunger seals and maintains a stable, low-friction surface for the plunger to glide along while maintaining the container closure integrity.

TriboFilm's technology – originally developed under a grant from the US National Institues of Health for prefilled syringes – has shown huge improvements over traditional silicone oil lubricants for syringe force profiles as well as a reduction in sub-visible lubricant particles in the drug medium. Given the success of this lubricant coating in prefilled syringes, an insulin pump manufacturer asked if the coating could improve pump performance.

COMPARING LUBRICATION SYSTEMS

The aim of this article is to highlight the effects of lubrication in pump applications and demonstrate how plunger forces affect pump response time and dose accuracy. The customer's infusion pump was mimicked using commercially available 1 mL long cyclic olefin polymer (COP) syringes with butyl rubber plungers. A Zwick universal testing machine was used as the pump drive mechanism, which also measured the force required to advance the syringe plunger.

A comparison of lubrication systems was performed between silicone oil, the industry standard syringe and cartridge lubricant; and TriboGlide DS®, a silicone-free immobilised lubricant. The syringes were filled with purified water to represent insulin, and attached to a time-stamped microbalance using an infusion tube and cannula. Water was dispensed through the tubing and into a beaker on the microbalance with a thin film of paraffin oil on top to prevent evaporation of the water. Weight readings were recorded every 10 seconds so that pulse-to-pulse variability could be analysed. A schematic of this test set-up is shown in Figure 2.

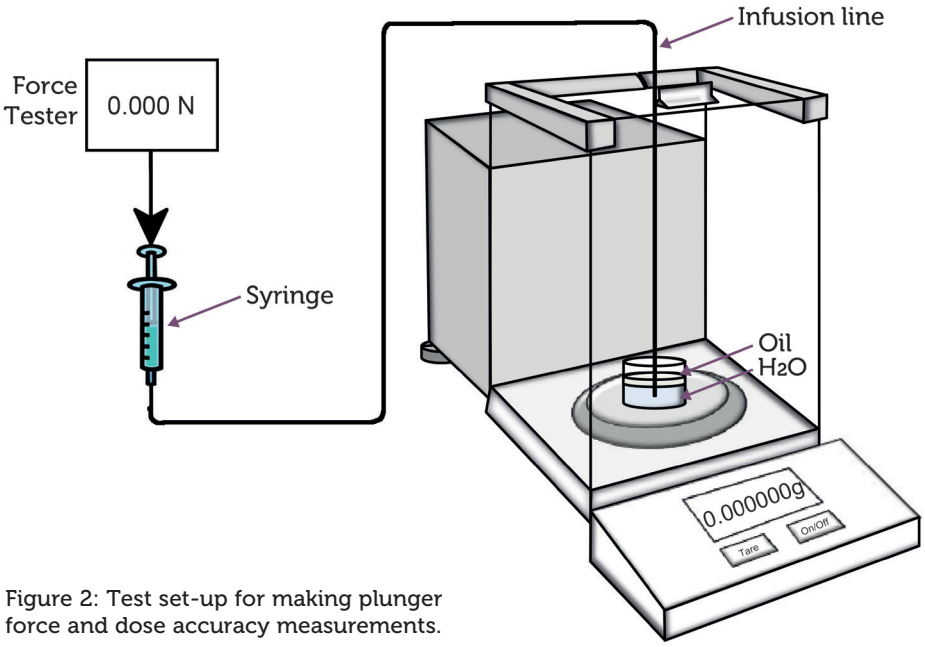

Figure 2: Test set-up for making plunger force and dose accuracy measurements.

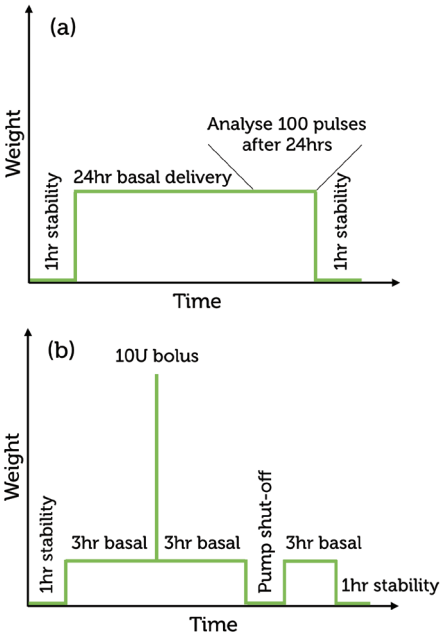

Figure 3: (a) Dispensing profile for the international standard EN 60601-2-24, which uses a 24-hour stabilisation period at the basal dose, followed by analysis of 100 pulses; (b) modified dispensing profile used in TriboFilm's study to simulate a realistic dosage scenario for a diabetic patient.

MEASUREMENT OF DOSE ACCURACY

Currently, insulin pump manufacturers specify ±5% delivery accuracy using methods established in the international standard EN 60601-2-24. The standard calls for a 24-hour stabilisation period followed by the measurement and averaging of 100 consecutive pulse deliveries as shown in Figure 3a. Averaging over many pulses after a 24-hour stability period provides limited information about the initial pump start-up, accuracy of the individual pulses and quick response to changing dose requirements, all of which have become increasingly important as the industry moves toward an artificial pancreas. Thus, the EN 60601-2-24 standard may provide misleading results for an insulin infusion pump.

Tests were performed using the EN 60601-2-24 standard (data not shown), and as expected, both the silicone oil and TriboGlide-DS® coated syringes passed. This data can be found on our website at tribofilmresearch.com/doseaccuracy. However, an insulin pump will also deliver several bolus doses throughout the day based on the needs of the user, along with extended periods of basal delivery and complete pump shut-off in emergencies – and thus it never experiences a 24-hour stabilisation phase.

"An understanding of how plunger forces affect infusion pump dosing accuracy provides tremendous benefit for improving device function."

To improve on the testing method and provide more suitable data for artificial pancreas devices, the standard testing sequence was modified to simulate a realistic dose scenario for a diabetic patient as shown in Figure 3b.

TriboFilm Research developed a real-patient simulation standard to mimic how diabetic patients use their pumps. Like the international standard, this test method delivers a constant basal phase but in this test method the basal dose is broken up by a mealtime bolus and pump shut-off. These two additional features are used to evaluate how changes in the pump delivery rate affect the plunger force and dose accuracy. For the real-patient simulation, the pumping sequence had five distinct segments:

1 **Basal period 1:** Dispense 0.05 IU pulses every three minutes for three hours while the patient enjoys some afternoon shopping.
2 **Mealtime bolus:** Provide a 10 IU mealtime bolus prior to eating dinner with friends.
3 **Basal period 2:** Continue with the 0.05 IU basal dosing for three hours after dinner while getting ready for bed.
4 **Pump shut-off:** Stop the flow of insulin due to a hypoglycaemic event during sleep.
5 **Basal period 3:** Continue with the 0.05 IU basal dosing once blood glucose returns to an acceptable level.

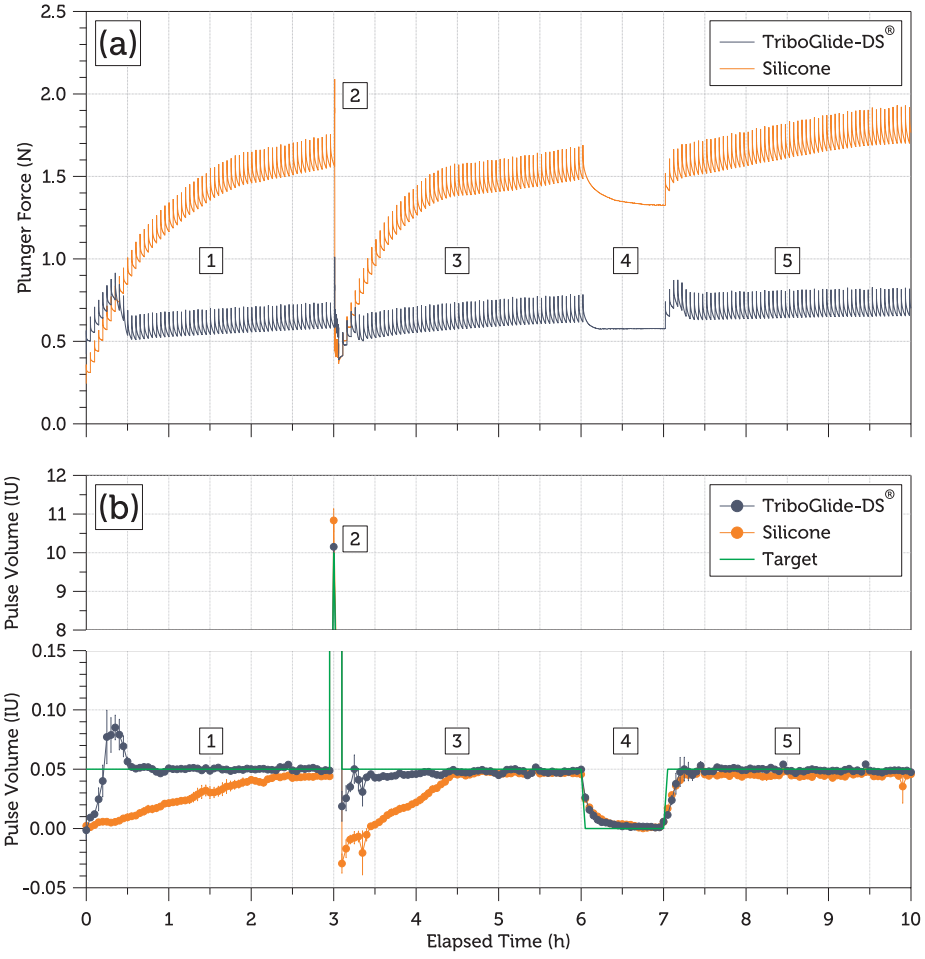

Figure 4: (a) Plunger force versus test time and (b) individual pulse volume versus test time for the realistic pump profile. The five different pump regions are labelled on the plot where [1, 3, and 5] correspond to basal delivery, [2] is a mealtime bolus and [4] is a pump shut-off.

RESULTS

The plunger force *versus* time and individual pulse volume *versus* time for the real-patient simulation is shown in Figure 4. Each plotted data series is the average of 10 measurements. The five segments listed above are readily distinguished in the figure, and observations of these regions are described in Table 1.

The results in Figure 4 are attributed to the effects of plunger compression. Whenever an elastomeric sealing member is used to dispense fluid – such as the plunger in a syringe or cartridge – there is the potential for compression of the plunger, which can store unwanted stresses. A free lubricant, such as silicone oil, will be displaced from

Observation	Implications/Notes
1. **Basal period 1:** As the plunger transitions from static to dynamic friction conditions, the TriboGlide DS® syringes underdeliver the target volume for the first 15 minutes and then compensate by an equal overshoot for the next 15 minutes. At the 30-minute mark the cumulative amount delivered by TriboGlide DS® syringe is 95% of the target volume. Following this initial peak, the system delivers the target volume. The silicone oil-lubricated syringes underdeliver for over two hours while compressing the plunger and accumulating stress. After two hours, the plunger continues to move forwards in a stressed state. At the end of the first 30 minutes the silicone syringe only delivers 10% of the cumulative target dose.	Stress retained in the plunger causes severe deviation in the delivery targets for silicone oil-lubricated syringes. The displacement of the silicone oil due to plunger compression causes frictional forces to rise, leading to under-delivery of the target dose.
2. **Mealtime bolus:** A spike in force, followed by relief of the built-up stress in the plunger is observed during the mealtime bolus. The TriboGlide DS® lubricated syringes require 50% less force than silicone oil-lubricated syringes and the stress release is minimal because there was not much accumulated stress. With the silicone oil-lubricated syringes, all the plunger compression stress built up during the basal dose in step 1 is relieved causing an overshoot in bolus delivery by almost 1 IU. Following this bolus dose the plunger force returns to its pre-stressed state.	The lower force requirements for TriboGlide-DS® lubricated syringes can allow a smaller battery to be used for a pump, ultimately resulting in a smaller form factor. Additionally, the improved dose accuracy with TriboGlide DS® would improve patient safety.
3. **Basal period 2:** After the mealtime bolus, the basal phase continues where the TriboGlide DS® coated syringes remain at the steady state force observed before the bolus delivery, and the silicone oil-lubricated syringes require another two hours to return to equilibrium. The delivery accuracy results mimic the plunger forces.	Since all built-up stress in the silicone oil-lubricated syringe was released during the previous bolus, the plunger begins to compress again and accumulates stress which leads to severe under-delivery. This is attributed to slip-stick behaviour.
4. **Pump shut-off:** A pump shut-off occurs after the second basal period for one hour. Both lubrication systems significantly reduced fluid output within a few minutes when the pump sequence was halted. The plunger force for TriboGlide DS® returned to initial levels immediately. However, the silicone oil-lubricated syringes remained at a higher force level – retaining the stress in the plunger seals.	The retained stress in the silicone oil-lubricated syringe has the potential to deliver an unwanted bolus if the plunger decompresses due to an accidental mechanical shock to the pump. The potential for an unwanted bolus, especially during a hypoglycaemic event, is a liability for the device as it could be harmful to the patient and lead to a product recall.
5. **Basal period 3:** The third basal delivery continues for three hours after the pump shut-off with both syringe lubricant types remaining in the steady state of force that they were in prior to pump shut-off. The final basal dose is delivered at the 0.05 IU target very quickly for both syringe types.	While both systems show similar accuracy during this segment, the plunger in the silicone syringe advances at an elevated force level indicating that it is stressed.

Table 1: Observations of the five segments of the real patient simulation testing set-up.

Region	Target	Silicone Oil		TriboGlide-DS®	
	Net Volume (IU)	Net Volume (IU)	% of Target	Net Volume (IU)	% of Target
Basal 1	3	1.65	55%	**2.98**	99%
Bolus	10	10.84	108%	**10.15**	102%
Basal 2	2.95	1.82	62%	**2.69**	91%
Shutoff	0	0.11	N/A	**0.10**	N/A
Basal 3	3	2.65	88%	**2.88**	96%

Table 2: Total delivery volume dispensed versus target delivery volume for silicone oil and TriboGlide DS® lubricated syringes.

the plunger/barrel interface and the slowly advancing plunger will compress and plough through the silicone oil layer as it advances.

This is observed in the force curves where the silicone oil-lubricated syringes build up force for the first two hours while the plunger is compressing, and then plough along the barrel in the compressed state. This plunger compression and accumulation of stress leads to under-delivery of insulin for over two hours. In the case of the TriboGlide-DS® cross-linked lubricant, the coating is never completely displaced from the plunger/barrel interface and the plunger can glide on top of the lubricant layer. The TriboGlide-DS® coated syringes slightly underdeliver for the first 15 minutes as the plunger overcomes the static friction followed by compensating with an equal over-shoot for the next 15 minutes. Table 2 quantifies the delivery accuracy for both lubricant types in all five segments.

CONCLUSION

An understanding of how plunger forces affect infusion pump dosing accuracy provides tremendous benefit for improving device function. This study compared the force and dose accuracy of containers lubricated with traditional silicone oil and TriboGlide-DS®. Outcomes from the study include:

1. The TriboGlide-DS® lubrication system significantly reduced the plunger forces compared with traditional silicone oil. Lower forces require less battery power, which can reduce the size and weight of the overall device. Smaller form factor is a competitive advantage in the wearable insulin pump market.
2. A reduction in forces also allowed for significantly faster response time for the infusion pump to deliver the desired dose accurately. Faster response times will improve the feedback control for closed-loop artificial pancreas systems. Dose accuracy is crucial for the next generation of automated insulin delivery devices.
3. Higher plunger forces in silicone oil-lubricated syringes led to stress build-up and compression of the plunger for hours before equilibrium was achieved. If the pump were jarred accidentally, this stress could be released and dispense an unwanted and potentially harmful bolus to the patient. The lower forces and retained plunger stresses with TriboGlide-DS® reduce liability and recall risk resulting from unwanted boluses being administered to patients in a completely automated delivery system.
4. A modification of the standard dose accuracy test method was developed to show how realistic changes in the dosing rate throughout the day would affect the accuracy of a pump. We believe that the current standard does not require the precision and accuracy that will be needed as insulin delivery moves to a closed-loop automated system.

This research shows how the TriboGlide-DS® lubrication system provides a means to continue the trend of developing smaller, smarter and safer infusion pumps. However, this research is only the first step. We look forward to collaborating with the industry on the following issues:

- Working together to develop a new international standard that reflects the realistic usage of closed-loop insulin devices with integrated monitoring and delivery. In this article, we propose one possible starting point for work on this standard. More work will be required to define a comprehensive standard for a fully automated smart pancreas device.
- Replicating these tests on custom insulin delivery devices and improve dose accuracy and device performance even further.

Our primary research mission is to improve patient safety and disease management through innovation. If your product can benefit from improved dose accuracy, we look forward to validating these test results on your specific device.

ABOUT THE COMPANY

TriboFilm Research, Inc, based in Raleigh NC, US, is a one-of-a-kind entrepreneurial research incubator that develops advanced technologies for pharmaceutical packaging applications. With extensive knowledge and experience in surface engineering, TriboFilm has focused its research efforts on one critical aspect of parenteral packaging: device lubrication.

With research grants from the US National Institutes of Health, TriboFilm has developed two advanced lubrication technologies: TriboLink-Si™ and TriboGlide-DS®. TriboFilm has established worldwide patent protection on both lubrication technologies, and licenses these patents to medical device and pharmaceutical companies in targeted fields of use. Our research facility contains state-of-the-art equipment for product development, performance testing and small-scale manufacturing. TriboFilm has all the tools, experience and expertise necessary to create turnkey solutions to even the most demanding of customer challenges.

ABOUT THE AUTHOR

Dr Jackson Thornton is the Associate Director of Research at TriboFilm Research. With a PhD in Materials Science from North Carolina State University, Dr Thornton's expertise in plasma chemistry, surface modification and materials testing is applied to help the largest pharmaceutical companies in the world, as well as start-up biotech and medical device makers. He helps them reduce friction, stiction and sub-visible particles, which in turn reduces product recall risk and improves patient safety.

Vinay Sakhrani is Vice-President of Technology at TriboFilm Research. Since founding TriboFilm in 1997 with National Medal of Technology Laureate and IBM Inventor, Dr Jerry Cuomo, he has advised companies ranging from big pharmaceuticals to start-up device makers.

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FROM VIAL TO WEARABLE INJECTOR

While auto-injectors are often the delivery method of choice for patient self-administration, there are occasions when a vial and syringe format is required. However, this method has a number of drawbacks such as risks of user error, dose inaccuracies and several challenging user steps. To overcome this problem, Medicom has developed a flexible, wearable patch pump which can accept a simple glass vial and provide a fully automated injection system. Directors of Front-End Innovation at Medicom, Hans Jensen, MBA, and Kate Hudson-Farmer PhD, MBA, explain how it works.

Although the vial is a well-established primary container for the delivery of injectable drugs – and is usually the quickest route to market – it is not without its drawbacks. This is particularly true for self-administered subcutaneously delivered drugs, and even more so for self-administered drugs that require reconstitution prior to injection.

Trying to promote a drug in a vial and syringe format against competition from a liquid form with a disposable auto-injector is not an easy task. The number of user steps in preparing and administering a drug product from a vial can be prohibitive to launching a new drug product, even if the drug is safer, more efficient and proven to have fewer side effects.

Healthcare professionals will, of course, assess the drug profile (efficacy, safety) and peer recommendations, in addition to personal knowledge and preferences. However, a growing number will also look at the capability of their patients to self-administer the drug – the simplicity of administration being an important factor in choosing a prescription. The many years of success for the simple-to-use auto-injectors, associated with some of the world's best-selling drugs such as Humira and Enbrel, is testament to this.

Recent user research carried out by Medicom with immunology specialists indicates that the majority clearly prefer to prescribe self-administered biologics to patients – primarily because patients do not need to go to a clinic for infusions or injections, but can administer them by themselves in line with their daily routines. The simplicity of the self-administration provided by auto-injectors is an important consideration, as making the task easier and less prone to medication errors is associated with safety, efficacy and patient adherence.

> "Being able to manage the lifecycle of a drug utilising the same primary container is a significant bonus to a pharma company from both a time and cost perspective."

THE CHALLENGE OF PATIENT SELF-ADMINISTRATION

Changing a drug into an auto-injector formulation, at least for the two drugs already mentioned, was not an overwhelming task despite some

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challenges, as the drugs were already approved in the pre-filled syringe used with the auto-injector. Being able to manage the lifecycle of a drug utilising the same primary container is a significant bonus to a pharma company from both a time and cost perspective.

But what if you have a drug product that has not progressed beyond the vial and you still want it to be provided in some form of self-injection system? And what if you do not want to go through all the time and cost associated with the regulatory aspects of changing the primary container? Or what if the volume is too large for delivery by auto-injector?

If the drug is lyophilised, it has to be reconstituted, usually manually by injecting a diluent into the vial and then transferring it manually to a syringe, often involving changing the needle to a thinner one before subcutaneous injection. Here it may be inserted manually into an auto-injector if the volume is relatively low, say below 1.5 mL, or injected into a reservoir in a wearable self-injection system for higher volumes. This all assumes pretty much immediate use of the drug, so that the in-use time for the injection system drug contact interface, is short enough to ensure only limited additional stability validation studies are needed.

On top of these complexities a further complication comes from repeat use of the vial. A number of drugs are provided in vials that contain a larger volume of drug than required for a single individual dose. These vials may be placed in the fridge in between use and the drug extracted using a syringe each time a dose is required, but the mandatory routines to administer manually remain nonetheless.

Figure 1: Pump set up to initiate reconstitution (upper picture) and after removal of vial and ready to be mounted on body (lower picture).

MEDICOM'S FLEXIBLE WEARABLE PATCH PUMP

The key inherent problems with the above scenarios relate to the risks of user error regarding correct reconstitution, risks of resulting dose inaccuracies and finally a challenging number of user steps requiring extensive patient training (and retraining). Therefore Medicom decided to develop a solution to these problems which would provide a more convenient and safe alternative to conventional manual practice (Figure 1).

Medicom's flexible, wearable patch pump is designed to accept a simple glass vial and provide a fully automated subcutaneous injection system, without any need for reformulation and/or repackaging of the drug. It consists of a reusable electronic control module which combines with a disposable drug module containing all components with drug or patient contact. It is equipped with an integrated needle that automatically inserts prior to injection initiation and is covered after dismounting. Furthermore, it builds on standard syringe formats for the interior reservoir to leverage opportunities such as allowing existing diluent to be preinstalled in its disposable module.

The combination of this is a platform that achieves a number of benefits (Table 1).

Through employing its novel and optimised electromechanical drive system capable of accurately controlling the plunger movement in both directions, diluent can initially be mixed with the lyophilised drug and subsequently the reconstituted drug transferred back into the syringe ready for injection. Depending on the specific drug properties, the user may be required to swirl the mixed substance manually as part of the reconstitution process and here the electronic pump module will help monitor and interpret or guide when sufficient physical agitation has been provided.

After visual control and confirmation, the pump will draw back the accurate amount of drug ready for injection. Additionally, a novel drive system supports a compact form factor, not least from a length perspective, whilst still using standard syringe sizes of up to 5 mL or even 10 mL.

If faced with a drug already formulated into a stable liquid, the system naturally also allows such liquid in a vial to be

Benefit	Associated Attributes
Automated preparation and dosing of lyophilised drug in vial	• Reconstitution of the drug in the vial is performed automatically preferably with diluent in pre-mounted prefilled syringe • Pre-set dosing back into syringe, e.g. patient adjusted • Automated needle insertion following pump mount on skin and activation • Pre-programmed dosing duration, e.g. patient controlled
Automated single or multiple dosing from liquid in vial	• Transfer of the drug from vial to interior syringe and subsequent injection etc. • Pre-set dosing volumes either pulling one single or several individual doses from a vial
Reduced regulatory time, risk and cost	• Standard vial and syringe and commercially available vial adaptor etc. • Intelligently automating already approved manual preparation and administration processes • Final pump system based on platform adjusted to specific patient population and dosing volumes

Table 1: Key benefits associated with Medicom's flexible, wearable patch pump.

Design Parameter	Device Details
Cost efficient	• Device consists of low-cost, disposable module and a higher-cost reusable electronic control module, allowing cost-efficient support of chronic diseases through reuse of expensive pump components • Low-cost disposable module contains all drug and patient contact components
Motor controlled electronic platform	• Bi-directional motorised plunger operation supports automated reconstitution process or simple withdrawal of drug product from a vial • Controlled and consistent injection speed and time (i.e. independent of temperature, viscosity, variability, inner needle dimension tolerances etc.) • Extended user interface opportunites (controls and feedback, e.g. audio, visual, tactile, user steps gudiance etc.)
Wearable	• Pump attached to body using adhesive during injection, e.g. for extended injection procedures • Integrated needle with automated insertion and post-injection needle protection • System optimised for medium to large subcutaneous dose volumes (e.g. up to 10 mL) • Due to a novel plunger interface system, the device length is kept minimal even with a standard syringe installed
Connected health	• Interface to connected health systems from reusable module • Detection of critical process parameters (e.g. orientation, temperature, occlusion etc.) to monitor and assist use • Link to specific app or other interface to enable patient engagement, learning, training

Table 2: Attractive features and functionalities of Medicom's flexible, wearable patch pump.

"Having a device that enables not only automated reconstitution of a drug, but also its transfer and injection administration, significantly benefits the user."

applied – it does not have to reconstitute a drug. It also allows partial transfer of the drug into the device, e.g. supporting an administration setting where the patient needs to withdraw a number of individual doses from a vial over a number of days. A vial could therefore be attached and part of the drug transferred to the device ready for injection. The vial containing the remainder of the drug can be stored between uses and reattached for another administration. This provides a solution addressing user errors associated with manual drug transfer to devices, in addition to wastage issues.

Furthermore, if during lifecycle management the drug should be reformulated into a prefilled syringe presentation, the pump will still be supportive as the prefilled syringe can be installed in the disposable pump module. The patient will be able to benefit from the easy administration but is completely free from even the minor complexities of handling the vial as part of the injection preparation – simply mount and activate the pump.

The split reusable and disposable platform offers a wearable, low-risk and low-cost approach with a wide range of flexible design opportunities to be optimised towards individual diseases and patient populations. These include the ability to optimise delivery of medium to larger volumes, adjust plunger speeds and dose volumes, supportive graphical user interfaces and safe needle handling etc. (Table 2).

APPLICATION OF CONNECTED HEALTH SERVICES

Apart from the advantages more directly related to drug preparation and delivery, a key aspect is the ability to add connected health features to the device. These could aid not only adherence monitoring, but longer-term patient engagement through the use of associated apps and other platforms that could assist with training, education and data transfer from and to the patient.

Services supporting self-administration with the device, such as reporting of symptoms and side effects, allow healthcare professionals to focus assistance and therapeutic intervention on patients who really need this.

CONCLUSION

Medicom's flexible wearable patch pump provides a range of key benefits that differentiate it from a market perspective. Having a device that enables not only automated reconstitution of a drug, but also its transfer and injection administration, significantly benefits the user.

Simply attaching the vial to the device and allowing the device to perform reconstitution and transfer cuts out the need for the user to engage with syringes, and particularly needles, and decreases the total number of user steps, as well as addressing potential reconstitution and transfer inaccuracies and risks. In addition, the fact that the vial remains the same and that standard components are used throughout the drug path – i.e. a prefilled syringe with water for injection – cuts down on both regulatory costs and time.

This makes Medicom's pump ideal not only for an initial launch device but also for the initial lifecycle management update of an already marketed drug in a vial indicated for patient self-administration.

ABOUT THE COMPANY

Medicom Innovation Partner (a Phillips-Medisize Company) is a leading global innovation, development and low-volume production provider focused on drug delivery devices and connected health solutions. Medicom Innovation Partner was established as a technology venture of Bang & Olufsen A/S in 1989 and the company has been a dominant player within the drug device world for more than 25 years. Medicom holds a dedicated staff of more than 90 high-calibre innovation specialists, mechanical, hardware, software, quality assurance, regulatory and production engineers based in Struer, Denmark, and Cambridge, UK. Medicom has experienced considerable growth over the last five years.

As of May 31, 2016, Medicom became part of Phillips-Medisize Corporation. Phillips-Medisize is a leading global outsource provider of design and manufacturing services to the drug delivery and combination products, consumable diagnostics and medical device, and specialty commercial markets. The company has annual sales of over US$700 million with 80% of the total revenue coming from drug delivery, medical device, primary pharmaceutical packaging and diagnostic products such as disposable insulin pens, glucose meters, specialty inhalation drug delivery devices, single-use surgical devices and consumable diagnostic components.

Together Phillips-Medisize and Medicom are becoming one of the leading players within the growing drug delivery device and connected health market.

ABOUT THE AUTHORS

Hans J Jensen has been with Medicom Innovation Partner, a Phillips-Medisize company, since 1991, and is responsible for managing Medicom's sales activities as well as managing front-end projects developing drug delivery device strategies and design concepts. He is an industry expert with more than 25 years of experience working with advanced electronic auto-injectors and connected health systems, wearable injectors and pharmaceutical markets and strategies.

Kate Hudson-Farmer is responsible for working with companies to develop drug delivery strategies and innovative solutions that improve patient outcomes and strengthen competitiveness. She has over 15 years' experience and has worked extensively at the front-end of drug delivery, in addition to conducting numerous strategic, technology and commercial consulting assignments across the pharmaceutical and medical device industry. She has held senior consulting positions, in addition to business development roles for both industry and academia.

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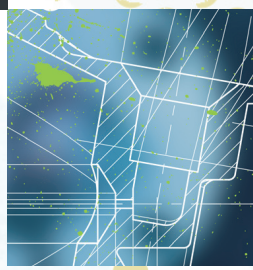

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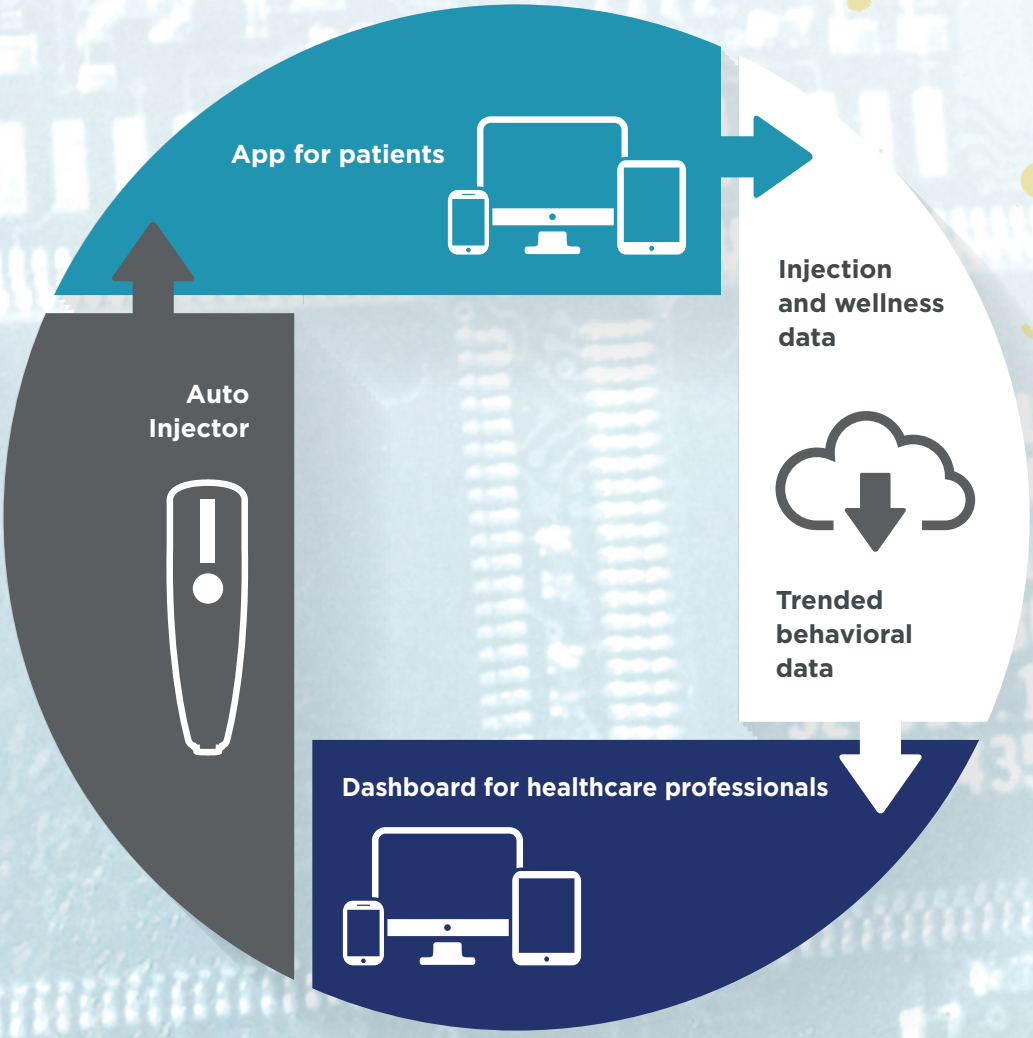

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DEVICE TRAINING AND ONBOARDING CONSIDERATIONS FOR ON-BODY DELIVERY SYSTEMS

New delivery systems for larger volume and more complex drugs, such as wearable injectors, are revolutionising patient treatment. However, research has shown that patients need to receive quality training and onboarding to ensure they use the devices properly and retain the information. Joe Reynolds, Research Manager at Noble, explores the factors that need to be considered in developing optimal training devices for patients.

While still a younger segment in the broader scope of health care 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. From its early origins in the 1980s and the US FDA's approval of Humulin, 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 6,300 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]

> "Research suggests that the strength and retention of training and treatment information increases through experience and repetition overtime."

In addition to serving as a strong base for future therapy, 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 the unmet patient, clinical and economic needs of society. While these medications have the potential to augment and enhance the prognosis of rare, debilitating and under-served conditions, novel approaches to drug delivery are often required to ensure that patients realise the full therapeutic benefits of these innovative compounds.

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, have historically been administered using pre-filled syringes, safety systems, injection pens, autoinjectors or other conventional device platforms. Over the years, these delivery devices have

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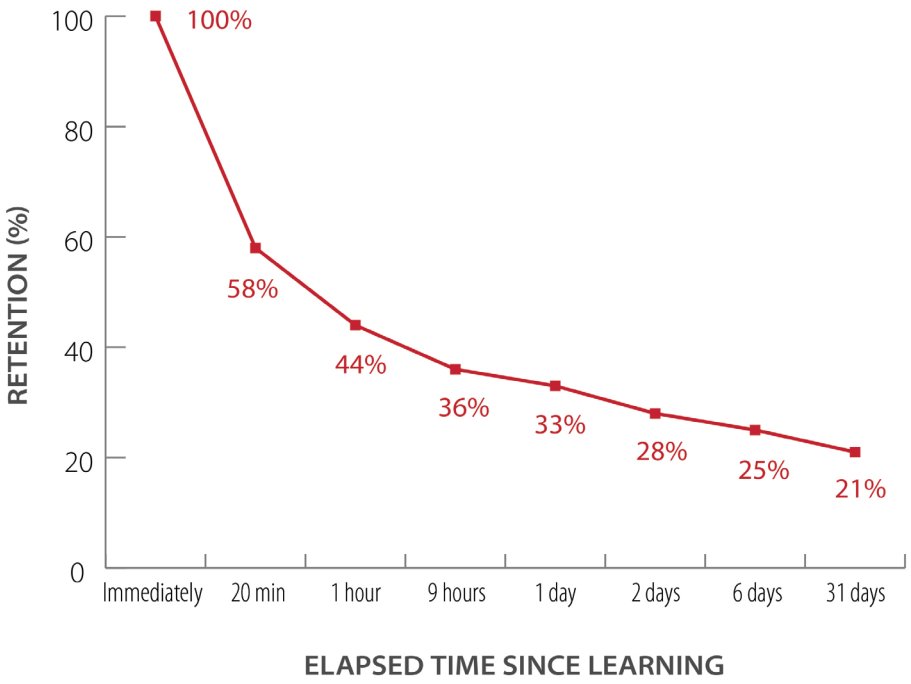

Figure 1: Forgetting Curve theory illustrating the decay in training and treatment information over time.

significantly improved user experiences and safety; however, they also present technical constraints and limitations for drug developers, particularly associated with dosing characteristics such as volume, concentration and viscosity.

WEARABLE INJECTORS

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 and importance of patient training and onboarding.

THE ONBOARDING PROCESS

Within healthcare and drug delivery, the onboarding process is commonly viewed as patients' first 30, 60 or 90 days of therapy and where their initial treatment attitudes and behaviours are first established. While the duration and key onboarding considerations vary across therapies, research suggests that the strength and retention of training and treatment information increases through experience and repetition overtime.

> "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."

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 supporting learning theories and methodologies to develop the most optimal training devices and onboarding experiences for patients of 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 manage their treatments confidently, 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, ensuring that every patient receives a consistent and meaningful onboarding experience.

DEVELOPING TRAINING DEVICES

Similarly 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.

External features

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 patients can familiarise themselves with the complete user interface and task flow.

Internal mechanics

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 for patients and other stakeholders. To accomplish this, human factors are taken into consideration throughout the design process to ensure

Figure 2: West Pharmaceutical Services Inc. 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]

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 maximises 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; however, internally it will be vastly different.

Adhesive simulation methods

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

Incorporating these features into reusable training devices requires careful consideration for sanitation, biocompatibility and other design trade-offs that must be evaluated when determining 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 forces may ramp up slowly while others have a fast onset for activation. Within the on-body market, there are also devices that have unique steps for loading, priming, unlocking and other functional features that need to be replicated by a trainer.

Other considerations include representing the audible and haptic feedback levels that are present and integrating tactile feel elements, such as subtle internal vibrations associated with drive elements. In addition to these items, along with the fact that it needs to be easily resettable versus 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.

NOBLE'S TRAINING DEVICE PORTFOLIO

To address the demand for this emerging market, Noble has developed a broad portfolio of on-body training solutions and platform technologies which can be leveraged by manufacturers to meet the onboarding needs of patients and other stakeholders. Designing the most optimal training device comes down to the unique needs of patients and other user populations.

Knowing this, Noble's development process and proprietary portfolio of multisensory, error detecting, wireless, smart and other technologies support manufacturers in prioritising requirements and developing solutions that maximise training value for patients and other stakeholders (Figure 2).

CONCLUSION

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-centered, 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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