WEARABLE INJECTORS

ON drugDELIVERY

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WEARABLE INJECTORS

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2017 Jan	Ophthalmic Delivery
Feb	Prefilled Syringes
Mar	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Devices Focus
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Front cover image, "Wearable injection device in position on the abdomen", supplied by Adhesives Research, Inc. Reproduced with kind permission.

CONTENTS

CORRECTION

In the July 2016 issue of ONdrugDelivery Magazine (Issue 69, "Novel Oral Delivery Systems"), on page 36, we stated that the Pharmaburst® ODT technology was from Catalent. This was incorrect since Pharmaburst® ODT technology is manufactured and marketed by SPI Pharma (Wilmington, DE, US). We apologise for this error, which has been corrected in live electronic versions of the publication.

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SENSILE MEDICAL

UNDERSTANDING THE MARKET FOR WEARABLE LARGE VOLUME INJECTORS

By Clare Beddoes, PhD

The injectable drugs and devices market is a dynamic and exciting sector to be involved in, and remains a healthy one. Globally, this market is continuing to grow, with recent forecasts estimating a compound annual growth rate (CAGR) of 13.2% over the next 10 years to reach approximately US$824 billion (£616 billion) by 2025.[1]

There are, of course, many different devices available to deliver injectable drugs, with new types being launched all of the time. Furthermore, many of these devices have been – or are being – developed specifically for patient self-administration. There are many factors driving demand for these devices, most of which have been written about before.

> "What will the addressable market for these LVI devices actually be? How many of the biologics coming through the pipeline will be formulated for SC delivery? How many of those SC formulations will be launched to market at volumes >2 mL?."

Wearable bolus injectors, also known as large volume injection (LVI) devices, represent a new and innovative sector within the injectable drug delivery market. They provide the opportunity to deliver large (>1-2 mL) volumes of drugs subcutaneously together with the many associated benefits this offers to drug developers, clinicians and patients.

Biologic therapeutics typically require parenteral (i.e. intravenous (IV), subcutaneous (SC), intramuscular (IM)) delivery, and high volumes per single dose are often needed. This particular group of drugs is growing; one-third of annual drug approvals are of biologics and there is a healthy pipeline of over 900 biologics in development.[2] It is this growth in the biologics market that is thought to be one of the key drivers that will forge the emergence of LVI devices.

The size of the market opportunity for LVI devices alone has been estimated at $8.1 billion by 2025, with over 50% of this driven by devices to deliver drugs for cancer and related conditions,[3] and indeed the biologics pipeline is dominated by oncology drugs (Figure 1).

Much is written about the market need for LVI devices, not only for delivery of high volumes, but such devices are also seen as a means of extending the lifecycles of drugs nearing the end of their patent life by, for example, reformulating from IV to SC.

But what will the addressable market for these LVI devices actually be? How many of the biologics coming through the pipeline will be formulated for SC delivery? How many of those SC formulations will be launched to market at volumes >2 mL? And what should LVI device companies focus on during development, to meet the requirements of the drug, the pharma companies and – perhaps most importantly – the patients?

It is of course not possible to predict accurately which drugs currently in development will be formulated for SC delivery in volumes requiring an LVI device. However, if we respond to predictions and focus for now on cancer, there are many challenges that device developers could face when considering a suitable solution, especially working on the premise that LVI devices are ultimately intended for patient self-administration of therapeutics.

This article doesn't claim to have all of the answers but aims to pose questions which will provoke thought, discussion and perhaps generate proposals for potential solutions.

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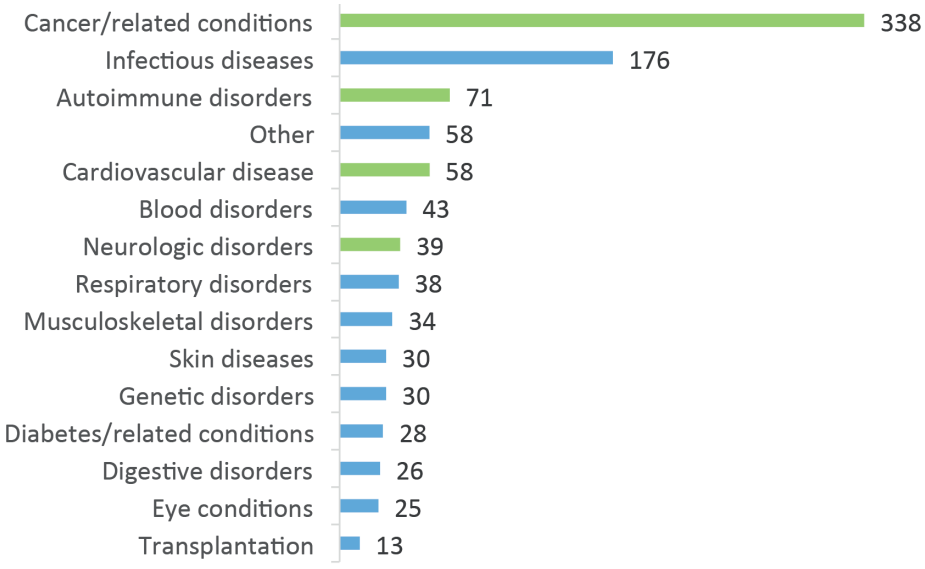

Figure 1: Biologic medicines in development by therapeutic category (some medicines are listed in more than one category).[4]

IS CANCER THE REAL DRIVER?

The global burden of cancer continues to increase as the world's population grows and ages. In 2012 there were an estimated 14.1 million new cancer cases and 8.2 million cancer deaths, as opposed to 12.7 million new cancer cases and 7.6 million cancer deaths in 2008.[5] Which cancers, disease stages and associated therapies and, of course, patients would actually be applicable to LVI devices? The majority of injectable cancer therapeutics are currently administered IV and many have potentially serious side effects for which close hospital monitoring is required. How many of those could be reformulated to SC format? How many would be suitable (safe) for a patient to self-administer at home and realistically how many SC oncology drugs would need an LVI device to enable self-administration?

There are several drugs for cancer and associated conditions that are already available for SC delivery, but most are currently indicated only for use within, or treatment initiated within, a healthcare setting. In several cases this may well be because a suitable drug and delivery device combination for self-administration is not yet available, but if there were, what type of cancer patients would be appropriate candidates to administer their own cancer therapeutic outside of a healthcare setting? What profile of cancer patients would be willing to self-administer an injectable oncology drug at home? What are the attitudes of oncologists to sending patients home to self-administer (often very expensive) drugs?

> "There are many other therapeutic areas beyond cancer with drugs either on the market or in development, which may be applicable to LVI devices."

During the early stages of cancer, or as a result of successful treatment and ongoing management of the disease, many cancer patients could be described as otherwise well, wishing to continue with normal life as much as possible. This wish is often hindered by regular, and often lengthy, trips to a healthcare setting for treatment, constantly reminding patients of the burden of their disease, and often associated with negative psychological effects. Therefore, an alternative means of drug delivery, allowing quicker treatment, is a clear benefit to those patients.

This certainly appears to have been in part, the premise behind Herceptin SC (subcutaneous trastuzumab) from Roche (Basel, Switzerland), which is in clinical trials in an LVI device. Although the marketed product is currently still only administered within a healthcare setting using a syringe, it has been shown to save significant time – taking just 2-5 minutes to administer 5 mL subcutaneously, as opposed to 30-90 minutes IV, for the same therapeutic benefit. Those time saving benefits are also seen with Mabthera SC (subcutaneous rituximab), the second of Roche's mAbs to be made available as SC formulation, allowing a 11.7 mL therapeutic dose to be administered in 5-10 minutes compared with 2.5 hours for standard IV delivery.

It is worth noting that the speed with which 5 mL and 11.7 mL can be delivered and tolerated by patients is made possible by co-formulation of the drugs with the excipient of recombinant human hyaluronidase technology – also known as Enhanze™ – from Halozyme Therapeutics (San Diego, CA, US). The excipient technology removes the traditional limitations on the volume of drugs and biologics that can be delivered subcutaneously[6] by effectively (and reversibly) degrading hyaluronan – a component of normal tissue – thus allowing the drug to disperse into the "space" and not simply leak back out, or cause local oedema and pain during injection. Many pharma companies have signed deals with Halozyme for access to this technology.

Currently, like Herceptin SC, Mabthera SC is delivered via hand-held syringe by a healthcare professional (likely a nurse), who administers the injection by simply holding the syringe in place for the required amount of time.

Could patients tolerate self-injecting large volumes using a standard syringe over several minutes? And what of large volume SC drugs not co-formulated with an excipient such as Enhanze™? How long would it take to administer 5 or even 12 mL of drug? Will these factors drive demand for wearable LVI devices capable of delivering a drug over a longer period of time, whether for use within the clinic or home setting?

What of patients with cancer at a later stage who are likely to be receiving a combination of different therapeutics, may require periods of hospitalisation for that therapy and thus may well be receiving many of those drugs IV? Would a patient receive some drugs intravenously and others subcutaneously if available in an LVI? Would that provide any efficiency in a hospital setting?

There is increasing focus on combination therapies for cancer and this seems set to continue with the growing interest in immunotherapeutics. At the recent ASCO 2016 conference in the US, much data was presented on studies combining treatments. Indeed drug company executives told Reuters there is increasing "focus on how best to combine therapies to attack multiple mechanisms of the disease, determine which patients are most likely to respond to them and how long patients will likely need to be treated".[7] So what of LVI in this context?

Oncologists we speak to seem a little hazy about this too. When it comes to the question of using SC drugs as monotherapy, but administered in the healthcare setting, the advantages associated with significantly quicker SC delivery seem clear: "It is more convenient for the patient and nurse, it is more cost effective." However, when an SC drug would be used in combination with IV drugs, opinion can be conflicting: "It is convenient even with IV chemo," *versus* "Time saving is key – but if patients are also receiving IV drugs there is no real benefit and it wouldn't make sense to give the SC version."

It seems, then, the practice of treating cancer is set to get even more complicated, and with combination therapies being developed and advanced, possibly even for early-stage disease, the scenarios in which the use of LVI in oncology will be considered are also set to increase in complexity.

IT'S NOT JUST CANCER THOUGH

There are many other therapeutic areas beyond cancer with drugs either on the market or in development, which may be applicable to LVI devices (including biologics, see Figure 1). Many questions also come to mind for other conditions such as autoimmune (AI), cardiovascular and neurological diseases.

Autoimmune

Many of the SC injectable drugs/biologics already on the market for AI conditions such as rheumatoid arthritis and multiple sclerosis are available in volumes of 1-2 mL, i.e. capable of delivery by standard syringes, pen injectors, auto injectors etc. Therefore, this is the market in which future SC therapies will have to play.

Would there be any benefit to having a large volume drug, or will efforts be made to formulate to volumes similar to those that competitors have already achieved and thus be made available in injection devices, with which many patients living with these conditions are already familiar?

Or could there be an opportunity to "roll-up" doses so that patients would have to self-administer drugs less often via use of a larger dose in a larger volume? i.e. reducing injection frequency and potentially the feeling of disease burden that more regular dosing can impose.

Cardiovascular

2015 saw a battle to be first to market with a new class of drug – a monoclonal antibody (PCSK9 inhibitor) injection –- for reducing cholesterol in patients with certain conditions that aren't responding to statins.

One such therapeutic, Repatha (Amgen), was launched in August 2015 as 140 mg every two weeks or 420 mg once monthly. The monthly treatment regimen involved three lots of 1 mL injections, using either prefilled syringes, or three lots of the SureClick auto injector. However, in July this year the US FDA approved a wearable injector – called the "Pushtronex" system to deliver the 420 mg (3.5 mL) monthly dose. Pushtronex is based on the Smart Dose technology platform of West Pharmaceutical Services. The device has been available in the US since August 2016 and it will be interesting to watch what happens with competitor drugs.

> "...it's a young, dynamic, exciting and highly innovative sector which holds great potential to change patients' lives radically and is one to watch very closely indeed."

Neurological

Neurological disease is an area that still has massive unmet therapeutic need, for conditions such as Alzheimer's and Parkinson's.

The blood-brain barrier (BBB) causes great challenges, potentially limiting successful drug development in this field and may push the drug volumes required to confer therapeutic benefit beyond those capable of delivery by standard SC devices.

Will successful drugs to treat neurological disease be launched (initially at least) in large volumes – to be able to elicit a therapeutic effect – and thus require large volume injection?

What groups of patients would be applicable? For example, many drugs currently in development for Alzheimer's are focused on treating early-stage disease, or those at high risk but pre-symptomatic. If indications are expanded beyond those with symptomatic disease, could LVI be used by patients with more advanced Alzheimer's symptoms? Would such a group tolerate a wearable device? What user experience issues would have to be given careful consideration?

BALANCING THE BOOKS

Then there is the issue of reimbursement. Who will pay for LVI delivery devices? What health economic evidence will those payers look for before accepting drug-device combinations into formulary and common practice? Despite studies suggesting that developing, or reformulating, biologics to SC, or even intramuscular, versions has the potential to lower healthcare administration costs,[8] this appears to depend on the healthcare system.

Back to cancer as an example; in the US SC forms of the mAbs Herceptin and MabThera are not yet available. This may well be because the patents in the US have not yet expired – they are due 2019 and September 2016, respectively – whereas they have already passed in, for example, Europe. However, talking to oncologists in the US reveals that some are not actually aware of the SC formulations of those well respected drugs, and if they are, they are often dismissive about the possibility of being able to use them in the US, certainly in the healthcare setting they are currently approved for, due to the way the reimbursement system currently favours IV over SC drugs.

For example, a leading US lymphoma oncologist told us: "There may be a financial barrier to SC [versions of these oncology drugs]. Oncologists in private practice are reimbursed for every IV infusion they give and so SC would be a huge economic disadvantage for those clinics." Whilst an experienced US breast cancer oncologist stated: "I am not sure why Herceptin SC is not available here, but it is potentially due to the fact that private practice can charge more for IV infusion."

It is unclear whether those are isolated views or facts which highlight barriers that payment models could pose to widespread uptake of future SC oncology drugs in the US – and elsewhere – and whether this differs for SC drugs intended for use within a clinic or for self-administration.

In Germany, a fairer reimbursement system is also being called for as some feel the current one is limiting the number of patients who receive SC formulations of oncology therapies due to economic reasons for the prescribing centres involved. It is believed that SC (and oral therapies), which still require medical staff to provide time-consuming services e.g. patient consultations, and monitoring of side-effects, are not

adequately reimbursed.

As a result, in 2014, SC Herceptin accounted for only 14% of the total amount of trastuzumab administered in Germany, compared with 60.1% in the UK and 76.4% in Sweden, over the same period.[9] These data obviously reflect the situation for use of SC drugs within the healthcare setting and was gathered before any SC oncologic therapies are being self-administered in the home setting, and so it is not yet clear how current reimbursement models would affect any switch of location of cancer treatment.

Yes, there are many questions raised in this article (and potentially still to be answered) about this market sector, but what is clear is that it's a young, dynamic, exciting and highly innovative sector which holds great potential to change patients' lives radically and is one to watch very closely indeed.

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ABOUT THE AUTHOR

Clare Beddoes is a Senior Consultant within the Medtech Services team at Health Enterprise East. She manages a wide range of medical technology projects across a diverse subject area, including those within drug delivery, and her experience lies in market strategy, needs analysis, and commercial and technical due diligence.

Dr Beddoes has worked with numerous medical technology companies from start-ups to multinationals and has a particular interest in understanding technology innovations within medical technology from the "technology pull" perspective, investigating the unmet needs of key stakeholders within care pathways and helping companies translate those into technology strategy and market approach. Dr Beddoes has a PhD in Biochemistry from the University of Manchester (UK).

SENSILE MEDICAL

PREFERRED BY PATIENTS... WITH IMPROVED THERAPIES

Wearable injectors, which allow patients to self-administer therapy in their own homes, are now becoming a reality. As well as minimising the need for hospital or doctor appointments, it can provide very high bioavailability. Sandra de Haan, Head of Business Development (outside America) at Sensile Medical, describes how the company's micro pump technology advances have enabled it to develop wearable injector patch pumps to deliver better care for patients.

The first wearable injectors are now starting to hit the market. Such devices, in development at many biotech and pharmaceutical companies around the globe, will now enable patients to self-administer medications at home. They will give patients the chance to live a more normal life without the need for a visit to a clinic or given themselves multiple injections instead.

> "Using a wearable device lowers the necessity for treatment in hospital or doctor's surgery. Patients regain independence and self-control as this is an easy-to-use device, with improved compliance a likely result."

The subcutaneous (SC) delivery from a wearable injector is less invasive from a patient's perspective than intravenous (IV) administration. This route of administration doesn't require special skills. It often provides very high bioavailability and in some cases offers a preferred pharmacokinetic profile over standard IV bolus.

Using a wearable device lowers the necessity for treatment in hospital or doctor's surgery. Patients regain independence and self-control as this is an easy-to-use device, with improved compliance a likely result.

In situations where drugs are reformulated, this technology enables the delivery of highly viscous drugs with injection volumes ranging well above what can be administered in a straight SC shot. Depending on the drug and the volume to be delivered, the duration of use for such devices can range from several minutes to hours or up to several days.

Needless to say, this kind of new delivery device must be compatible with a wide range of drugs and biologics in development. These drugs have a variety of specifications, delivery volumes, viscosities, durations of administration and dosage increments. In most cases, all this cannot be integrated in one single wearable injector design.

In addition to offering improved therapies, pharma companies have the potential for new branding opportunities and improved lifecycle management. A large number of pharma and biotech companies are currently seeking out wearable delivery systems and platform partners.

MICRO PUMP TECHNOLOGY SOLUTIONS

Sensile Medical has put enormous efforts into developing solutions and modular concepts in different technology areas around our core micro pump technology. This gives the flexibility to develop devices that support such drug-specific requirements and therapies.

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Sensile Medical's experience in multiple wearable injector projects has led to several modular concepts that we will focus on in this article. Sensile technology can offer some key advantages for the pharma company:

- Accurate dosing
- A high degree of independence from the primary packaging (can work with a standard vial)
- Cost-effective reusable/disposable concept.

SENSECORE – THE "HEART" OF SENSILE DEVICES

The SenseCore technology offers a wide range of advantages and is superior in many aspects over narrowly defined drug delivery systems or even syringe pumps, which may be used in clinical trials (Figure 1). SenseCore is a reciprocating-type positive displacement pump. Specifically, it is a piston pump (as is well known in pharmaceutical filling technology) with a ring-shaped piston area. The rotating piston together with an injection-moulded valve structure mechanically drives intake and outlet valves and additionally generates the correct pumping stroke derived from the primary rotation (Figure 2).

The design is flexible and can operate bi-directionally. As is typical of piston pumps, each pumping cycle:

- Generates a good suction pressure
- Takes in a well-defined volume of drug
- Accurately delivers a nominal pump volume at a defined delivery pressure and time.

The nominal delivery volume can easily be designed to the required optimum delivery volume per stroke, typically ranging (but not limited to) from <1 mL to 25 mL per cycle.

Regarding the viscosity of the liquids, SenseCore handles highly viscous liquids as well as gases and liquid/gas mixtures. It can also be used to reconstitute lyophilised products with diluents, mixing both products in a defined reconstitution process, transferring the reconstituted liquid into a primary container or administering it directly.

The delivery is highly accurate from the first until the last partial dose. As the drug leaves the cartridge, break-loose and/or glide forces of a rubber stopper or elastomeric relaxation do not affect dose accuracy (in contrast to delivery systems that push the stopper of a cartridge).

Figure 1: The SenseCore technology.

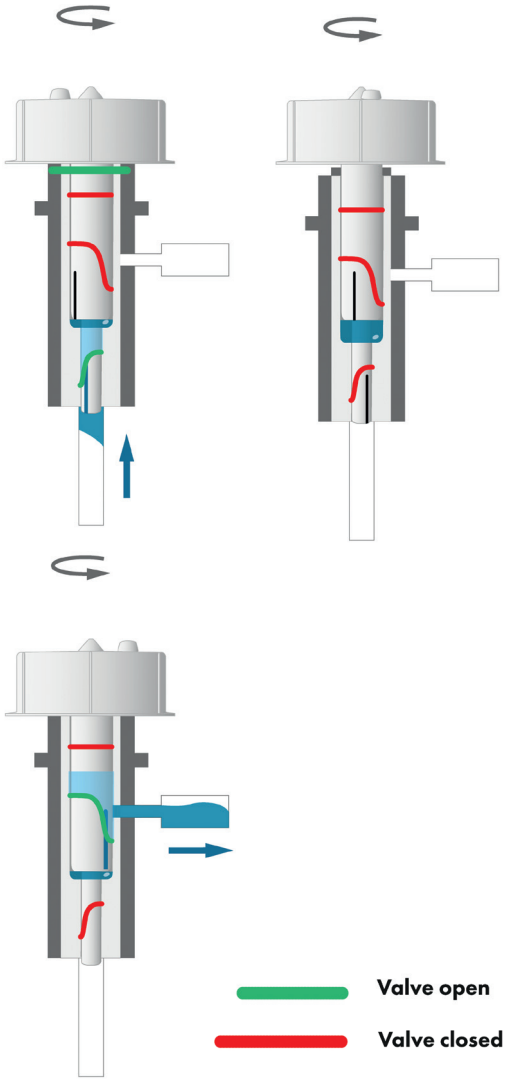

Figure 2: The pumping cycle of the SenseCore technology.

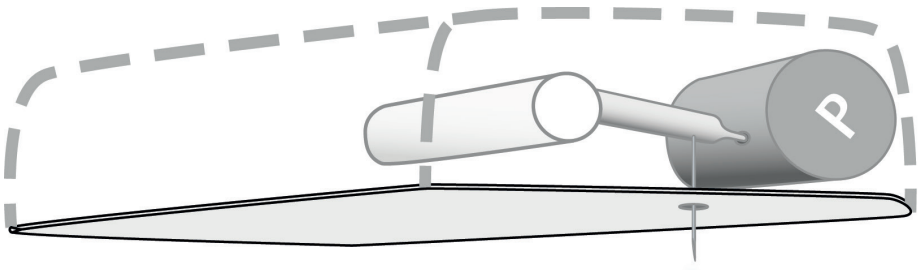

Figure 3: Needle insertion technology.

As drugs may react to plastic materials – even during the very short delivery process, we have experience with a range of materials for both the pump shaft and pump housing. Both parts are available with steel tools and can be tested at a very early stage to check drug compatibility.

Needle Insertion Technology

To allow a safe handling of the device, a fully mechanical design for needle insertion has been incorporated into Sensile's body-worn patch injectors. The needle is not visible to the user before or after injection. At the start of injection, the needle is mechanically inserted into the tissue. Once the injection is finalised, the needle automatically retracts. This integrated safety feature prevents any needle-stick injury (Figure 3).

Different needle sizes and diameters are often requested and can be carefully chosen in regards to viscosity of the drug product and required delivery speed.

A note on Freedom to Operate (FTO):

There are many patents on needle insertion technology. Sensile Medical's patented technology is integrally tied to our pump action and is completely different from all other injector solutions.

Sensor Technology

Safety is a high priority. With the use of a variety of sensors, issues like occlusion caused by crystals or increase in back-pressure from the patient's tissue can be detected and appropriate measures taken.

RFID detection is commonly used to avoid usage of the device with any other drug product. This protects from misuse or usage with a competitor product.

USER INTERFACE

Human factors considerations are playing an ever-increasing role, especially as novel drug delivery systems are coming to market. Health care professionals (HCPs), patients and caregivers need to be able to prepare, place, activate and remove the device safely with minimal difficulty.

The SenseCore technology allows for single-button operation with visual and audible signals that are easy to understand. The user interface can also incorporate a coloured touchscreen display, multiple language packages, etc. Options and alternatives are evaluated in human factors studies throughout the device development program. The devices can be pre-programmed for the desired drug delivery profile at the time of manufacturing. Alternatively, if the therapy requires a weight-based delivery adjustment, programming can be done by the doctor or even patients.

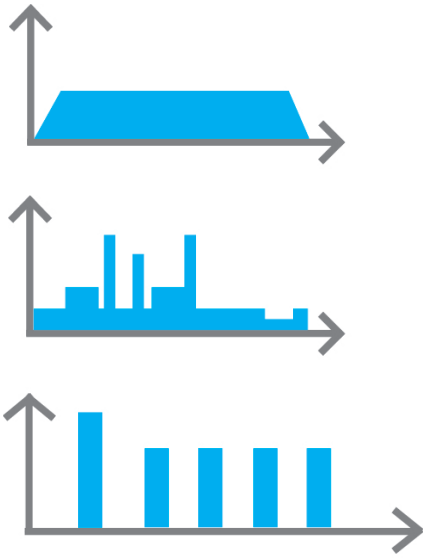

Figure 4: Possible delivery profiles over time.

Generally speaking, the system offers the possibility to adapt the delivery profile according to specific therapy needs, e.g. administration of drug over a defined period at a constant basal rate or using a specific profile with peaks. Integration of bolus deliveries is also possible (Figure 4).

COMMUNICATION & DATA MANAGEMENT

Sensile Medical's technology includes state-of-the-art electronics. Various types of communication or a data transfer protocol can be integrated if required. The devices can also offer an interface to download data from clinical trials to add to the documentation.

SENSILE MEDICAL'S WEARABLE INJECTOR PLATFORM

Disposable/Reusable Device Design

The SenseCore technology allows for the development of a small two-component device comprising a single-use disposable unit and a reusable unit:

- Disposable unit contains all parts in contact with the drug or the patient: the pump, fluidic channels, and patient interfacing elements like the needle and the adhesive or optional infusion set, sterile packaged.
- Reusable unit includes electronics, sensors, drive, rechargeable battery and the simple user interface.

This disposable/reusable concept offers several advantages:

- The design of the disposable unit enables a cost-efficient, high-volume production process. Using just two plastic parts for the SenseCore technology supports keeping the costs at a low level.
- Many therapies require frequent dosing or dosing for long periods. This can lead to high costs of goods if a delivery system is "fully disposable" and the device is discarded after each administration. With Sensile Medical's disposable/reusable concept, there is no need to discard the entire device after use, as the mechanism that provides the force and energy is part of the reusable unit that can be used over a defined period. This not only reduces costs significantly, it also leads to less waste, which can be important for environmentally conscious markets.
- The priming process is automatic and does not require separate handling steps. This integrated feature increases safety, saves time and helps prevent errors by HCPs, patients and caregivers.

Multiple Customisation Options

At Sensile Medical, we differentiate between:

- Body-worn patch injectors
- Off-body worn injectors
- Reconstitution devices
- Bolus injectors
- Usage of the SenseCore technology in various other combinations used in home care, hospital care, lab and diagnostics etc.

For all these devices, one option is to use a standard vial – often a pharma company's existing primary container. There is no need for a long and costly conversion to a cartridge.

We can either use vials of multiple sizes but also incorporate a cartridge into the device if this is our partner's choice of primary packaging. The benefits in terms of timelines and budgets are obvious.

BODY-WORN VERSUS OFF-BODY

There are several aspects:

Adhesive

Body-worn patch injectors use an adhesive to connect the device directly with the patient's skin. Depending on the size of the device, this adhesive area can reach that of a face of a mobile phone. In several human factors studies it has become apparent that the adhesive has to be carefully chosen. Aspects to consider include: duration the device is body-worn; patient activity level; skin moisture, exposure to water, skin types and so on. We also rely on external partners and their expertise, when appropriate.

On the other hand, some patients have very sensitive skin and cannot tolerate a long-term worn device. Here, we advise switching to an off-body worn injector with use of a standard infusion set with a much smaller footprint.

Delivery Volume

The larger the total drug volume to be delivered, the heavier the device. A body-worn patch injector can be acceptable for volumes up to about 20 mL. For volumes above that, it is advisable to switch to an off-body worn injector with a standard infusion set.

1 Disposable Cassette
2 Connection for Vial Adapter
3 Vial Adapter with Vial
4 Reservoir
5 Adhesive
6 Pump Body
7 Docking Station
8 **Start** Button
9 **Detach** Button
10 **ON|OFF** Button
11 Activity Ring
12 Status Indicators
13 Device Error Indicator
14 Battery State Indicator

Figure 5: Features of the large volume, body-worn patch injector – SenseTrial.

Figure 6: Small-volume body-worn patch injector – SensePatch.

Figure 7: The SenseLyo system for reconstitution.

Figure 8: The SensePen system for delivering a bolus injection.

LARGE-VOLUME BODY-WORN PATCH INJECTOR – SENSETRIAL

- SenseTrial (Figure 5, previous page) contains an integrated needle which is fully automatically injected and retracted
- SenseTrial delivers up to 20 mL from an integrated drug reservoir into the subcutaneous tissue
- SenseTrial offers variable and/or pre-programmed dosing regimens
- SenseTrial works with a standard vial as primary packaging
- SenseTrial offers an interface for data download to support clinical trials.

This device is now available for customisation to fit a drug product.

A SMALL-VOLUME BODY-WORN PATCH INJECTOR – SENSEPATCH

- SensePatch (Figure 6) contains an integrated needle which is fully automatically injected and retracted
- SensePatch is a drug delivery device to infuse up to 3 mL into the subcutaneous tissue. It is designed to be used with standard 3 mL cartridges (it can also be configured for larger cartridges)
- SensePatch offers variable and pre-programmed dosing regimens
- SensePatch delivers basal and bolus rates.

Both device concepts, large-volume and small-volume body-worn patch injectors can be customised to be used off-body with an infusion set.

OUR CONCEPT FOR RECONSTITUTION – SENSELYO

SenseLyo (Figure 7) is a reconstitution device which can infuse the drug directly via a standard luer infusion set or fill the drug into one or more primary packages.

The pump design allows a bi-directional operation. Using this function, a diluent and a lyophilised medium can be mixed at a predefined cycle time and duration. The transfer of the final drug product can be in one of the primary containers or directly infused into the patient's tissue:

- It can be programmed regarding pumping volumes, speed, breaks and number of cycles
- The fluidic adapter can be customised allowing connection of various types of primary packages.

OUR CONCEPT FOR BOLUS INJECTION – SENSEPEN

SensePen (Figure 8) is a drug delivery device which can reconstitute two drugs and infuse into the subcutaneous tissue. It:

- Contains an integrated needle which is fully automatically injected and retracted
- Offers variable and pre-programmed dosing regimens
- Delivers treatment-relevant data (e.g. injection times/doses) that can be downloaded from device.

CONCLUSION

Sensile Medical can provide lab-scale equipment to test your drug with its SenseCore technology. You can then simulate dosing, assess delivery accuracy and evaluate general device compatibility.

Sensile Medical offers proof-of-concept phases to de-risk a future development project by:

- Design & system brief protocol and kick-off workshop
- Scenario building & key design strategy
- Target group and market research
- Handling, usability, component arrangement and implementation of main functionalities, main key design elements, style directions
- Accompanied by presentations, mock-ups, first human factors study, if applicable, and report.

We are looking forward to building your bridge from drug to patient (Figure 9).

ABOUT SENSILE MEDICAL

Sensile Medical is a leading company in the area of advanced micro pump technology developing a broad range of customer-specific delivery and dosing solutions. Sensile Medical is a full-service provider of pump-based drug delivery solutions, with in-house specialists for engineering, electro mechanics, software development and more. Our partners include well-known pharmaceutical and biotech companies.

Figure 9: A patch pump in situ.

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Cambridge Consultants

LARGE VOLUME INJECTION – BEYOND VOLUME AND VISCOSITY

Large volume injectors are likely to have a growing impact on the delivery of parenteral therapy in the future. In this article, James Blakemore, PhD, Senior Consultant at Cambridge Consultants, uncovers the underlying reasons that drive the use of large volume injectors and make the case for a more extensive use of such devices based on the broader-than-expected purposes they can serve.

The use of large-volume injectors (LVIs) is predicted to have a significant impact on the parenteral drug delivery device landscape[1] in the near future. Medical device manufacturers including Unilife (York, PA, US), West Pharmaceutical Services (Exton, PA, US), BD (Franklin Lakes, NJ, US) and Insulet (Billerica, MA, US) are already active in this space and have developed devices capable of delivering a wide range of formulations.

> "LVIs play a role that is far more important than enabling delivery of high-volume drug formulation as they differentiate drugs, make them safer to use, reduce the injection workflow and facilitate self-administration."

Similarly, pharmaceutical companies – such as AbbVie (North Chicago, IL, US) and Amgen (Thousand Oaks, CA, US) – have started introducing LVIs alongside their medicinal products (Table 1).

To date, the case for LVIs has been relatively one dimensional and can be summarised in one sentence: R&D pipelines are dominated by biologics, biologic formulations can be viscous or in large volume, and hence LVIs are bound to play a key role in the future.

The fundamental reasoning of this case is correct. Biologic drug formulations, particularly those containing monoclonal antibodies (mAbs), are viscous at high concentration. Therefore, increasing the volume assists with the development of formulations that are ideal for infrequent dosing or depot administrations.

Nevertheless, LVIs can fulfill far wider demands than those usually discussed. Indeed the role of LVIs is in fact far broader than enabling the delivery of high-volume drug formulations, as they differentiate drugs, make them safer to use, reduce the injection workflow and facilitate self-administration.

LVI BENEFITS IN COMBINATION MEDICINAL PRODUCTS

Looking at a handful of marketed and pipeline combination products, we can derive insights into the wider benefits that an LVI device may facilitate (Table 2).

Slow Release

Infusion site reactions are a common issue with biologic formulations. Reactions may be typified by local swelling and pain, and

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Brand	Trevyent™	Neulasta® Onpro™	Herceptin® SC	Repatha® Pushtronex™
Generic name	Trepostinil	Pegfilgrastim	Trastuzumab	Evolocumab
Therapy area	Cardiovascular	Cancer	Cancer	Cardiovascular
Delivery time	Slow release[3]	45 minutes[4]	7 minutes[5]	9 minutes[6]
Drug manufacturer	SteadyMed	Amgen	Roche	Amgen
Device	PatchPump®	Omnipod® (design variant)	Single Injection Device	SmartDose®
Manufacturer	SteadyMed	Insulet	Roche	West Pharmaceutical

Table 1: Examples of LVIs and associated therapies.

may lead to systemic effects such as nausea, headache and fever.

To mitigate this risk, such therapies are administered by slow infusion for up to several hours, requiring the patient to remain in the infusion clinic for long periods. The ability to transfer these types of formulations into a suitable LVI that delivers its dose at a similarly slow flow rate enables ambulatory drug delivery, and has potential to improve the experience of both patients and healthcare professionals (HCPs) significantly.

One such example is Trevyent®, which has been reformulated for presentation in the PatchPump® device from SteadyMed (San Ramon, CA, US). It is under development for the treatment of pulmonary arterial hypertension. The device permits slow release of the drug which minimises the risk of infusion site reactions – an otherwise common side effect of the drug when administered via subcutaneous (SC) infusion line.

Timed Release

As a concept, delayed release of drug therapies is well-established, particularly for oral formulations. Translating this concept across to biologic therapies is more challenging, given that such formulations usually require parenteral administration. The introduction of timed release of biologic drugs brings about clinical benefit.

An example illustrating this benefit is Neulasta® Onpro™, marketed by Amgen for the treatment of chemotherapy-induced neutropenia (low white blood cell count). It consists of the drug in a single-use on-body injector. The system is designed to delay administration of the drug for up to a day following chemotherapy so that it can exert its therapeutic effects at the right time.

In doing so, the system avoids the need for the patient to present to the physician the next day after chemotherapy for their treatment. Practically, the system avoids dose-limiting side effects typically associated with chemotherapy as it is common for the patient to feel too sick to come back to the hospital for further treatment. Significantly, this novel presentation disrupts the care pathway, which otherwise requires the patient to present to the clinic.

Trevyent™	Neulasta® Onpro™	Herceptin® SC	Repatha® Pushtronex™
Slow release – continuous infusion	Facilitates dose scheduling / administration	Allows less frequent administrations e.g. every three weeks	Differentiation against other PCSK9 inhibitors
Reduces pain experience	Decreases IV- associated infection risk	Time saving during hospital administration[2]	Use allows a traditionally injection-free TA to maintain its patient convenience
Minimises risk of infusion site reaction		Self-administration	Allows less frequent administrations e.g. monthly
Self-administration			

Table 2: Summary of LVI benefits in selected combination products.

Patient Self-Administration

Certain care pathways, particularly in oncology, require the patient to present to the infusion clinic on a regular basis over an extended treatment period to receive drug therapy. This is because many oncology products are given by intravenous (IV) or SC administration, which requires HCP supervision and suitable facilities for infusion.

Although being in an infusion clinic setting provides back-up if there are adverse events to deal with, once a maintenance therapy phase is established, this requirement to present to the clinic becomes a significant burden on the patient. The ability for patients to self-administer in a home environment would reduce this burden.

An example of this is provided by a SC formulation of Herceptin® (trastuzumab), which is under development by Roche (Basel, Switzerland) for delivery via its proprietary Single Injection Device (SID) platform. The drug has been reformulated and contains a novel excipient (Enhanze®, from Halozyme, San Diego, CA, US) which permits bolus SC administration of large volumes. Typically, Herceptin® is administered weekly for up to three years, requiring the patient to present to the infusion clinic each time. Reformulation of the drug and its incorporation into a device permits patient self-administration, providing greater convenience to the patient and the basis for improved patient compliance.

Furthermore, a study by De Cock demonstrated that this SID presentation of Herceptin® reduces drug preparation and administration time in the infusion clinic, compared with the infused presentation.[2] Since infusion chair or bed "real estate"

is such a premium in infusion clinics, any intervention that reduces HCP workflow and patient time should have a positive commercial impact.

Reduced Dosing Frequency

It is common for biologic therapies with similar mechanisms of action to receive similar approval times. In these cases it is difficult for manufacturers to establish a material basis for product differentiation, other than perhaps incremental safety or efficacy claims. A favourable change in dosing frequency may be a principal route by which a drug could be differentiated from the competition.

For example, Amgen's Repatha® Pushtronex™ system comprises evolocumab, a novel PCSK9 inhibitor, packaged into a variant of West Pharmaceutical Sevices' SmartDose® electronic wearable injector. The system provides monthly dosing of evolocumab as an adjunct for statin therapy and as a primary treatment of hypercholesterolaemia, which improves patient convenience.

> "Innovator pharmaceutical companies should take note of the wider benefits of LVIs as they plan lifecycle management strategies, particularly in terms of implementing biosimilar defence strategies."

Sales of Repatha® are low, as expected in a field where statins are, on the whole, perceived by physicians as an adequate cholesterol-lowering class. Therefore, the Pushtronex™ system provides Repatha® with a means of differentiation against competitor PCSK9 inhibitors, notably Sanofi's Praluent®. The Pushtronex™ system will likely drive compliance of Repatha® which may in turn increase the chance of capturing data that proves better outcomes; ultimately the proof for improved outcomes data will push Repatha towards being positioned as a first-line therapy option.

Finally, it is worth noting that patients in this therapy area are likely to be needle agnostic. An LVI may be seen by pharmaceutical companies as presenting the less risky option to promote an injectable drug.

BENEFITS OF GREATER DIVERSITY IN LVI DESIGN

As seen in the above examples, it is not just volume and viscosity challenges that LVIs have the potential to address, but rather a wider set of clinical benefits. The benefits demonstrated in the therapy areas above apply equally to other therapy areas, particularly chronic diseases such as autoimmune disease, where regular dosing of increasingly biologic therapy classes is required.

In many cases, drug reformulation is required to facilitate a shift from IV to SC delivery by a LVI. Therefore, the application of suitable formulation technologies is a key technical and commercial consideration prior to the development of drugs for LVI administration.

LVIs provide a basis for product differentiation, through improving either safety, efficacy, tolerability or convenience. It is unlikely, however, that payers will acknowledge the value of LVIs through reimbursement until it can be demonstrated that these properties translate into significant improvement in patient outcomes.

Innovator pharmaceutical companies should take note of the wider benefits of LVIs as they plan lifecycle management strategies, particularly in terms of implementing biosimilar defence strategies. Likewise, generics companies that are focused on biosimilars development should consider LVIs as a basis for differentiation against both originator product and competitor biosimilar products.

The evidence above highlights that we should not expect the current crop of LVIs to satisfy the broad range of clinical needs; each patient's requirements are different for each therapy area. Therefore, we should expect rapid expansion in the LVI class, including bespoke design variations, in order to meet these clinical needs.

ABOUT THE AUTHOR

James Blakemore is a Senior Consultant in the Medical Technology division at Cambridge Consultants. He specialises in market strategy and transaction support within the pharmaceutical and drug delivery device markets. He manages drug delivery device development projects bringing together commercial insight and technical expertise. Prior to working in the healthcare consulting industry, Dr Blakemore worked in a number of business development and licensing roles for speciality pharmaceutical and biotechnology companies, working towards the identification, validation and commercialisation of broad new therapies. He holds a PhD in Molecular Biology from King's College, University of London, UK.

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AN INTRODUCTION TO YPSODOSE FOR THE LARGE-VOLUME INJECTION OF BIOLOGICS

In this article Ian Thompson, Vice-President Business Development at Ypsomed, describes self-injection device trends for larger injection volumes and introduces YpsoDose, a new prefilled large-volume wearable injector being developed by Ypsomed Delivery Systems.

Worldwide, pharmaceutical companies are focusing on biologic therapeutics, many based on monoclonal antibodies. Due to their molecular characteristics they are usually administered parenterally and, when self-injected, subcutaneously. Injections are infrequent – typically weekly, biweekly or monthly and there is a demand for less frequent injections e.g. every two, three or six months. The trend to fewer injections, ranging from traditional peptides/hormones to antibody therapies, means that larger doses and thus larger injection volumes are required.

> "For drugs with longer pharmacokinetic half-lives, pharma companies need to weigh up the pros and cons between more frequent injections from an autoinjector and less frequent injections from a wearable injector."

These larger volume injections are mainly being considered for treating autoimmune diseases such as rheumatoid arthritis, psoriasis and IBD/Crohn's, but also for new therapeutics such as the PCSK-9s recently launched for the treatment of hyperlipidaemia. Looking into the future the potential for new drugs for treating Alzheimer's, and immuno-oncology therapies to control already treated cancers, will further increase demand for larger volume infrequent self-injections.

TRADITIONAL 1 ML AUTOINJECTORS & NEW 2.25 ML AUTOINJECTORS

Since the introduction of prefilled syringe (PFS)-based disposable autoinjectors around a decade ago, the majority of devices have been based on the 1 mL-long PFS and there are now over 10 different devices on the market. For a number of years there was a general acceptance that 1 mL was the maximum volume that could comfortably be delivered by an autoinjector. With the increased need for higher payloads and following clinical testing this no longer holds true and the 2.25 mL PFS is now accepted as the standard primary container for injection volumes in the 1-2 mL range.

Based on the demand for less frequent injections, the interest in 2.25 mL prefilled syringe-based autoinjectors is growing significantly. The injections are often for slightly viscous drugs with injection times in the 10-15 second range.

Ypsomed is covering this demand with the YpsoMate 2.25, which serves patients with an easy and convenient two-step automatic injection. While the standard YpsoMate 1 mL version has been industrialised and is being customised for over 15 customers, the new YpsoMate 2.25 mL version has been adopted by first customers and is in development for clinical studies (Figure 1).

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Figure 1: YpsoMate® 1 mL and YpsoMate® 2.25 mL two-step customisable autoinjectors cover injection volumes up to 1 mL and 1-2 mL.

THE WEARABLE INJECTOR FOR VOLUMES ABOVE 2 ML

For volumes above 2 mL, which require longer injection times, there is a need for large-volume wearable injectors. This implies a disposable injection device that is worn and connected to the body with an infusion set or ideally attached directly to the skin with an integrated fluid path and needle system. Compared to an infusion pump, which performs drug infusions over hours or days, the large-volume wearable injector is intended to administer 2-10 mL or an even greater volume of drug typically within 2-15 minutes.

In the large-volume injector field there are a number of wearable device concepts available and in development covering a broad range of specifications including: prefilled but not assembled; fillable; prefilled and preassembled; mechanical; electromechanical; cartridge-based and collapsible container-based systems. It is clear that there will be a range of devices required to cover different drug and patient needs. Learning from both previously developed and current offerings, it is also clear that the key focus in the area of biologics is in the 2-10 mL injectable volume space requiring prefilled and preassembled, electromechanical, cartridge-based, connected wearable injectors.

> "Ypsomed has changed the rules in the market and accelerated customer projects by developing platforms, by engineering them, by patent protecting them and – this is key – also industrialising them."

AUTOINJECTOR OR WEARABLE INJECTOR?

For drugs with longer pharmacokinetic half-lives, pharma companies need to weigh up the pros and cons between more frequent injections from an autoinjector and less frequent injections from a wearable injector. Whether an autoinjector or wearable injector is selected for a particular therapy depends on a number of factors. Autoinjector technologies are established and proven and the prefilled syringe drug reservoir is typically also available for use by healthcare professionals (HCPs) or patients, in the form of a bare syringe or in combination with a safety syringe system. While an autoinjector typically contains a prefilled syringe, a skin-worn wearable injector requires a different drug reservoir – typically a cartridge, combined with a sterile fluid path and needle system.

Many more questions are being asked. For example, what is preferred by patients, four 10-second autoinjections per month or one 5-minute injection with a wearable device? Does a pharmaceutical company want to invest in a bespoke drug reservoir/fluid path system that can only be injected with the aid of a bespoke device? How much added value, convenience or differentiation does the wearable device add to the therapy regime compared with the autoinjector?

These questions can only be answered by extensive research into the way new therapies are provided to patients and a thorough understanding of patient preferences. But, it is clear that the wearable injector market will grow significantly over the coming years and establish itself as a third device class to complement the already well developed markets for pens and autoinjectors.

WEARABLE INJECTOR NEEDS

Ideally, a wearable injector should be as easy to use as a disposable autoinjector (or easier) based on less frequent injections, which means it must incorporate the following key technical features:

- Prefilled and fully disposable to remove any need to assemble the drug reservoir and device
- Easy adherence to the skin during injection; and easy to remove after injection
- Automatic insertion and retraction of the needle at the start and end of the injection process.

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

- Recognise that the device is ready to inject when attached to the skin
- Cover a range of fill volumes and viscosities and provide a reproducible injection time per drug
- Communicate via audio and visual signals clearly with the patient before, during and after the injection
- Ideally, have a wireless connection to allow patient monitoring.

All of these requirements mean that the wearable injector is a significantly more complex device than a disposable

Figure 2: YpsoDose®, the prefilled, preassembled, electromechanical wearable injector for injection volumes in the 2-5 mL range.

autoinjector but, in cost terms, this may well be compensated by the lower number of devices required compared with an equivalent therapy provided by an autoinjector.

YPSODOSE WEARABLE INJECTOR DEVELOPMENT

The development and manufacture of a wearable injector system brings with it a number of challenges to fulfil the device needs described above. Ypsomed has a proven track record of working on complex injection devices with in-house engineering expertise, combined with a high level of technological integration for manufacturing pens, autoinjectors, pen needles, insulin pumps and infusion sets under clean and cleanroom conditions. All these competencies are key in developing the subsystems required by YpsoDose (Figure 2).

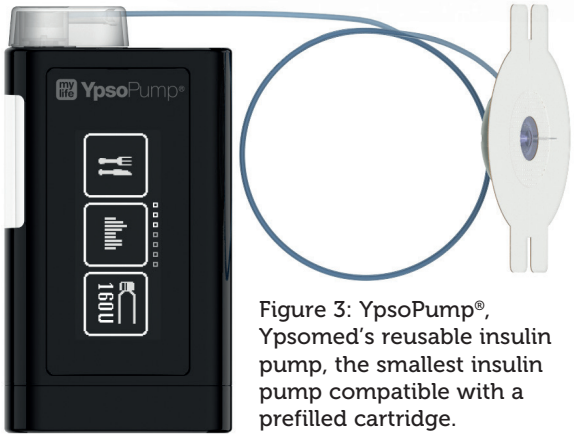

Figure 3: YpsoPump®, Ypsomed's reusable insulin pump, the smallest insulin pump compatible with a prefilled cartridge.

The subsystem development for YpsoDose focuses on the drug reservoir/fluid path, needle mechanism, drive mechanism, adhesive patch and electronic interface. With such a complex project the close proximity of development and manufacturing within the company and access to an existing supplier network in the heart of Europe help to simplify the development and industrialisation process.

Ypsomed has changed the rules in the market and accelerated customer projects by developing platforms, by engineering them, by patent protecting them and – this is key – also industrialising them. YpsoDose is no exception and the device is now moving from innovation into the realisation phase based on the following device features:

- Conventional cartridge technology for the primary drug container
- Proprietary integrated sterile needle unit and needle mechanism to complete the fluid path and insert the needle
- Low noise proprietary electromechanical drive programmable to accommodate different injection flow rates
- Electronics to provide patient feedback and connectivity
- A technical design that allows the pharma company or contract filler to easily assemble the device subassemblies with the drug cartridge.

CUSTOM PRODUCT APPROACH AND THE PATIENT JOURNEY

Implementing the Ypsomed Custom Product platform approach for the YpsoDose wearable injector is a clear aim of the project. This involves significant investment in resources and infrastructure for fully automated manufacturing of the needle unit under cleanroom conditions and assembly of the device subassemblies. Streamlining the device technology and manufacturing processes is important in order to achieve a scalable and cost-efficient device. At the same time, customers demand the ability to customise the device for different drugs and patient groups. This is why Ypsomed is investing heavily in modular product design and human factors engineering for multiple user groups.

There is a parallel between YpsoDose and the significant development and manufacturing investments that have been made for YpsoPump, Ypsomed's reusable insulin pump, the smallest insulin pump compatible with a prefilled cartridge (Figure 3). At half the size of existing pumps, with an intuitive icon-based touch screen, it is a prefilled solution that avoids cumbersome manual filling of insulin. This pump, weighing only 83 g, includes sophisticated electronics and has an integrated Bluetooth connection module.

For YpsoDose, the journey is at the realisation phase and the results of the most recent design studies will be presented at

the forthcoming PDA *Universe of Prefilled Syringes & Injection Devices* conference in Huntington Beach, CA, US, October 17-18, 2016. The dialogue with pharma customers is now intensifying as YpsoDose moves through the realisation phase towards the clinical phase.

ABOUT YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed is the leading independent developer and manufacturer of innovative autoinjector and pen injector systems for self-administration. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, 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 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 current Good Manufacturing Practice (cGMP) guidelines with operational quality assurancce (QA/QC) experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are successfully inspected on a regular basis by both pharma customers and regulatory agencies (including FDA) and supply devices for global markets including US, Europe, Japan and China. Ypsomed has more than 30 years' experience and well-established working relationships with numerous leading pharma and biotech companies. Ypsomed Delivery Systems continues to focus on the development and manufacture of next generation pen, autoinjector, wearable and connected injector technologies.

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 1979-1983, 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 autoinjector Custom Products for Ypsomed Delivery Systems.

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WEST'S SMARTDOSE PLATFORM: A WEARABLE ENGINEERED WITH BOTH PATIENT & PHARMA PARTNER IN MIND

In this article, Tom McLean, Vice-President, Delivery Systems, R&D, West Pharmaceutical Services, discusses the company's wearable technology platform. SmartDose is a customer-driven, patient centric device that was recently selected by Amgen for the Pushtronex™ system.

For patients with chronic conditions, the use of biologic therapies is on the rise. These drugs present several challenges for both drug manufacturers and patients. In particular, many biologics are highly concentrated, so a prescribed dose may be very viscous or require large volumes of the medication to be injected slowly over time. This can make it difficult to deliver a consistent dose, potentially impacting patient adherence to a given therapy.

Additionally, there has been a rise in popularity of wearable self-injection systems for biologics. Instead of scheduling a doctor's appointment for certain treatments, a wearable device allows patients to self-administer injectable medication without assistance from a trained medical practitioner. For some patients, an integrated delivery and administration system may be helpful when trying to comply with prescribed treatment regimens.

The market demand for biologics coupled with the growth of self-administration required the drug delivery sector to develop innovations, such as the West SmartDose® technology platform, to administer these very important therapies. SmartDose, shown in Figure 1, is a single-use, electronic wearable delivery system that adheres to the patient's body, usually on the abdomen, and is pre-programmed to deliver high volumes of viscous medications. It was designed with the goal of minimising discomfort, fostering an improved patient experience and offering accurate and timely drug delivery.

> "Amgen has selected SmartDose for a single, monthly 420 mg dose delivery option for its antihyperlipidemic, Repatha® (evolocumab). While this is the latest collaboration, the success of SmartDose is the product of many years of innovative research, design and implementation, based on input from both patients and pharmaceutical customers."

Earlier this year, Amgen (Thousand Oaks, CA, US) selected the SmartDose technology platform for a single, monthly 420 mg dose delivery option for Repatha® (evolocumab). While this is the latest collaboration, the success of SmartDose is the product of many

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Figure 1: West's SmartDose® technology platform.

years of innovative research, design and implementation, based on input from both patients and pharmaceutical customers. It promotes greater adherence, which benefits all parties involved.

THE PATIENT-CENTRIC SHIFT

Historically, the primary focus of pharmaceutical manufacturers has, appropriately, been on the efficacy and safety of their drug product. However, with more drugs coming onto the market as combination products – drug products paired with delivery devices – pharmaceutical companies are paying closer attention to the design, function and efficacy of integrated delivery systems as well.

A successful system will combine the needs of the patient, which can evolve throughout the treatment journey, with those of the drug, its primary containment system and delivery system.

The best way to incorporate meeting patient needs into a platform's design is to gain a considerable amount of user feedback before even prototyping a delivery system. It is also critical to understand how they feel about their journey from diagnosis through ongoing treatment, and how to make a delivery system that will both enhance the therapeutic experience as well as improve medication adherence.

This kind of development costs more than traditional approaches, and may take a bit more time at first. However, when built into the overall timeline of drug development, we believe this approach pays dividends by yielding medications with delivery systems that patients not only can use, but want to use. This helps promote patient adherence and ultimately contributes to improved chronic disease management and outcomes.

In the research conducted when developing the SmartDose technology platform it became clear that delivery systems that patients deem inconvenient can negatively affect their emotional attitude and motivation to sustain adherent behaviour. As a result, SmartDose was developed with extensive human factors testing and analysis to understand the interaction between the patient and the delivery system. The two most common human factors were:

- **Pain:** Patient concerns related to discomfort were certainly valid, as the device requires needle insertion for an extended period while affixed to the body using an adhered patch. As such, it was designed to minimise discomfort throughout the duration of the dosage and to be easily removed once the dosage was complete. There is also an automatic needle protection feature that can help prevent needlestick injuries.
- **Discreteness:** Many patients prefer not to have medication administered by visible delivery mechanisms. Special consideration was taken with SmartDose technology to ensure that it is easily concealed to avoid calling undue attention to the device or creating feelings of stigmatisation.

CUSTOMER-DRIVEN DESIGN

In addition to taking a patient-centric approach, it is also important to focus on

the specific needs of our pharmaceutical customers when pairing a drug with a delivery system. In designing the SmartDose technology platform, input from pharmaceutical companies was key to ensuring the system met their requirements.

One of the more important customer-facing features of SmartDose technology is its adaptability. Its design allows the dosage amount and length of time to be adjusted to the drug maker's specifications. If a pharmaceutical customer needs a 3 mL dose delivered over 30 minutes or a 2 mL dose delivered in five minutes, the SmartDose technology platform can accommodate the unique properties of the drug. Beyond the actual delivery the aesthetic features such as colour scheme can be customised to maintain branding.

West's dedication to working with its customers to deliver new solutions also requires paying close attention to emerging trends, such as cold chain storage. Some new therapies require the drug to be stored in sub-freezing temperatures prior to use. To ease impact on shipping and cost, West has traditionally kept the drug and device separate.

"West is currently in the process of expanding the SmartDose technology platform to ensure continued leadership and innovation in this area. The next-generation products include a prefilled option, with the objective of reducing user steps while maintaining sterility."

However, there is increased demand for a prefilled version of the SmartDose technology platform that would require the device to be stored in the same cold environment as the drug. As a result, we are exploring engineering and design methods that would allow for cold storage without impacting the mechanical components of the SmartDose technology platform.

A notable example of the customer-facing engineering of the SmartDose technology platform can be seen in Amgen's decision to utilise the delivery system for the company's single, monthly dose delivery option of Repatha, marking the first use of SmartDose technology with a commercialised product. The combination of Amgen's innovative treatment with West's patient-focused technology platform is an example of how West closely collaborates with its pharmaceutical and biotechnology partners to deliver advanced, integrated solutions for drug delivery and containment.

Amgen is one of a number of pharmaceutical partners that have considered West and the SmartDose technology platform to assist in the development of an innovative delivery solution. There are multiple active programs at various stages of pre-commercial development utilising SmartDose.

Additionally, West is currently in the process of expanding the SmartDose technology platform to ensure continued leadership and innovation in this area. The next-generation products include a prefilled option, with the objective of reducing user steps while maintaining sterility. The newer version will include:

- Additional design flexibility based on the use of a customised Daikyo Crystal Zenith® container, commercially available plungers with Flurotec® barrier film technology and rigid needle shields
- Optimised manufacture, filling and sterilisation for manufacturers to help ensure cost effectiveness and leverage established filling equipment.

IMPROVING ADHERENCE

The end result of the innovative engineering research necessary to strike the perfect balance between what is best for both the patient and customer, ideally, is increased patient adherence and outcomes. According to estimates from the WHO, adherence is still a very real issue globally, with adherence to chronic medication therapies remarkably low – about 50%.

Non-compliance can lead to a number of complications, including poor clinical outcomes, increased costs for many healthcare stakeholders (including the patients themselves) and lost revenue for pharmaceutical companies. To combat the adherence issue, injectable drug administration systems should be intuitive, efficient and non-

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PATIENT-CENTRICITY IN WEARABLE TECHNOLOGY TRAINING

A recent study conducted by Noble® (Orlando, FL, US), a leader in onboarding and device training, and analysed by Auburn University (Auburn, AL, US), found that more than 60% of patients self-reported that they did not thoroughly read the required steps outlined in a self-injection system's Instructions for Use document prior to beginning drug treatment, potentially leading to administration errors and impacting compliance with prescribed therapies.

Research from both Noble and West has revealed that patient-friendly drug delivery systems and comprehensive education around self-injection are needed to improve the patient experience. To address this adherence challenge, West and Noble have worked together to offer a multisensory-based educational and training program for the SmartDose® technology platform to pharmaceutical and biotechnology customers. West brings its expertise in human factors testing and analysis to the design and development of drug delivery systems, and Noble incorporates a similar approach into the development of the SmartDose patient onboarding support materials which include a smart training device and packaging, Instructions for Use and more. Through this collaboration West and Noble aim to help improve the patient experience, reduce errors and anxiety and potentially increase adherence to prescribed injectable therapies that utilise the SmartDose platform.

This collaboration with Noble complements West's established relationships with other technology innovators such as Insight Product Development (Chicago, IL, US) and HealthPrize Technologies to enhance its patient-centric approach to the SmartDose drug delivery system.

disruptive to the patient's daily routine.

After all, a drug can only have the desired patient benefit if it is taken as prescribed and delivered effectively. SmartDose integrates innovative features that may help to encourage patient compliance, including:

- **Ease of use:** Because injectable medications are administered completely by the patient with SmartDose technology, the process needs to be so intuitive that only minimal instruction is required. To this end, SmartDose is equipped with an easy-to-load cartridge that contains the drug, a user-friendly activation button on the front of the device and LED indicator to let the patient know that the dose delivery is in progress.
- **Dose notification:** Perhaps the most critical aspect of the SmartDose platform is how it addresses the possibility that user did not receive the full dose, or did not receive their medication at all. To account for this possibility, the device is equipped with a microprocessor that is designed to offer immediate feedback via a dose confirmation window and audible cues indicating whether the prescribed medication was delivered.

Additionally, in 2014, West collaborated with HealthPrize Technologies (South Norwalk, CT, US) to develop a connected health offering that is designed to improve and reward medication adherence with unique technologies in a gamified environment. In our first offering, patients can manually scan barcodes or otherwise enter data about their medication compliance into a smartphone/tablet app or on an Internet browser from a computer. Patients are then rewarded for compliance, and other forms of engagement.

In the near future, using the app will be even more automated, streamlined and interactive by enabling West's drug delivery systems, including SmartDose, to signal the smartphone with data points about each instance of medication self-injection. For example, the app would automatically, in real time, confirm that a particular dose was used, the needle protection system was deployed, that the entire dose was injected, and other details.

CONCLUSION

In developing SmartDose, West has further broadened its ability to balance the safety and well-being of patients and the technical demands of our pharmaceutical partners. As the wearable drug delivery market expands, West will continue to develop and engineer innovative platforms to ensure greater patient adherence and outcomes and assist drug companies to bring safer and more efficacious new therapies to market.

SmartDose® is a registered trademark of Medimop Medical Projects Ltd., a subsidiary of West Pharmaceutical Services, Inc. West seeks partners for its SmartDose® injector technology platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/biotechnology company. Repatha® is a registered trademark of Amgen Inc.

ABOUT THE AUTHOR

Tom McLean leads West's Delivery Systems R&D Organisation where his responsibilities include the development of delivery system products from concept through product design verification and validation. Mr McLean holds Six Sigma Black Belt Certification and Six Sigma Master Black Belt Certification. He received a B.S. in Mechanical Engineering from Purdue University (West Lafayette, IN, US).

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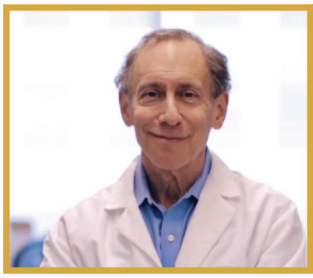

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CANÈ

MEDICAL TECHNOLOGY

ABOUT CANÈ

Based in north-west Italy, Canè SpA is a leading manufacturer of ambulatory infusion pumps for the administration of pharmaceuticals.

Canè was founded in 1978 as a manufacturer of ambulatory infusion pumps for treating thalassaemia. Over the last 35 years it has grown to become the leader in the segment addressing drug deliveries ranging from 10 to 100 mL. Starting from the first syringe drivers, which were relatively bulky thus causing patient compliance to suffer, Canè's products have evolved into the Crono line of miniature pumps which may be worn without impacting patients' normal daily routine.

THERAPEUTIC AREAS

Canè's Crono series is comprised of the ambulatory infusion pumps and the dedicated CRN® CRONO® Syringes which are used with them. Depending upon the therapy the syringes may have volumes of 10, 20, 30, 50 or 100 mL. Most of the pumps are designed for a specific therapy, so that their features and programmability are tailored to the way in which the drug will be used by the patient.

The Crono series of ambulatory infusion pumps addresses four main therapeutic areas: primary immunodeficiency; Parkinson's disease; pain control; and thalassaemia. In addition, Canè has models dedicated to pulmonary hypertension and fertility treatment, and it is working with partners in areas as diverse as hormone replacement therapy, radiopharmacology and skin care.

The majority of the pumps are intended for use by patients at home, and are designed to allow them to receive medication almost continuously while maintaining as normal a life as possible.

Crono PAR

Crono PAR pumps (Figure 1) are for the subcutaneous infusion of apomorphine in the treatment of Parkinson's disease. There are models for reservoirs with volumes of 20 mL, 30 mL, and 50 mL, and they offer two different programming modes:

- Free mode which allows the patient to freely select one of the three available flow rates pre-programmed by the physician
- Auto mode, which automatically administers a daily flow rate profile, pre-programmed by the physician. The profile may be programmed hourly over a 24-hour period.

The Crono PAR pumps also have priming, bolus dose and partial volume functions.

Crono S-PID

Crono S-PID pumps (Figure 2) are for controlled subcutaneous administration of immunoglobulins. Models are available for 20 mL, 30 mL, 50 mL and 100 mL. This therapy generally requires rapid infusions, and flow rates of up to 300 mL/h are available, depending upon the model. The main features of the pumps are:

- The possibility of selecting between time or flow rate programming mode (50 mL and 100 mL models)
- The possibility of automatically pausing the infusion in order to allow the patient to divide the syringe contents over several infusion sites (50 mL and 100 mL models, available in flow rate mode only)
- Flow rate and infusion time can be varied during the infusion
- Priming and partial volume functions.

Crono SC

Crono SC pumps are designed for use in pain treatment. The two models of Crono SC, with 20 mL and 50 mL syringes, have several features which allow the control and, if necessary, the limitation of drug administration such as:

- The display of the volume administered thus far through the basal rate
- The display of the total volume administered through bolus doses
- The display of the total volume administered thus far in an infusion
- A bolus dose counter
- The display of the total volume administered using clinician's bolus doses (bolus administration generally only accessible to the clinician)
- Limitation of the number of bolus doses administrable in an hour
- Limitation of minimum time between bolus doses.

The Crono SC 20 has a 5 mL/h maximum flow rate, and therefore uses a 5 µL shot size so that at low infusion rates the concentration of drug is kept as constant as possible.

The Crono SC 50 has a maximum flow rate of 35 mL/h and delivers 20 µL shots (Figure 3).

DESIGN AND MANUFACTURING

All pump R&D and design work is done in-house, as are final assembly and testing. Canè's dedicated syringes are designed

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in-house and are manufactured by an Italian partner. Canè prides itself on the fact that where possible all components are locally sourced, which carries the added advantage of being able to maintain the highest standards of quality.

While Canè has its own series of products, it also provides ODM services to pharmaceutical companies who require customised pumps, be it in limited numbers for clinical trials or for mass-produced, private-labelled devices.

CUSTOMISATION

Canè's products are developed using a platform-based approach, in which the same hardware is used as a basis for many different models. It is therefore easy for us to provide pharmaceutical companies and other medical device manufacturers with customised solutions which perfectly match their specific device requirements.

Canè can produce limited numbers of special pumps for clinical trials or for investigatory purposes which then become a part of Canè's standard product range. One example is the Crono P (Figure 4) which was developed for hormone infusion according to strict circadian and ultradian rhythms, mimicking the body's normal hormone production cycles. It is the only ambulatory infusion pump of this type on the market today.

Another example is the Crono Twin, (Figure 5) developed for the delivery of immunoglobulins into two infusion sites. Normally infusion into two infusion sites is via a Y-set, which has the disadvantage that if one branch becomes occluded the entire volume is delivered via the unoccluded branch. The Crono Twin has two syringes, so that it is impossible to deliver more than 50% of the total volume to each infusion site.

In other cases Canè has developed privately labelled models which it manufactures exclusively for the customer. These can be either based on its standard platforms or can be completely new designs. Pump characteristics which may be customised include:

- Programmability in terms of flow rate or infusion time
- Bolus doses volume and interval control
- Partial volume function (for partially filled syringes)
- Selectable occlusion alarm pressure
- Infusion line priming and anti-freeflow systems
- Lockable keyboard, so patients can't change medical practitioners' settings
- Multiple pre-programmed flow rates which are selectable by the patient during an infusion
- Automatic flow rate profiles through the day
- Bluetooth interface.

Figure 1: The Crono PAR (shown with the protective syringe guard), for the treatment of Parkinson's Disease, has both manual and automatic flow profile operating modes.

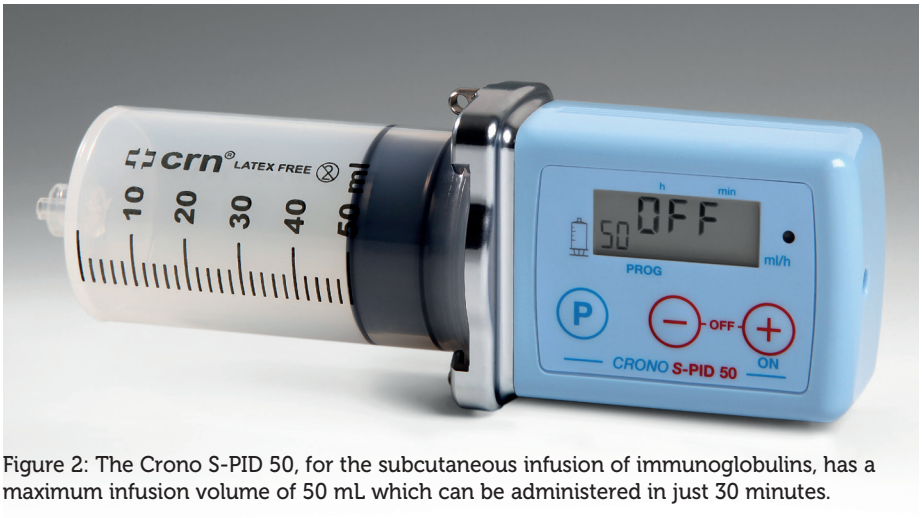

Figure 2: The Crono S-PID 50, for the subcutaneous infusion of immunoglobulins, has a maximum infusion volume of 50 mL which can be administered in just 30 minutes.

Figure 3: The Crono 50 SC is for the subcutaneous infusion of drugs in the treatment of pain. It has a series of functions for controlling the number and interval between bolus doses, and for verifying how the pump has been used during an infusion. The shot size is 20 µL, and the maximum flow rate is 35 mL/h.

Our latest product: Crono S-PID 100

The Crono S-PID 100 ambulatory infusion pump is designed for the subcutaneous infusion of immunoglobulins and drugs in general, and is a union of high technology and innovative design. Its reduced dimensions and weight make it ideal for

home use, giving the patient the freedom to engage in everyday activities during the therapy. The main features of the pump are:

- 100 mL reservoir with luer lock connector
- The possibility of selecting between time or flow rate programming mode:
  - o Delivery time from 20 m to 500 h
  - o Flow rate from 0.2 mL/h to 300 mL/h
- Partial volume Selectable, from 1 to 100 mL in 1 mL increments
- Available priming volume 3.0 mL
- Pump dimensions 88 x 59 x 56 mm, weight 140 g (including CR 123A battery).
- Ingress protection rating IP 42
- Flow rate precision +/-3%
- The possibility of automatically pausing the infusion in order to allow the patient to divide the syringe contents over several infusion sites (this feature is available in flow rate mode only).

The pusher mechanism, which operates directly on the rubber piston of the reservoir, enables the pump to combine high maximum delivery pressure (to maintain flow rate even with a partially occluded or kinked infusion set) with excellent precision. The pump administers micro doses (shots) of fixed volume, and the interval between them determines the flow rate and the configured delivery time.

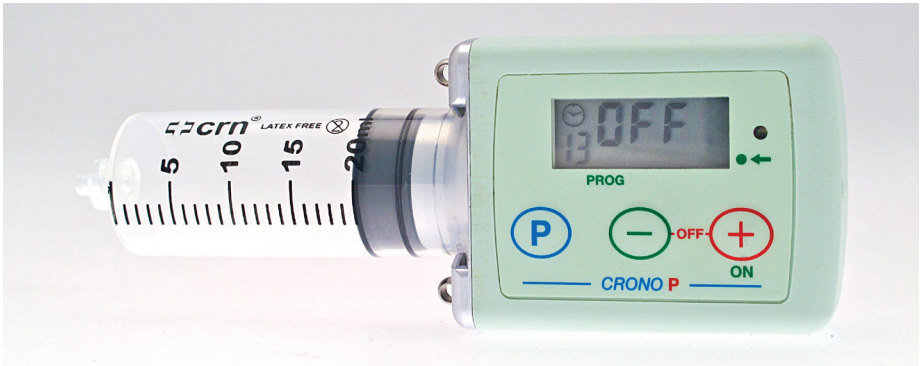

Figure 4: The Crono P is a pump for the infusion of hormones following the body's natural rhythms. The infusion takes the form of a series of boluses at intervals of either 90 or 180 minutes, with a volume which may be programmed from 5 µL to 1000 µL. The day can be divided into up to three periods, with a different bolus volume programmed for each, such that the circadian and ultradian cycles may be reproduced as required.

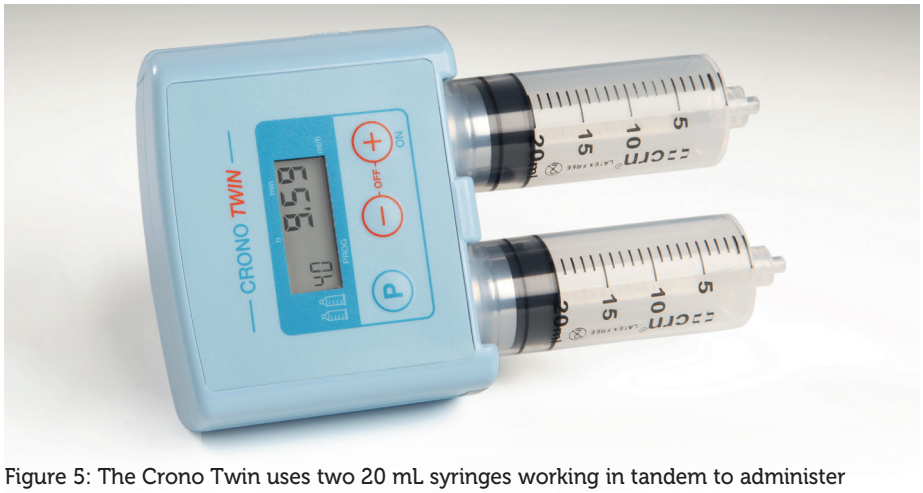

Figure 5: The Crono Twin uses two 20 mL syringes working in tandem to administer immunoglobulins in two or more infusion sites.

PHARMA COMPANY INNOVATION & LIFECYCLE MANAGEMENT: DELIVERY DEVICES AS THE NEW KEY TO PRODUCT SUCCESS

In this article, Jeannie Joughin, PhD, Vice-President, Corporate Development, Enable Injections, describes how on-body delivery systems for the subcutaneous delivery of high volumes of viscous formulations can solve the challenges rapidly emerging as pharma companies advance their biologics pipelines. Focusing on Enable's own platform, Dr Joughin shows how these devices are enabling and enhancing the development of biotherapeutics for the benefit of all stakeholders including patients and pharma companies.

Due to the high cost of bringing a single novel pharmaceutical to market, estimated to be US$2.6 billion (£2 billion) in 2015, pharma companies have greater pressure to maximise revenue and stay ahead of the competition.[1] Taking into account that programs for innovative products are high risk/high reward, many companies continue to focus activities on developing first-in-class treatments. But the most innovative among them, and companies looking to harness their investment in commercial products that are approaching the end of the patent life, are once again turning to novel formulation strategies and delivery systems that can vastly improve the patient experience, the next frontier in drug development.

To help pharmaceutical companies realise their opportunities, new delivery device technologies are in development and available for partnering. These advanced devices make possible subcutaneous injection of up to 50 mL of even the most viscous formulation of large doses to enable, or enhance and differentiate injectable therapies (Figure 1). Patients can easily and comfortably self-administer therapies delivered with the new devices at home, providing biopharmas with an innovative, cost effective mechanism for user acceptance.

> "These advanced devices make possible subcutaneous injection of up to 50 mL of even the most viscous formulation of large doses to enable, or enhance and differentiate injectable therapies."

A well-balanced biopharmaceutical product portfolio and a focus on a pathway for continual product innovation can lower product development strategy risks and lead to a greater overall success in the marketplace.

INNOVATION PROPELS PRODUCT LEADERSHIP

Roche/Genentech and Novartis offer innovation in treatment to specific customer groups as well as increased patient convenience, which has led to a focused

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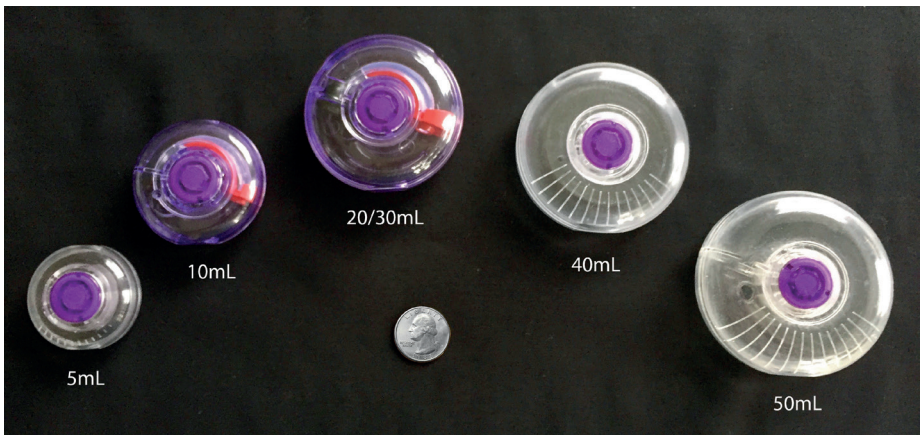

Figure 1: Enable Injections' OBDS: Self-administration of subcutaneous delivery volumes of 5-50 mL. The 10 mL and 20/30 mL injectors with syringe-transfer are ready for clinical application.

product development pipeline. Some of these companies' most successful products of the previous ten years include their first-in-class therapies, such as Avastin (bevacizumab), Rituxan (rituximab), Herceptin (trastuzumab) and Gleevec (imatinib). These products have far higher average projected sales than follow-on products. But maintaining this leadership position requires continuing support of the customer base and innovating around the patient experience with new treatment paradigms.

Many other companies are striving for leadership positions in multiple high-value product franchises. Nowhere is innovation to enhance the patient experience more critical than with high-volume, viscous biologics. The number of biological drugs continues to increase. They now comprise more than 50% of products in pharmaceutical development.

IMPROVING BIOLOGICS' BIOAVAILABILITY, ENABLING SC INJECTION

Although progress has been made in the manufacturing of biologics, particularly in the past few years, advancements in the development of delivery systems able to improve the bioavailability of biologics remained rather limited – until now.

Subcutaneous (SC) delivery may be the preferred way to administer an injected therapeutic. However, SC injections have been limited in the amount of drug substance that can be reasonably delivered and tolerated by the patient in a single injection. One of the main concerns in formulation development is the exponential relationship between the concentrations of biologics and viscosity of the formulation. The highly viscous formulations often required to assure a desired concentration cannot be readily injected.[2,3] Generally, the volume of a bolus subcutaneous injection has been limited to no more than 1-2 mL.

> "Brand loyalty and recognition with a device can be extremely powerful in maintaining market share once the product is commercialised."

Several ways to circumvent these volume limitations, including increasing the concentration of the active ingredient in the formulation, are being pursued. For proteins, issues of viscosity, solubility, and protein aggregation become major obstacles, especially with the smaller-gauge needles that patients prefer.

For large protein biologics such as monoclonal antibodies (mAbs), companies must overcome volume and bioavailability constraints before SC injections can mirror intravenous-like dosing regimens. MAbs often have high dose requirements, so they must be formulated at very high concentrations. At low concentrations, an antibody solution's viscosity increases moderately as a function of protein concentration. But at the high concentrations of some molecules, (>100 mg/mL), viscosity increases exponentially.

Concentration to the necessary level in the final product may not be possible for all products because in many cases upstream purification and manufacturing processes may be the limiting factor in achieving maximum concentration for the final drug product, more so than delivery and fill/finish processes. And drug-product properties, such as pH and osmolality, along with the use of certain excipients, may also limit the most appropriate drug-product concentration.

These properties may need to be kept within certain ranges to prevent patient discomfort and injection-site reaction. This leaves increasing the administered volume of drug product as the solution to deliver a larger dose, but this approach can have disadvantages. There are limitations to how rapidly a volume of drug can be injected subcutaneously. Although the optimal injection time varies greatly by individual drug product, and the literature regarding the relationship between injection volume and speed is limited, the subcutaneous space cannot necessarily tolerate rapidly injecting larger and larger dose volumes. Tissue disruption and site reaction may occur.

Second, if the injection is rapid and the volume is too large, there is potential for the product to leak back from the injection site, reducing the bioavailability relative to the total dose. Lastly, a larger volume of product may require a larger device for self-delivery, and, potentially, a longer injection time, increasing the difficulty for the patient to hold the device at the injection site and the potential for an under dose.

Understanding SC tissue pressure is critical for the design of injection devices acceptable to the user. A recent study found that increased pressure and mechanical strain in the subcutaneous space is more directly related to increasing flow rate rather than to volume.[4] Therefore, it is imperative to ensure the user is not inconvenienced during a potentially lengthy administration of therapy.

A potential new solution to large-volume injection challenges is the development and use of systems that administer the dose into the subcutaneous space more slowly. Such systems can expand the possibilities for self-injection.[4,5] Due to the need for longer duration of injection, the device or system may need to be temporarily attached to the body at an appropriate injection site; thus, the current industry interest in large volume wearable injectors (on-body delivery devices).

The rise of viscous biologic drugs, the shift towards patient self-injection and the emergence of these safer, simpler, and more convenient devices are all contributing to the expansion of a new delivery mechanism for large volume, viscous, subcutaneous administration.

ADDRESSING COSTS: ENABLE EASY SELF-ADMINISTRATION OF BIG BIOLOGICS AT HOME

On-body delivery systems (OBDS) can be leveraged by a pharmaceutical company to accommodate preferential attributes for patients, prescribers, and payers, with the potential to improve therapy adherence, build or protect market share, and lower overall health system costs.

The newest, most advanced of these high volume delivery devices can move the treatment of patients with injectable products from the hospital to the home, reducing costs while providing the innovator drug company with increased return on investment, and patients with a potentially more favourable treatment option for adherence to chronic and/or maintenance therapies.

A time-and-motion study undertaken in eight countries reported significant time savings for both healthcare professionals and patients through use of rituximab SC *versus* intravenous (IV). These findings suggest potential for reduced waiting times, greater appointment availability, and improved efficiency of oncology units with the SC formulation. SC injections can be administered by the patient. The injections are not generally painful and carry a reduced risk of infection and other complications.

Compared with IV drugs, the majority of participants considered SC drugs clinically safer and more cost-effective, resulting in higher patient satisfaction.[5]

Wearable injectors are designed to address the challenges of complexity, patient compliance and cost. Enable Injections' focus on human factors in the design and development of high volume delivery devices makes self-injection safe, easy, comfortable and convenient for patients – yet cost-effective for the pharmaceutical industry and payers.

CONSIDERATIONS IN CHOOSING A HIGH VOLUME DELIVERY DEVICE

It is important to select the right device to deliver the right drug with the right viscosity and the right dose volume over the right period of time. Factors to consider include injection frequency, dose volume, drug viscosity, delivery rate and duration. Among human factors to consider are pain, portability and convenience, which can drive therapy compliance and preference rates amongst target patient populations.

Device-related factors that may play a significant role include dose variability across a patient population, ease of use, the need for dose adjustment and whether the drug must be refrigerated or kept at room temperature. Parenteral drug products are typically stored refrigerated at 2-8°C. A decrease in temperature will cause viscosity to increase exponentially. Bringing refrigerated drugs to room temperature can take 30 minutes, an inconvenience for patients. Consequently, there is a need for a delivery device capable of transferring highly viscous product and eliminating waiting time for the drug to rise to room temperature.[6] Other enhancements, including simple data capture technology, can be incorporated to monitor compliance and adherence to therapy.

The right balance between dose volume, viscosity and, in particular, delivery duration is becoming increasingly important to pharmaceutical and biotechnology companies for SC injection therapies.[7]

Enable Injections' wearable high volume injectors are capable of delivering higher volume (up to 10 mL and up to 20/30 mL) products at a desired flow rate over periods suitable for a particular product, minimising pain and delivering product in a predictable manner. The 10 mL and 20/30 mL injectors are ready for clinical application. The delivery of larger volume product in Enable injectors – for example up to 50 mL – is also possible. The devices to deliver higher volumes are currently in the development stage.

The Enable injector and transfer system are customised to the specific product

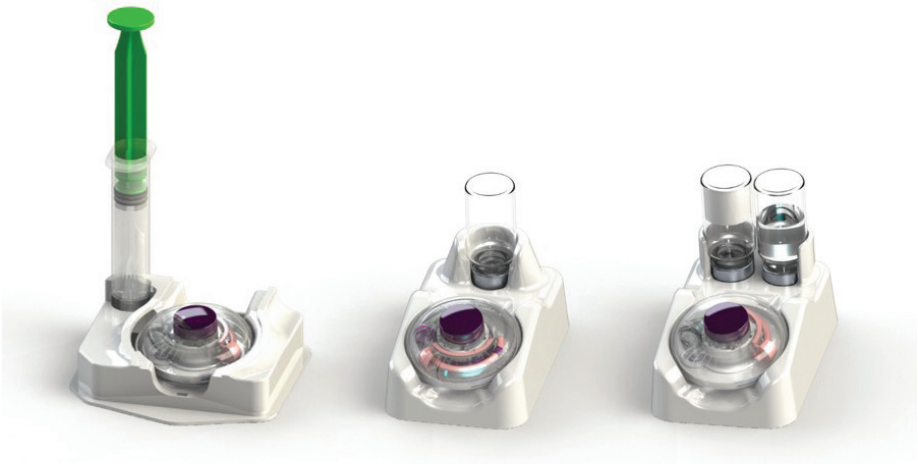

Figure 2: Platform technology that utilises standard vials or syringes and offers automated mixing and reconstitution.

Figure 3: The "3 P's" of Enable Injections: Place the injector onto the skin; Pull the safety tab; Press one button.

characteristics. By using three different transfer platforms, which utilise established primary containers (syringe and vial), the advantages to the product manufacturer include cost savings and shorter time to market (Figure 2).

Today's most sophisticated drug delivery devices are differentiated from legacy injection systems by:

1. Utilising standard vials or syringes to minimise drug stability issues often encountered in new container closure development
2. Automatically warming the drug as the injector is filled, thereby removing the typical wait time to use the device for a refrigerated medication
3. For lyophilised drugs, completely automating mixing and reconstitution – removing any patient variability from the mixing process
4. Using the smallest needle size possible to improve patient comfort
5. Adjusting flow rate to reduce discomfort
6. Designing small systems with a low profile that can be discreetly worn on the body, which also allows greater freedom and mobility
7. Incorporating simple data-capture technology which can aid in monitoring patient compliance and adherence to therapy.

ELIMINATE PATIENT CONFUSION & ERRORS WITH DOSING SIMPLICITY, FLEXIBILITY

Minimising user error is an engineering and design challenge for wearable injector developers. Today's most advanced injector minimises any confusion by requiring only a few simple steps for patients – the "3 P's" of Enable Injections: Place the injector onto the skin; Pull the safety tab; Press one button (Figure 3).

EARLY CLINICAL USE DETERMINES OPTIMAL DOSING, FLOW RATE, COMPLIANCE

With devices becoming increasingly integral to the clinical development, regulatory approval, and lifecycle management of drug-device combination products, the ability to provide a solution for flexible dosing for the Enable Injections on-body delivery system has resulted in the ability to gain data during early clinical/dose finding studies. The company's syringe-based OBDS, for example, supports data collection on the performance and acceptance of the device while determining the optimal dose and flow rate. Obtaining this information provides confidence for future development of larger volume biologics for in-home use and demonstrates acceptability and likely product uptake. Once these important factors are known, the system can be readily adapted to accommodate a fixed dose vial for product transfer if required.

STUDIES: PROVEN USER ACCEPTANCE OF ENABLE INJECTIONS' OBDS

Although the Enable OBDS is yet to be commercialised, independent User Preference studies have demonstrated a high acceptance of the Enable technology by patients and caregivers.

BESTING THE COMPETITION

For innovative pharma companies looking to extend their leadership position and for companies manufacturing biosimilar products looking to bring a differentiated offering to market, patient friendly self-administration by subcutaneous dosing holds the promise to provide greater success in commercialisation.

EASIER CLINICAL TRIAL RECRUITMENT – READY TO PARTNER

Several companies are developing their own versions of biological therapies for the treatment of cardiovascular, autoimmune and neurological diseases and are often in direct competition with respect to patient recruitment for clinical trials. Utilising a delivery device to improve patient comfort and convenience could provide benefits beyond those experienced from a safety and efficacy perspective.

Brand loyalty and recognition with a device can be extremely powerful in maintaining market share once the product is commercialised, one example being EpiPen.[8] There are several recent examples that biopharmaceutical companies' established track record in product development, in partnership with an innovative drug delivery company, can assist in a faster time to market by providing greater motivation and patient participation in clinical trials. Enable Injections provides the smallest profile wearable device for large volume product delivery (see Figure 4) and is ready to partner with the biopharmaceutical industry to enable and empower patients requiring chronic administration of lifesaving or life enhancing therapies.

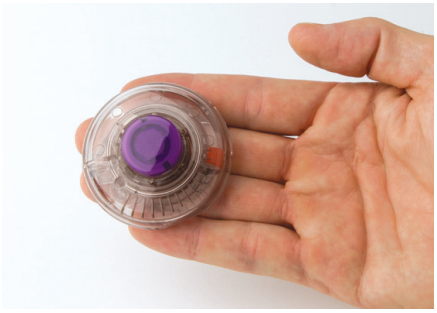

Figure 4: Enable Injections' technology is designed to have a friendly appearance with a low profile that can be discreetly worn on the body to also allow for greater freedom and mobility.

……..Enable their Day!

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PROVIDING PHARMACEUTICAL COMPANIES WITH MARKET-LEADING WEARABLE INJECTORS, PARTNERS AND PEOPLE

This article by Stephen Allan, Senior Vice-President, Marketing & Communications, at Unilife, highlights some of the key reasons the company's customer-centric strategy is helping it establish long-term, commercial relationships with many leading pharmaceutical companies and industry suppliers.

In response to unmet and emerging market needs for the containment and delivery of injectable biologics, Unilife has created a market-leading portfolio of wearable injectors that is backed by an expert team and a strong network of industry partners to help pharmaceutical companies minimise risk and maximise brand differentiation.

Pharmaceutical companies continue to prioritise the clinical development and commercial marketing of injectable biologics such as monoclonal antibodies that target the long-term treatment of chronic or rare diseases with well-defined patient populations. Whenever feasible, companies will strive to develop these biologics in a patient-centric, subcutaneous (SC) formulation that strikes the right clinical and commercial balance between injection frequency, dose volume and drug viscosity.

Traditionally, a key gating factor has been the limitation of conventional hand-held devices such as prefilled syringes or disposable auto injectors to dose volumes of up to 1.2 mL, potentially forcing companies to compromise on sub-optimal injection frequencies or viscosity levels that may reduce rates of user acceptability or comfort.

Disposable wearable injectors, such as those which can be prefilled and supplied in a ready-to-use format like auto injectors yet pre-configured to contain doses up to 10 mL over a specific rate and duration, are increasingly being leveraged to enhance the provision of care, improve therapy adherence and maximise brand preference amongst patients, prescribers and payers.

> "A core, competitive strength of Unilife's wearable injector portfolio is the ability for any pharmaceutical company to have their drugs Pre-filled, Pre-assembled and Pre-configured for supply to patients as a fully integrated, ready-to-inject system."

Over the last year, a first wave of pharmaceutical companies has begun to market some of their lead biologics in wearable injector technologies. While such first-generation wearable systems can have technical and functional limitations, such as having to be filled and assembled by the patient prior to use, their market entry marks the beginning of a new era of innovation and growth for drug delivery.

More than a dozen pharmaceutical companies are targeting the use of

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wearable systems for new product launches or to optimise the commercial lifecycle of approved drugs via strategies such as conversion from intravenous (IV) infusion to SC injection. While some therapies will require 100% use of wearable injectors, some companies are expected to make them available as an additional option to better address the needs of patient sub-segments that are under-served by hand-held products.

Whether a pharmaceutical company has multiple drugs being targeted for use with wearable injectors, or a single therapy with multiple target indications or delivery profiles, it has become common for them to conduct upfront due diligence to select a preferred device partner and technology that can best address their long-term clinical, commercial and operational requirements. Typically, pharmaceutical companies will assess prospective wearable suppliers and their respective technologies across a range of factors which are as equally important, if not more so, than price. They include:

1) Ease of use by target patient populations
2) Flexibility for efficient customisation and scale-up across target molecules, brands or indications
3) Integration with standard filling and packaging processes, and material component preferences
4) Long-term continuity of product supply, with the potential to secure exclusive or non-exclusive access for defined drugs or indications.

In response to these and other customer requirements, Unilife has created the industry's first full portfolio of pre-filled, pre-assembled and pre-configured wearable injectors that are platform-based and leverage standard primary container materials and industry processes. The breadth and depth of this proprietary portfolio gives Unilife the flexibility to enhance virtually any wearable therapy regardless of dose volume, delivery rate, viscosity or administration duration. The market-leading attributes of this portfolio, the expertise and commitment of the people and partners behind it, and the company's commitment to helping customers enhance and differentiate their therapies under low-risk, long-term relationships, has allowed it to enter into commercial programs with many leading pharmaceutical companies.

THE P-3 ADVANTAGE

A core, competitive strength of Unilife's wearable injector portfolio is the ability for any pharmaceutical company to have their drugs **P**re-filled, **P**re-assembled and **P**re-configured for supply to patients as a fully integrated, ready-to-inject system that requires only three intuitive steps to commence therapy.

We call this the **P-3** advantage, and it provides customers with significant opportunities to optimise rates of user acceptability and product differentiation against brand-name or biosimilar rivals. By eliminating the need for users to assemble, load or pre-set the drug-device combination prior to use, pharmaceutical companies can reduce therapeutic and packaging complexity, as well as the risk of use error.

PRE-FILLED AND PRE-ASSEMBLED

Unilife wearable injectors are designed to mimic the standard assembly process used across the industry for the filling, assembly and packaging of disposable auto injectors. Standard syringe filling and inspection lines are used to fill tubs of primary drug container cartridges with a measured dose of drug, prior to the insertion of the elastomer. Low or high speed fill-finish equipment from well-known equipment suppliers can be utilised, with only change parts required. The prefilled cartridge is then assembled with upper and lower housings, electronics and a window during final assembly to complete the drug-device combination product. The process maintains container closure integrity and sterility using three barriers. Critically for the protection of the biologic, the design process enables the sterilisation of components without the need for terminal sterilisation.

PRE-CONFIGURED AND SUPPLIED READY FOR INJECTION

Unilife's wearable systems can be pre-configured to deliver a measured dose precisely at a specific rate and duration according to customer requirements. Instant, delayed or on-demand bolus or variable rates are available through the use of mechanical or electromechanical drive systems that can facilitate the controlled delivery of the dose at rates between 0.001 mL and 0.1 mL per second.

While it is most common for pharmaceutical companies to target the delivery of biologics over minutes or hours, Unilife has the capacity to customise its devices for precise delivery in less than 10 seconds or over multiple days.

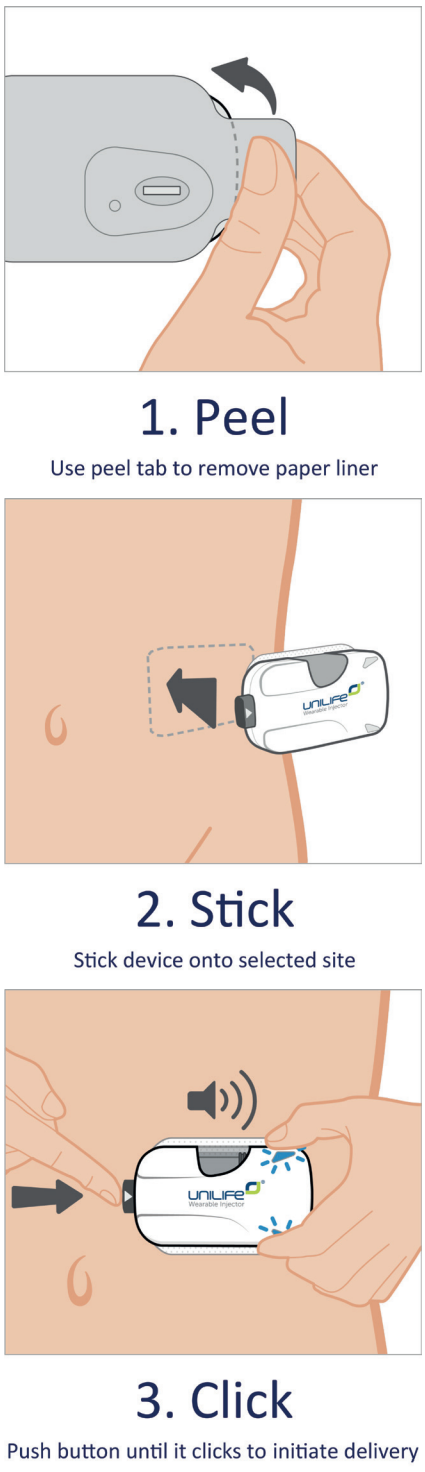

Figure 1: Prefilled, pre-assembled, pre-configured and supplied ready for injection, with only three intuitive steps required to commence therapy.

THREE STEPS TO THERAPY

To initiate dose delivery, a patient has only to undertake three device-related steps that are popularly summarised as "Peel, Stick

Figure 2: A 1 mL product configuration from Unilife's wearable portfolio designed to enhance biologics constrained by the limitations of conventional hand-held systems.

and Click" (see Figure 1). By comparison, other wearable injector technologies that require loading and assembly with the drug can take up to nine device-related steps or more to initiate dose delivery, significantly increasing preparation times and the risk of user error.

One example of Unilife's design commitment to safe, simple patient use is the inclusion of an on-body sensor that automatically prevents the risk of premature activation until the sensor has depressed against the body. A safety guard, which covers the sensor during packaging, is removed by the patient as they peel off adhesive liner.

CLEAR, CONFIDENT AND COMFORTABLE USE

Unilife has created various features available across its portfolio of wearable injectors that are designed to provide patients with clear, confident and comfortable use during all stages of therapy.

- **Single push activation:** On standard Unilife wearable injectors, a single button is situated on the side of the device to reduce the sense of downward pressure being applied onto the body during activation. Minimal force is required to push the button, with the start of dose delivery occurring virtually simultaneously to help build user confidence.
- **Audible & visual status alerts:** Clear audible and visual alerts inform the patient of dose initiation, in-progress status and completion. Should pharmaceutical companies identify that patients may desire discretion during therapy use, Unilife can configure the device so that users can easily turn off these alerts.

> "Unilife has developed wearable injector configurations with integrated Bluetooth LE that provides customers with significant opportunities to improve connections with patients, prescribers and payers. Together with smart phone apps developed by Unilife, patients can receive injection reminders and prompts, access to historic data regarding their therapy regime, and access to technical or steps of use information."

- **Wide medication viewing angle:** A large window provides a clear, unobstructed view of the medication prior to and during use.
- **Medical-grade adhesive skin patch:** The medical-grade adhesive patch that is applied against the skin is designed to provide comfort and security over periods of up to one day across a range of normal physical activities.
- **No needle visibility:** Upon activation, a soft cannula is automatically inserted into the administration site at a pre-configured depth to initiate drug delivery. No needle is visible during any stage of use, with patients able to dispose of the device safely and conveniently as per recommended guidelines.

SMALL DOSES FROM 0.5 ML TO 2 ML

Unilife has created various device configurations designed to enhance the containment, portability, delivery and disposal of injectable therapies that might traditionally be administered in prefilled syringes, disposable auto injectors or insulin pumps (Figure 2). One device configuration developed by Unilife for the bolus delivery of doses up to 1.2 mL is approximately 25% smaller in volume, 60% shorter in length and 90% lower in height than a popular disposable auto injector with an equivalent dose.

Another Unilife configuration combining constant basal infusion with on-demand bolus represents the world's first prefilled, disposable insulin patch pump.

The small size, ergonomic shape and robust materials utilised with Unilife's small dose wearable devices can optimise user portability prior to use, as well as discreet, under-clothing wear during use. With the ability to pre-configure the delivery of the dose over a specified number of minutes, hours or days, Unilife also has the potential to assist pharmaceutical companies seeking to minimise the sense of patient pain or sense of discomfort that occur with the rapid injection of a dose with some auto injector technologies.

LARGE DOSES FROM 2 ML TO 10 ML

Unilife has created a broad portfolio of wearable injectors for the delivery of injectable biologics with dose volumes between 2 mL and 10 mL. The Precision-Therapy platform (Figure 3) leverages a mechanical drive system for immediate bolus injections, and is designed for use with therapies where the specific dose delivery volume helps to determine clinical outcomes. The Flex-Therapy platform

Figure 3: Precision-Therapy wearable injectors are designed to optimise the bolus delivery of injectable biologics with dose volumes greater than 2 mL.

(Figure 4) has an electromechanical drive system for delayed bolus, variable or intermittent bolus injections, and is designed for use with therapies where the specific delivery rate profile helps to determine clinical outcomes.

Figure 4: Flex-Therapy wearable injectors are designed to optimise the variable rate delivery of injectable biologics with dose volumes greater than 2 mL.

PRIMARY CONTAINER DESIGN AND MATERIALS

Unilife's primary drug container is designed with industry standard borosilicate type 1 glass and well characterised lubrication oils and elastomers for long-term drug containment and sterility assurance. A sterile path to the prefilled container is only opened when the user has pressed the button to initiate drug delivery.

Unilife has established a broad, flexible supply chain to provide customers with access to preferred materials from various component suppliers that are well known across the industry. Unilife is also able to provide pharmaceutical companies with primary drug container cartridges, together with other technical information regarding container closure integrity and sterile barrier integrity, separate from its full wearable injector system, for testing and evaluation purposes.

DEVICE CUSTOMISATION

All product configurations across Unilife's platform-based portfolio of wearable injectors are based upon a modular system designed to allow the customisation of one element without creating a need to redesign the others. This provides customers with a modern, flexible, and easily scalable technology platform that can be efficiently tailored to specific drug, patient or brand requirements with minimum risk or incremental cost. In addition to standard customisation options relating to size, look, shape and materials, a number of advanced customisation options are also available (see Table 1).

For example, Unilife has developed wearable injector configurations with integrated Bluetooth LE that provides customers with significant opportunities to improve connections with patients, prescribers and payers. Together with smart phone apps developed in collaboration with Unilife, patients can receive injection reminders and prompts, access to historic data regarding their therapy regime, and access to technical or steps of use information. When combined with RFID or Quick Response (QR) codes, use of the correct prescribed dose and expiration status may also be verified. To improve monitoring of therapy adherence rates by specific patients or entire patient populations, data, including successful dose delivery, may be sent in real-time to secure data hubs.

CONTINUITY OF SUPPLY AND SPECIAL ACCESS

Unilife's business is structured to provide pharmaceutical customers with long-term continuity for production and supply to minimise risk and maximise choice during the clinical development, approval and commercial marketing of the drug-device combination. Partnerships are in place with a range of global industry leaders that are regularly utilised by pharmaceutical companies for production and commercial supply, elastomers, glass forming, injection moulding, equipment automation, contract filling, electronics and sterilisation.

In addition to a provision of supply-chain continuity, Unilife is open to long-term business relationships that provide customers with some level of exclusive or non-exclusive access to its proprietary technology, including a customised look and feel, for use with specific drugs or drug areas.

Such mutually favourable access rights, where it does not conflict with other customers, can allow pharmaceutical companies to leverage the benefits of Unilife's technology fully, to differentiate its therapies from brand-name or biosimilar competition.

Unilife's team of industry professionals is ready to serve the needs of pharmaceutical companies seeking to enhance and differentiate the delivery of their small or large volume biologics.

Unilife Wearable Injector Portfolio Customisation Options		
Shape, Look and Feel	Materials and Components	Advanced Customisation
Ergonomic shape	Glass or plastic tubing (material / supplier)	Bluetooth LE or other
Activation button (Nº, size, force, position)	Elastomer (material / supplier)	Smartphone apps
Adhesive design (Nº and size of tab)	Silicone oil (material / supplier)	RFID scanning
Viewing window design	Rigid needle or soft cannula	Drug warming
Pad printed label / Laser marked		Temperature sensing
Rubber grip		
Removable electronics		
Lighting (Nº, colour, size, position)		
Sounds (tones, sequence)		
Tactile (clicks, vibration)		

Table 1: Unilife wearable injectors are platform-based with a variety of customisation options available, enabling the efficient tailoring of one element within the system without the need to redesign others.

Adhesives Research®

IMPORTANCE OF ADHESIVE SELECTION IN WEARABLE DEVICES FOR DRUG DELIVERY SYSTEMS

In this article, Gozde Karabiyik, PhD, Product Development Scientist, Adhesives Research, highlights the crucial role that the adhesive plays in the success of a wearable injection device, describes in detail some of the challenges relating to skin adhesives – both general and specific to their application in wearable injectors – and provides advice and solutions to help with successful adhesive selection.

"When developing an effective and robust wearable drug delivery system, it is important to understand the factors influencing adhesion of the device to skin. During wear, the adhesive and skin bond of a device are constantly challenged by external factors."

UNDERSTANDING ADHESIVE CHALLENGES WITH WEARABLE DEVICES

The development of wearable devices is rapidly increasing in various areas of healthcare and wellness. Medical devices are advancing from portable equipment to small devices that can be worn on the body for several days of continuous physiological monitoring and delivery of certain biologics. Wearable drug delivery devices have become very important in the delivery of insulin and other large compounds to subcutaneous tissues. These wearable devices utilise skin adhesives to secure bonding to skin to deliver target therapeutic doses reliably.

When developing an effective and robust wearable drug delivery system, it is important to understand the factors influencing adhesion of the device to skin (see Figure 1). During wear, the adhesive and skin bond of a device are constantly challenged by external factors which cause the edges of the adhesive to lift off of the skin, making the device vulnerable to premature fall off. Factors that cause this type of edge lifting include: friction (created from clothing, moving and stretching due to physical activity), as well as moisture exposure, and varying skin types. In wearable device applications such as patch pumps, infusion sets and continuous glucose monitoring devices further challenges arise from the weight of a device or limited moisture vapour transmission from under the device. Differences in skin surface energy and stretching resulting from age, race, and patient health also contribute to variation in adhesion levels. Likewise, placement of a device on different body locations affects wear performance.

UNIQUE CHALLENGES FOR SKIN ATTACHMENT

The performance of a wearable drug delivery device depends on how reliable and reproducible the attachment is on the body for the targeted wear time. It is important to consider the physiology of the skin to develop skin-friendly adhesive

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platforms. Wearable device applications present unique adhesion challenges due to the skin's complex structure that changes based on each individual's age, gender, race, and diet. Skin is a living and breathing substrate; therefore, numerous properties of skin affect wear performance, making it challenging to design a skin adhesive that performs the same for every patient within a large population.

Skin has an irregular surface with hair, pores and wrinkles. As a result, an adhesive should have good balance of viscoelastic properties to be able to flow on the skin surface for efficient bonding and remove cleanly with no residue. In addition, skin has a low surface energy for which the adhesive must replicate an equivalent or a lower surface tension to achieve sufficient bond to skin surface. The surface energy is variable depending on the area of the body. Clean, dry skin has a lower surface energy than the forehead, which is typically oilier than the rest of the body. Another critical factor is the placement of the device on the body as it plays an important role due to differences in curving and stretching of skin.

For example, placing a device on the abdomen (see Figure 2) will create different stress on the adhesive compared to the shoulder (Figure 3) or arm during daily activities. In some cases, such as patch pump users, patients prefer to place the device on different parts of the body and expect the same wear performance.

Moreover, the activity levels for specific patients can be dynamic where the user needs to carry on daily activities including exercise and showering. Environmental factors such as relative humidity and temperature depending on seasonal changes can also have an impact on adhesion to skin. Therefore, it is critical to understand the skin type, activity level of the target population, location on the body and environmental conditions related to a specific application.

ADHESIVE REQUIREMENTS: BIOCOMPATIBILITY & BREATHABILITY

The application of pressure-sensitive adhesives (PSAs) in skin-contact products requires several important features that predetermine their composition, structure, and processability. These features are connected with the biological properties of skin and its nature as a substrate.

Figure 1: Factors to consider for adhesives used in wearable devices.

Figure 2: Adhesives Research's skin-friendly wearable adhesives for abdomen placement.

Figure 3: Adhesives Research's skin-friendly adhesives for shoulder placement.

Adhesive biocompatibility is a significant concern in any skin adhesive application. Medical devices may be applied to skin that is compromised due to acute, chronic, or systemic conditions; therefore, it is important that no component of the adhesive aggravates the skin further. Skin adhesives should be formulated carefully to provide a biocompatible adhesive system to prevent any adverse skin reaction. There should be no toxic components that can be absorbed through broken or compromised skin, but there should also be no residual components that could cause an allergic sensitisation response or an acute chemical irritation. Presence of any residual unreacted free monomers, stabilisers, cross-linking agents, residues from initiators, surfactants, and processing aids could potentially cause skin irritation and sensitisation.

Skin breathability through the adhesive is essential to prevent maceration and irritation during wear due to lack of water transport from the skin. In some applications, maintaining a certain hydration level at skin and adhesive interface is critical for enhancing drug flux. In this case, the skin becomes weak due to maceration and it can result in potential tearing and pain during device removal. Moreover, it is also prone to infection. Skin breathability affects device wear ability, depending on the moisture vapour transmission rate (MVTR) of the device design as well as the adhesive construction. Breathability of skin adhesives can be increased via adhesive and substrate selection, lowering adhesive coat weight, and zone or pattern coating. Adhesive tapes with high MVTRs prevent accumulation of moisture at the skin/adhesive interface which typically causes premature device fall off.

Wear performance of an adhesive tape also depends on device design, i.e. size and shape of the device and how it fits body contour. Variations in device designs and skin property of the target population result in the need for customisation of skin adhesives specific to each application. In terms of device design, height of the device is critical as the profile of the device influences probability of getting caught by clothing. Devices that are bulky and heavy create bonding challenges. Moreover, device weight exerts shear force yielding failures, therefore selection of the adhesive at correct levels of aggressiveness to tolerate device load is important. In addition to size and weight of the device, the area of the device that covers the skin adhesive influences wear performance. If the footprint of the device is the same as the skin adhesive, the breathability is limited and the moisture build-up under the device may result in delamination. If the skin adhesive layer

is extending around the perimeter of the device, the wear performance is enhanced by breathability of the additional adhesive.

A good balance of adhesive and cohesive properties provides sufficient bonding to the skin and prevents sliding of the device while on the skin due to the forces exerted by the weight of the device. The adhesive needs to have adequate shear strength to carry the device with no creep and no residue. Cohesive strength prevents sliding of the device on skin over time and avoids formation of a black ring around the device patch. Formation of a black ring is usually encountered with adhesives that are soft and aggressive where lint and dirt adheres to the adhesive edge so when the patch is removed it leaves a black residue trace. In addition to cohesive strength, adhesives with a high level of initial tack perform better due to the need for a quick stick of the device on the skin soon after it is applied. If the adhesive requires a certain amount of dwell time on the skin to build adhesion, then the device may prematurely lift off due to its weight.

Depending on the application, the device including the adhesive may be sterilised via gamma, e-beam or EtO sterilisation. In these instances, it is important to ensure that adhesives that retain adhesive and cohesive properties upon sterilisation are utilised in device design.

In summary, it is critical to understand device design, dimensions, weight, and patch design and application duration to develop a skin adhesive specific to an application.

LOW-TRAUMA ADHESIVES FOR SHORT-TERM WEAR

There is a growing need for low-trauma adhesives to provide reliable adhesion on different skin conditions and age groups with gentle removal experience. Moreover, treatments for chronic conditions require repeated application and removal of a skin patch on a specific skin site. Adhesives Research is addressing the need for gentle and repositionable skin adhesives through the development of low-trauma adhesive (LTA) technology for gentle removal (SoftWear®). This customisable PSA platform technology maintains intimate skin contact for up to three days with painless and residue-free removal.

The SoftWear® adhesive platform is repositionable and allows a clean release from skin and hair. Silicone and non-silicone formulations are available under this adhesive platform. Unlike traditional skin adhesives, SoftWear® adhesives do not lose tack after removal from skin; therefore it can be applied to the skin and removed multiple times allowing users to reposition the devices on their skin if needed. SoftWear® adhesive has thinner product profile that provides reduced edge lift and grab to clothing. Gentle removal of this adhesive makes this adhesive platform ideal for paediatric and geriatric applications. The adhesive is formulated to release from hair and the top layer of skin cleanly with a pain index <1 on the Wong-Baker FACES® Pain Scale. For comparison purposes, a standard skin-friendly adhesive has a pain index rating of 4-5 on this scale based on internal studies. In addition, LTA formulations exhibit resistance to radiation sterilisation techniques.

SKIN-FRIENDLY ADHESIVES FOR LONG-TERM WEAR

Wearable drug delivery devices are designed for long wear times extending adhesion on skin beyond seven days. Adhesives Research has designed a tailorable biocompatible adhesive technology that provides an aggressive long-term wear (LTW) adhesive platform to secure a wearable drug device on skin for up to 14 days. This adhesive platform ensures bonding of the tape to skin with minimal edge lift during the course of wear and removes from the skin cleanly without leaving any residue. In spite of its strong adhesion on skin, LTW adhesive does not cause disruption of the stratum corneum after removal. Studies have also shown that pain experienced upon removal of the tape is tolerable and results in a pain index of <2.5 on the Wong-Baker FACES® Pain Scale. This adhesive platform provides high MVTR for breathability and good wear properties with no edge residue or cold flow. It can be further tailored to customise the wear time and adhesion levels depending on the wear duration and device design of a specific application.

CONCLUSION

It is challenging to have one adhesive that performs well across all variables. It is critical that the device is designed to understand adhesive tape behaviour and challenges with various skin types, age groups, activity levels and living environment. Adhesives Research understands the unique challenges of skin attachment due to load created from the weight of the device, the need for immediate adhesion to skin and the complex nature of skin.

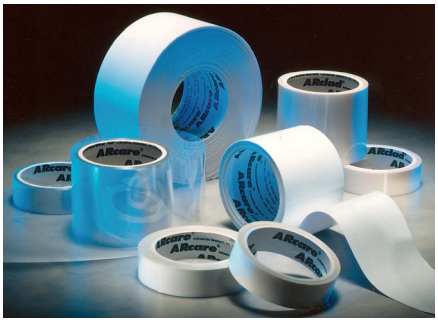

Figure 4: Adhesives Research's skin-friendly adhesives.

Consideration of physiology of the skin and device design led Adhesives Research to develop skin-friendly adhesive platforms to provide custom solutions to unmet needs of various skin attachment applications (Figure 4). Skin-friendly adhesive platforms include SoftWear® (gentle adhesives), long-term wear adhesives which are biocompatible per ISO 10993, non-cytotoxic, non-irritating or sensitising. These platforms are ideal for providing skin attachment of numerous devices such as sensors, infusion pumps, and patch pumps with various sizes, weights and application times. The adhesive platforms have been integrated in many skin adhesive products for a number of wearable device applications.

ABOUT THE AUTHOR

Gozde Karabiyik is R&D Product Development Scientist for the Medical and Pharmaceutical divisions at Adhesives Research. Since starting with Adhesives Research in 2009, Dr Karabiyik has focused on the custom development and manufacturing of adhesive technologies for diagnostics, wearable medical devices and wound care applications. In 2011, her co-authored paper won the Carl Dahlquist Award by the Pressure Sensitive Tape Council, (PSTC). Dr Karabiyik earned her PhD in Macromolecular Science and Engineering from Virginia Tech (Blacksburg, VA, US), her MSc in Materials Science and Engineering from Sabanci University (Istanbul, Turkey) and her BSc in Chemistry from Izmir Institute of Technology (Izmir, Turkey).

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