

INJECTABLE DELIVERY: WEARABLE BOLUS INJECTORS



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**Injectable Delivery:
Wearable Bolus Injectors**

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

EDITORIAL CALENDAR 2014/15

- Sep: Prefilled Syringes
- Oct: Drug Formulation & Delivery Solutions & Services
- Nov: Pulmonary & Nasal Drug Delivery
- Dec: Delivering Biotherapeutics
- Jan: Ophthalmic Drug Delivery
- Feb: Prefilled Syringes
- March: Transdermal Delivery, Microneedles & Needle-Free Injection
- April: Pulmonary & Nasal Drug Delivery
- May: Injectable Drug Delivery: Devices Focus

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Front cover image: "A wearable injector applied to the abdomen.", kindly provided by Unilife Corporation (see this issue, page 8).

CONTENTS

4 - 5	Editorial Comment Guy Furness
7	Introduction: Pharma Perspective Paul Jansen, Associate Vice-President, Medical Device Development Sanofi
8 - 13	Criteria for Selecting a Wearable Injector Technology and Partner Alan Shortall, Chief Executive Officer Unilife Corporation
16 - 19	Large-Volume Injector Enables Anytime Anywhere Delivery of Parenteral Drugs Dr Pieter Muntendam, President and CEO scPharmaceuticals Inc Dr Gerhard Mayer, Vice-President, Business Development North America Sensile Medical, USA Dr Lars Krinelke, Head Product Management, Head Medical Affairs Sensile Medical AG
22 - 24	PatchPump: Expanding the Limits of Parenteral Administration Marylyn Rigby, Director of Business Development & Marketing SteadyMed Therapeutics, Inc
26 - 28	Integrated Solutions for the Delivery of High-Volume Biologics Mr Graham Reynolds, Vice-President, Marketing & Innovation, Pharmaceutical Delivery Systems West Pharmaceutical Services, Inc
30 - 33	People Power: Inspiring & Delivering a Unique Wearable Bolus Injector Enable Injections, LLC
34	Safe & Reliable Primary Drug Container Manufacturing Gerresheimer AG

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These products have not yet been evaluated by the FDA

EDITORIAL COMMENT



I'm pleased to present to you here the first ever issue of ONdrugDelivery Magazine to focus wholly on the topic: "Wearable Bolus Injection Devices". These devices, also known as patch pumps or high-volume injectors, typically carry out automated subcutaneous (SC) delivery of large volumes of potentially highly viscous drug formulation whilst worn like a patch, adhered to the skin. They are distinguished from long-term infusion devices which have existed for many years now in that, rather than delivering a constant amount of drug per minute or sequential small regular doses in order to maintain specified drug plasma levels over time, wearable bolus injectors deliver a single bolus SC dose and are then removed and disposed of or recycled.

I've heard of, read about and written on a number of "hot topics" over the decade or so since drug delivery became my career focus – some of them weren't hot at all it turned out, others were important but destined for failure, and a fair few of them have changed the pharmaceutical industry forever. I have never been able to say this about a class of novel (pre-approval) drug delivery systems with such certainty before, but wearable bolus injection devices belong in the latter category. They will change the pharmaceutical industry forever, and they will do it relatively soon.

Why so sure? In short, this class of devices has found the sweetest of sweet spots for a major technological innovation. On one hand, a cluster of wearable bolus injectors are coming through their own development process timed perfectly to be available and ready to fulfil a huge need in the market as it arises – in this case the need comes from the wave of biologics moving through the latter stages of their clinical development towards approval, combined with the rapidly increasing emphasis being placed on Human Factors and Usability, and the mere acceptance of self/home subcutaneous administration evolving into a requirement. On the other hand, wearable bolus injectors can fulfil this massive market demand without themselves needing to be especially far advanced, technologically-speaking, from their predecessors. No wild leaps into the unknown. Clever design approaches in safe pairs of hands have enabled companies to bring forward this new class of devices very rapidly. To a greater or lesser extent many of them are able to avoid

the usual detailed and lengthy regulatory requirements by using, or only incrementally modifying, existing components, especially those that contact the drug formulation itself. So a game-changing new class of delivery systems can be realised using highly intelligent and innovative, yet relatively incremental technological advances.

"I have never been able to say this about a class of novel (pre-approval) drug delivery systems with such certainty before, but wearable bolus injection devices ... will change the pharmaceutical industry forever, and they will do it relatively soon"

More detailed explanations as to exactly why this is such a particularly important area of drug delivery today and why it will have such an impact can be found in the articles that follow in this issue, beginning with the Pharma Perspective article from Paul Jansen, Vice-President, Medical Device Development at Sanofi Aventis (Page 7). Jansen is positive in his assessment of the potential of what he calls "large volume delivery (LVD) devices" saying that industry is competing aggressively for access to LVD technology.

I'm very pleased indeed to have such a great spread of device feature articles in this issue, contributed by the majority of the main players in this closely competitive sector of the injectable drug delivery sector. Before going on briefly to introduce those companies and technologies which do appear here in this issue, I should mention a couple of those which have been unable to contribute. Firstly, BD is developing its MicroInfuser – recently rebranded as the Libertas Patch Injector – a single-use, disposable system, hands-free during drug delivery, the duration of which can range from seconds to several minutes. Secondly, Ratio Drug Delivery, which said it couldn't contribute to this issue for confidentiality reasons, is developing NuPrivo-SC, which it calls a "bandage with a

button". NuPrivo-SC is due to enter clinical trials shortly, making it the most advanced in Ratio's portfolio of patch-injection devices, which includes an intradermal injector and a continuous infusion system.

The first of the companies contributing to this issue which should be mentioned is Unilife, to which I'm most grateful for its strong support for this edition of ONdrugDelivery as our Outstanding Issue Sponsor. Company CEO Alan Shortall has written an insightful piece (Page 8), which sets Unilife's two electronic wearable bolus injectors – Flex-Therapy and Precision-Therapy – in the context of an integrated offering as part of Unilife's highly customisable range of injectable drug delivery devices and safety syringes.

Continuing the theme of wearable-bolus injection devices as part of an integrated drug delivery offering, Graham Reynolds of West Pharmaceutical Services argues that as self-injection at home becomes more commonplace, it becomes increasingly clear that there is no "one size fits all" device solution (Page 26). Preferences differ from one patient to another, with some people feeling more confident and in control using a "naked" prefilled syringe with simple needle-safety device, for example, while others prefer everything to be taken care of by a wearable injector. But Reynolds also points out that an individual patient's preference could change over the long time (perhaps a lifetime) that they could be taking an injected therapy for a chronic condition. For each pharmaceutical product, a variety of integrated injection devices is essential, therefore, to cater for these changing inter- and intra-patient preferences.

Enable Injections is taking a unique approach as it races towards US approval with its wearable bolus injector. I had the privilege of meeting Enable Injections' Founder and CEO, Mike Hooven, earlier this year after one of Management Forum's many excellent London conferences. I was genuinely inspired, not only by Mr Hooven's formidable track-record in other medical device-related business endeavours, but also by the complete grasp he has of very precisely where and why wearable injection devices slot in to the current parenteral drug delivery arena, and also by the passion he has for his current project,

the mechanical Enable Injection Device. Enable's very high volume, small, wearable bolus injection device is described in this issue on Page 30, together with the reasons why Enable has avoided a prefilled system and gone for a patient-loaded drug transfer system. These reasons are backed by robust data from numerous intensive user studies.

All of the drug delivery technologies featured in this issue of ONdrugDelivery have their own unique and particularly interesting characteristics and, for SteadyMed's PatchPump device (Page 22), this is the E-Cell, which provides the driving force for delivering the drug. The E-Cell is similar to a normal alkaline battery and it does generate the electric power for the PatchPump's electronics. However, unlike a normal alkaline battery, as current flows the E-Cell's electrolytic materials expand in a flexible housing, thus generating a mechanical force which drives the delivery of drug formulation from the device to the patient. Unlike the other companies featured in this issue, SteadyMed is developing its device for incorporation into its own specialty pharma business model. The lead internal product development programme is treprostinil

PatchPump for pulmonary arterial hypertension, for which US NDA submission is planned for the second half of 2015.

The final wearable bolus injector technology to introduce here is the result of a successful classic pharma/drug delivery partnership. Swiss device company Sensile Medical together with US pharmaceutical company scPharmaceuticals are collaborating on the development of a bolus injector device built around Sensile's SenseCore micropump, for the delivery of scPharmaceuticals' pipeline of products (Page 16). The companies highlight advanced safety features made possible only with their pump mechanism and electronic device. The focus is on enabling a portfolio of pharmaceutical products suitable for "anytime-anywhere" delivery – specifically SC administration via a wearable device – which, among other applications, could either completely replace, or supplement, IV delivery.

Also featured in this issue of ONdrugDelivery Magazine is a brief article from Gerresheimer on the manufacture of glass primary parenteral drug containers (Page 34). As mentioned at the top of this piece, many wearable bolus injectors use

existing components, including a standard primary drug container, to which the same rigorous inspection standards will apply during scale-up to commercial manufacturing.

At the rate things are moving, full-scale commercial manufacturing of approved and marketed wearable bolus injectors is just around the corner.

The next issue of ONdrugDelivery Magazine focusing wholly on this exciting topic will be out in July 2015. By that time, as well as having published various further issues, each focusing on specific topics within drug delivery, such as "Prefilled Syringes", "Transdermal, Microneedles & NFIs", "Ophthalmic Delivery" and others (see the Editorial Calendar on Page 15), ONdrugDelivery Magazine will have also celebrated its Tenth Anniversary (in early 2015). To coincide with our one decade milestone, we are launching some exciting new information and intelligence offerings for you, fit for the next decade to come, all still tightly focused as ever on the global drug delivery industry ... watch this space!!

Guy Furness

Publisher, ONdrugDelivery Magazine

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INTRODUCTION

PHARMA PERSPECTIVE

By Paul Jansen, PE

Pharmaceutical industry pipeline trends reflect a significant increase in biologicals, namely monoclonal antibodies (mAbs), in clinical development with most being in Phase II clinical trials. The majority of these mAbs in the drug pipeline are highly viscous and need to be administered subcutaneously with drug delivery systems in volumes that exceed the standard fill of a 1.0 ml prefilled syringe. The emergence of biosimilar and interchangeable

The current status of LVD includes a plethora of emerging technologies focused on delivering >1.0 ml volumes of viscous drugs/biologics with lower complexity and lower cost as compared with conventional infusion pumps. The primary packaging of some of these technologies are being developed with novel materials and containers.

It is important to remember that primary packaging is an essential interface between drug/biologic formulation and a deliv-

“The emergence of biosimilar and interchangeable mAbs may actually be differentiated based on these delivery device offerings”

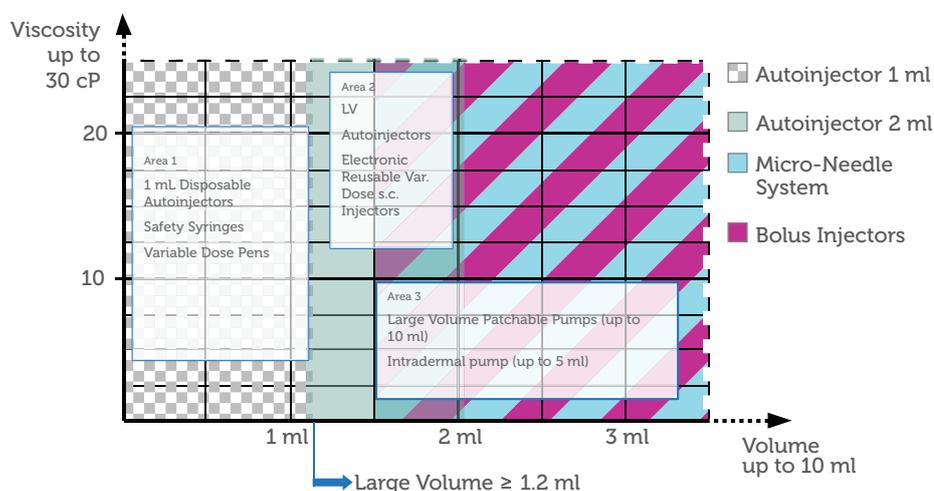


Figure 1: LVD Landscape: Subcutaneous Large Volume Delivery Devices are becoming more diverse.

mAbs may actually be differentiated based on these delivery device offerings.

The evolution of subcutaneous drug delivery devices includes: syringes, pen injectors, autoinjectors, infusion pumps and, most recently, also so-called large volume delivery (LVD) devices (see Figure 1). The group of this emerging device class is still heterogeneous but it seems that LVD devices are typically electromechanical with low complexity and use standard primary packaging (containers). On the other hand, over the last few years, infusion pump technology has evolved to being tubeless, integrated systems reflecting the migration toward bolus injectors and patch technologies.

Currently, the acceptable volume of subcutaneous injections as a bolus is defined as injections of 1.0-2.5 ml.¹ When reviewing the PDR Nurse's Drug Handbook² and nurse guidelines in different institutes and hospitals, injection volumes up to 1.0 ml appear to be considered standard and volumes >1.0 ml up to 2.5 ml are acceptable in special patient populations, such as palliative care.

Meanwhile, the International Organization for Standardization (ISO) has taken the initiative to create a new standard on such bolus injectors as an extension to their standard series 11608 ("Needle-based injection systems for medical use – Requirements and test methods") to provide guidance in technical terms.

Industry is competing aggressively for access to LVD technology that can be industrialised for a variety of platform and drug-specific options. While this is an exciting horizon for subcutaneous delivery of mAbs, it is not without risk with regard to potential issues with Intellectual Property (IP). For example, LVD automatic needle/cannula insertion can be a minefield of IP challenges.

Regulatory evolution includes drug/biologic development requirements such as "to-be-marketed" devices to be used in clinical studies as well as in Phase III. For example, US FDA Center for Devices and Radiological Health (CDRH) requirements of usability/human factors validation studies have increased as the

FDA focuses on addressing safe use of medical devices for home or self use. This, combined with regulatory feedback will determine specific usability and safety requirements for LVD.

LVD may provide significant advantages and options to patients with regard to home use based upon usability and safety as well as the integration of wireless connectivity for monitoring and information capture and exchanges which will ultimately improve drug adherence, healthcare outcomes and the lives of people living with chronic disease.

The market will sort out proven and acceptable delivery mechanisms which may differ based on patient group drug requirements, based upon patient group (e.g. rheumatoid arthritis as compared with asthma). Patient acceptance is based on the adoption of wearable injectors due to form factor, complexity and duration of drug delivery. The journey has just begun....

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CRITERIA FOR SELECTING A WEARABLE INJECTOR TECHNOLOGY AND PARTNER

In this article, Alan Shortall, Chief Executive Officer, Unilife, provides a detailed account of the significant opportunities that wearable injection devices present pharmaceutical and biotech companies, the specific criteria that such devices must meet, and how Unilife's Precision-Therapy® and Flex-Therapy® ranges have been designed to fulfil these requirements comprehensively.

Pharmaceutical and biotechnology companies continue to shift their investment towards the development and supply of biologics and other drugs that are targeted for subcutaneous self-administration by well-defined patient populations. In addition to the commercialisation of a new wave of patient-centric biologics such as monoclonal antibodies, pharma companies are seeking to convert a multitude of approved therapies from IV infusion to subcutaneous injection.

"More than 1,000 people in the US, Europe and Asia have participated in user and marketing studies undertaken either by Unilife or its pharmaceutical partners"

These efforts by pharma companies create a significant opportunity to redefine the provision of healthcare and reduce treatment costs across a range of chronic disease areas including oncology, auto-immune disorders, cardiovascular diseases and respiratory ailments.

However, gaps in the traditional device market have impeded the commercialisation and lifecycle management of many of these drugs, which come in a liquid format and are best suited to large dose volumes requiring subcutaneous injection over a pre-programmed period from minutes to hours.

Conventional hand-held devices such as prefilled syringes and auto-injectors are designed to deliver doses no greater than 2 ml over injection periods of up to 20 seconds. When used with drugs that require larger dose volumes or longer durations, these types of hand-held devices may create risks including drug wastage, misalignment of the needle and patient discomfort resulting in sub-optimal therapy outcomes. At the other end of the device spectrum, reusable insulin pumps are too expensive and complicated for the injection of these drugs, which typically only require the periodic injection of a fixed-dose volume of drug every one, two, four, six weeks or beyond.

In recent years, a number of device manufacturers including Unilife have created single-use wearable device technologies that are designed to deliver large volume drugs to the patient over long durations. Known as wearable injectors, this relatively new but fast-growing segment of the device industry is poised to enable and enhance the delivery of countless injectable therapies over the coming decade.

As an industry leader for injectable drug delivery systems, Unilife is building long-term relationships with a multitude of pharmaceutical and biotechnology companies who have each identified up to a dozen or more approved and pipeline molecules that are being targeted for use with wearable



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Simple to Customise	Unilife
Dose Volume	2 ml to 10 ml (or greater)
Viscosity	up to 100 cP (or greater)
Delivery duration	Seconds to hours (up to 24 hours)
Delivery rate	Bolus, basal or variable
External design	Customisable look and feel
Product disposal	Optional removable electronics
Needle type	Flexwear comfort catheter or needle
Patient wear	On-body (adhesive patch) or off-body (belt clip)
Simple to Commercialise	Unilife
Platform architecture	Ability to customise one part without redesigning others
Primary drug container	Standard glass and elastomer materials
Maintaining sterility	Sterilisation only required for drug and human contacting surfaces (no terminal sterilisation)
Fluid Path	Only accessed at commencement of injection
Container closure integrity	Maintains drug integrity throughout shelf-life
Supply for filling	Standard syringe handling processes
Filling equipment	Standard syringe filling equipment
Material selection	Open architecture (multiple options from range of suppliers)
Simple to Use	Unilife
Final supply to user	Pre-filled. Pre-assembled. Ready for injection.
Attachment to body	By patient at time of use
Environment of use	Clinical and non-clinical environments (home etc.)
Insertion site	Subcutaneous tissue (abdomen, arm, buttock, thigh)
No. of steps of use	Three (peel, stick and click)
User Interface	Electronic (audible, tactile, visual indicators)
Drug security	Safety lock prevents premature activation
Sharps protection	Needle auto-retracts after soft cannula insertion
Type of cannula for injection	Soft cannula for comfort during wear
View to medication	Large window with wide viewing angle

Figure 1: Table summarising key criteria for a wearable injection device.

injectors. With every drug having specific formulation, patient and commercial requirements, these pharmaceutical companies have taken a platform-based approach towards the appointment of a preferred device partner and wearable injector technology.

Unilife recognises that the conventional “one-size-fits-all” approach to device development is too inflexible to accommodate the breadth of customer requirements for portfolios of biologics, small molecules and vaccines that can each have particular

requirements. That is why Unilife has pioneered a new customer-centric model for injectable drug delivery systems that enables the efficient customisation of each product within a platform to address specific customer, drug and patient needs.

When it comes to selecting a preferred partner and device technology for wearable injectors, Unilife recognises that pharmaceutical companies have three key criteria:

1. **Simple to Customise:** How does it allow customisation to fit all of the customer’s

operational, sales, marketing, and therapeutic needs?

2. **Simple to Commercialise:** How seamlessly can it be integrated with approved manufacturing methods and materials, allowing rapid development to get a customer’s drug onto the market quickly and minimise regulatory risk?

3. **Simple to Use:** How well does it enable an intuitive, effective, comfortable and confident user experience by the target patient population?

To facilitate the long-term needs of pharmaceutical companies who are evaluating prospective wearable injector technologies and device partners, Unilife has created a list of selection criteria that cover important factors across each of these three key areas. The criteria are summarised in the table shown in Figure 1, and detailed below.

SIMPLE TO CUSTOMISE

For a pharmaceutical company with a broad portfolio of injectable therapies, a wearable injector platform should provide it with the flexibility to have devices individually customised for optimal configuration with each target molecule and patient population. Criteria that should be used in the selection process for customisability include dose volume, drug viscosity, delivery duration, delivery rate, external shape and feel, user notifications, user initiation, product disposal, needle type and mode of patient wear.

Pharmaceutical companies evaluating prospective wearable injector technologies and partners should assess the modular design flexibility of a device platform to ensure it can deliver the right therapy, user experience and brand message for a portfolio of target drugs.

DOSE VOLUME

Many pharmaceutical companies recognise the therapeutic and commercial benefits of striking the right balance between

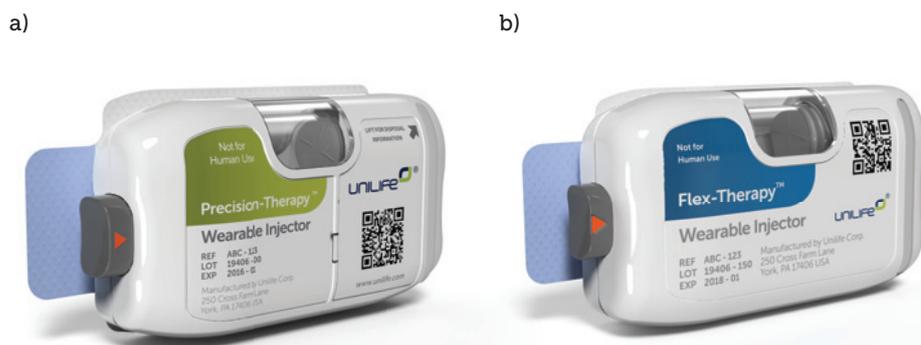


Figure 2: The Precision-Therapy™ range (a), for delivering large dose volumes over a few minutes, and the Flex-Therapy™ range (b), for long-duration therapies that require delivery of large volumes with a specific rate profile.

dose volume, drug viscosity and injection frequency. A common goal is to select the formulation that is least invasive to the user experience and requires a less frequent dosing regimen.

One recent survey of physicians in a significant disease area being targeted for both auto-injectors and wearable injectors highlighted that, when all other things are equal, 76% would prescribe the drug with a large dose volume for once-a-month dosing as opposed to a competitor product requiring dosing of a smaller volume every two weeks. In such cases, wearable injectors represent a significant opportunity to drive patient or physician preference and differentiate a drug from its competitors.

While Unilife has received enquiries to utilise wearable injectors for drugs with target dose volumes of between 30 ml and 100 ml, the overwhelming majority of customer requirements range between 2 ml and 10 ml. A platform of wearable injectors should be able to accommodate the full spectrum of target dose volumes required by a pharmaceutical customer across its portfolio of injectable therapies. With some other wearable injector technologies marketed by other pharmaceutical companies being limited to use with doses of 2-3 ml, it's important for a pharmaceutical company to understand the range of anticipated dose volumes expected across a drug portfolio.

DRUG VISCOSITY

Viscosity is a common factor that can influence the decision of a pharmaceutical company as to whether to utilise a hand-held device such as a prefilled syringe or auto-injector, or a wearable injector. As a general rule, the lower the viscosity of the drug, the more comfortable and easy it will be to use by a target patient population.



Typically, it is those molecules which are considered too viscous for a liquid dose of 1 ml or less that are selected for use with wearable injectors. Based upon the requirements of many pharmaceutical companies engaged with Unilife, the standard range of viscosities being targeted for use with wearable injectors is between one and 100 cP. Unilife's wearable injectors have been proven to accommodate viscosities of greater than 100 cP.

DELIVERY RATE AND DURATION

A wearable injector should be pre-programmable to facilitate the accurate delivery of a fixed dose at the controlled rate and duration that can provide the best clinical outcome for the patient. The selection of rate-controlled or duration-controlled for a target therapy will be determined by the specific delivery rate profile, or the delivery volume requirements.

Unilife works with its customers to adopt the simplest solution for their needs to avoid them having to pay for added complexity that is ultimately unnecessary. Customer options that are provided by Unilife include bolus, basal or variable rates over very tightly controlled delivery durations. The option to pre-programme the device for an immediate or delayed start to the injection is also available.

Unilife's Precision-Therapy™ range of wearable injectors (Figure 2a) is best suited to short-duration therapies that require the delivery of large dose volumes over pre-programmed periods such as a few minutes. The Flex-Therapy™ range of wearable injectors (Figure 2b) is best suited to long-duration therapies that require delivery of large volumes with a specific rate profile. This platform-based flexibility enables Unilife to ensure each of its devices can be pre-programmed to the optimal delivery

rate and duration period specifications for each drug within a customer's portfolio to best serve the therapy needs of a target patient population.

EXTERNAL DESIGN

Drug delivery systems are increasingly being used by pharma companies to generate brand differentiation against competitors. Furthermore, human factors have become integral to securing the regulatory approval of drug-device combinations, as well as optimising rates of therapy adherence. A platform technology for wearable injectors must therefore not only be simple to use, but also easily customisable with respect to look, feel and functionality.

Unilife's platform of wearable injectors provides pharmaceutical customers with the flexibility to have the external design and functionality of each device tailored to match their requirements in several important ways. Options extend far beyond brand labelling or colors to include single button or dual-button activation, the button force required for activation, button size for population needs, and an ergonomic and distinctive external design that best fits the grip of the user and enables comfortable wear during the injection period.

PRODUCT DISPOSAL

Unilife has developed its platform of wearable injectors with the option of removable electronics to enable the recovery, reuse and recycling of electronic waste. This removable electronics option enables pharmaceutical companies to strike the right balance between patient usability and green disposal and recycling.

OTHER CUSTOMISATION OPTIONS

Other customisation options include the gauge of needle used for automatic insertion of the Flexwear comfort catheter (see Figure 3), on-body or off-body wear options, and packaging design.

SIMPLE TO USE

Unilife is committed to the design, development and customisation of injectable drug delivery systems that are as safe, com-

portable and easy to use as possible. As a general rule, intuitive devices with fewer usage steps are most likely to reduce the risk of error, minimise the need and cost of training, optimise rates of therapy compliance and drive patient preference rates amongst patients, prescribers and payers. Such device-related benefits can be leveraged by a pharmaceutical company to build or protect market share and differentiate a drug brand from the competition.

FINAL SUPPLY TO USER

To overcome the inability of most wearable injector technologies to be terminally sterilised (see under Sterilisation Method), many device manufacturers have developed products that cannot be supplied in a pre-filled, pre-assembled and read-to-inject format. Such products require the user to load a pre-filled cartridge into the device prior to use or they may require the user to first load the drug from a vial with a syringe, and then fill a reservoir in the injection device.

Delivery systems with multiple parts that place an extra burden on the user are not only less convenient, but they may create additional risks of error, result in sub-optimal rates of therapy adherence and reduce levels of acceptability amongst patients or prescribers. Some wearable injector products have failed user studies conducted by pharmaceutical companies evaluating various technologies due to these extra steps of use associated with a patient having to load the drug into the device at the time of use.

Unilife's platform of wearable injectors can be pre-filled and pre-assembled in their final-packaging by the pharmaceutical manufacturer and then supplied to the patient in a ready-to-inject format. Compared with some other technologies that necessitate seven, twelve or even more steps of use, Unilife's wearable injectors require only three simple steps to deliver a therapy that are commonly described as "Peel, Stick and Click".

This convenient, ready-to-use format has been found to be strongly accepted and preferred in user studies. It can also help to minimise the need for additional training and associated overheads that a pharmaceutical company may otherwise incur which can impair its broader acceptance into the market.



Figure 3: A metal needle automatically retracts into the device after insertion of the FlexWear comfort catheter to maximise patient comfort during the injection.

USER STUDIES

Usability and human factors represent a strong area of focus for pharmaceutical companies evaluating wearable injector technologies. Common criteria for pharmaceutical companies conducting user studies for wearable injectors include: ease of use, button force for activation, sharps protection, insertion comfort, wear comfort, premature activation, user interface simplicity and convenience of disposal.

Data generated through these user studies can be of critical importance in the successful clinical development, regulatory submission and lifecycle management of a therapy. To develop the most intuitive design with the simplest user interface for its wearable injectors, various iterations of Unilife's devices have undergone extensive human factor testing and device evaluations across a wide vari-

In one user study, 100% of users understood and successfully executed proper device activation with only a basic description of the goal. The presence of user-vetted visual and audio-indicators that are designed to convey the status of the device clearly at all times during use was also strongly favoured.

ERGONOMICS AND PATIENT WEAR

As a new technology platform, wearable injectors have significant potential to enable or enhance the self-injection of injectable therapies by patient populations or demographic groups where hand-held devices such as syringes may not be appropriate. With wearable injectors ergonomically designed to be comfortably attached, activated and worn on the body, the level of dexterity required to maintain control during an injection is relatively low.

Such benefits may create opportuni-

"The level of dexterity required to maintain control during an injection is relatively low"

ety of patient populations and geographic territories. In total, more than 1,000 people in the US, Europe and Asia have participated in user and marketing studies undertaken either by Unilife or its pharmaceutical partners during the evaluation of its wearable injectors.

A key finding of these user studies was that the minimal steps of use, as well as other integrated features, associated with Unilife's wearable injectors can help minimise the risk of user error and maximise levels of acceptability and preference.

ties to convert IV infusion drugs or other injectable therapies previously recommended only for administration by healthcare workers into a subcutaneous injection formulation ready for intuitive self-injection by the patient. Areas of the body suitable for the subcutaneous administration of a drug using a wearable injector may include the anterior abdomen, rear upper arm, upper outer quadrant of the buttock and the anterior upper thigh.

When used to deliver drugs over periods longer than a few minutes, wearable



Figure 4: The proprietary safety interlock mechanism, which must be depressed on the body prior to the start of an injection.

injectors should enable the user to wear the device discreetly underneath clothing. Conceivably, any routine behaviour that a patient may undertake during their normal daily life should be feasible during the period of use. Environments where a wearable injector could conceivably be used by a patient include home, work, cafes, restaurants, gymnasiums and outdoors.

The ability to wear a device in itself is however insufficient to help optimise rates of therapy adherence and drive patient preference towards a particular drug product. Factors that can influence the level of user acceptance towards a particular therapy can include the degree of ease and comfort associated with the attachment, activation,

may exacerbate levels of patient discomfort over duration periods longer than a few seconds and upon removal. Unilife is able to provide either rigid needle or soft cannula options depending upon the specific customer and target therapy requirements.

Most pharma customers working with Unilife have cited a preference for its proprietary FlexWear comfort catheter™ technology, a compact self-contained needle insertion mechanism that automatically inserts a FlexWear comfort catheter into the administration site. The needle is then automatically retracted following the insertion of the catheter for optimal patient comfort during the period of administration, and sharps-free disposal of the used device.

Factors such as patient comfort and confidence can greatly impact rates of user acceptance and preference for a therapy. In line with the growing trend towards personalised medicine, Unilife provides its pharmaceutical customers with a multitude of other customisation options including on-body or off-body wear, button positioning or a one or two-button design. This flexibility can enable a customer to have the look and feel of each wearable injector tailored to the specific requirements of a drug, its commercial brand strategy and target patient population.

USER INTERFACE

An effective user interface for a wearable injector should enable a patient to visually inspect the drug before and during administration, facilitate the initiation of an

ness. An audio status feature, which informs the patient of the commencement, status and completion of an injection, is able to be silenced for discreet use. Various light colours, illumination patterns and tone frequencies can also be customised based upon customer and brand requirements and user study outcomes.

DRUG SECURITY

A wearable injector technology should not only protect the drug during shipment and storage but prevent potential drug wastage prior to the point at which the user is ready to commence the injection of the dose. Unilife's wearable injector technology features a robust, tamper-evident external casing and is suitable for final shipment in sturdy yet easy-to-open packaging. A proprietary safety interlock mechanism must also be depressed on the body (Figure 4) prior to the start of an injection, to prevent premature activation. These safety features help to minimise the risk of drug wastage, and enable clear and confident use during the injection period.

SIMPLE TO COMMERCIALISE

A fundamental goal of any wearable injector business is to ensure that each pharma customer can easily get its products to market with as minimal risk as possible. The incorporation of new materials, new filling processes or novel methods of delivery represent examples of unnecessary risk that can be mitigated through the upfront development of a robust, modular platform that is customer-centric in design and fully scalable.

Unilife's philosophy is that wearable injectors should leverage well understood materials and fit seamlessly into approved manufacturing methods to mitigate the need for a customer to change any of its standard processes and preferred equipment suppliers.

PLATFORM ARCHITECTURE

To support the rapid commercialisation of several injectable molecules in parallel for a customer, Unilife has developed its wearable injector platform under a modular framework that enables customisation to one component without the need to redesign the other components. Unilife can therefore efficiently customise each product to a range of customer specifications such as dose volume, drug viscosity and duration rate.

“Wearable injectors should leverage well understood materials and fit seamlessly into approved manufacturing methods to mitigate the need for a customer to change any of its standard processes and preferred equipment suppliers”

wearing and removal of the device from the body. In addition to the size, shape and adhesive of a wearable injector, the method at which a needle or cannula is inserted into the body during the period of injection can be a particularly important factor for patient comfort.

Some wearable injector technologies are restricted to the use of a rigid needle, which

injection with minimal force and provide accurate visual, audio or tactile indicators relating to the status of an injection.

Unilife's wearable injectors provide a 180° viewing window to the medication during all stages of use. Likewise, electronic and mechanical systems can provide visual, audio or vibratory indicators to facilitate user confidence and under-clothing aware-

PRIMARY DRUG CONTAINER

Unilife follows an open architecture model in the selection of components and suppliers to provide customers with a level of flexibility that is typically not possible with traditional device suppliers. Rather than having to rely on a device to sell a specific material, each of Unilife's products exists to meet the specific needs of customer, its target drugs and associated patient populations. Most importantly, the primary drug container for Unilife's platform of wearable injectables is designed to utilise standard materials including standard borosilicate type I glass and commonly used elastomers.

Customisable aspects of the primary drug container include the use of silicone oil, baked silicone or coated elastomers. Unilife can also provide products with a plastic (polymer)-based primary container should the customer desire it.

STERILISATION METHOD

Many biologics and other injectables are not recommended to go through a terminal sterilisation cycle due to the risk of causing damage to the molecule. Unilife has developed a unique, proprietary system that enables sterilisation only of the required components which are exposed to the drug or the patient.

Unilife wearable injectors can be aseptically filled and then pre-assembled in a non-aseptic environment without any special processes. Sterilisation of all drug contacting and fluid-path components can occur without full terminal device sterilisation or sophisticated assembly steps.

The primary drug container is only accessed once the injection sequence has been initiated by the user. The successful development of a wearable injector technology that can be pre-filled and pre-assembled without terminal sterilisation allows a great deal of flexibility in the supply chain without creating new manufacturing technologies or compromising the biologic or drug.

SUPPLY FOR FILLING

Wearable injector technologies should be designed to enable seamless integration into standard filling systems and processes.

Technologies which require a pharmaceutical manufacturer to modify existing processes, purchase extra equipment or invest in new or unconventional filling processes may encounter customer resistance and potentially impact commercialisation timelines for a programme. To support regulatory processes and enable modular scale-up during clinical trials and commercial rollout, wearable injector technologies should also be designed to enable filling to occur on multiple scales.

Unilife has developed a robust and modular-based design platform to ensure each product is thoroughly engineered and aligned with established manufacturing processes. Unilife's wearable injectors can be integrated seamlessly into filling and inspection equipment with no major changes. Filling and stoppering can be conducted in high-speed syringe filling equipment in aseptic operations. Unilife can provide pharma customers with an in-depth evaluation of how its devices can be integrated into established syringe filling equipment, and to be filled on multiple scales up to hundreds of units per minute. Unilife's existing relationships with well-known CMOs and filling equipment manufacturers can also be leveraged to support the commercialisation pathway for a customer's target drug products.

OTHER FACTORS TO CONSIDER IN THE SELECTION PROCESS

The selection of a wearable injector platform should not only be based on how simple it is to customise, commercialise and use. As a preferred wearable injector technology will ultimately play a significant role in the approval and commercial success of a target therapy, pharma companies should carefully consider how a device manufacturer can serve their long-term requirements with speed, agility and reliability.

In addition to having world-class, US manufacturing facilities and unparalleled innovation credentials, Unilife has developed a company structure and culture that is highly customer-centric. The company strives to understand customer needs fully and to ensure that the right balance of resources and expertise are applied to meet them. Each wearable injector team established for a customer is comprised of engineers, scientists and other experts from the drug delivery industry, with many having experience in class-three devices and infusion pumps. Unilife has established arguably the largest team in the wearable injector market, which boasts deep technical knowledge and advanced industry expertise.

Unlike other companies where the business is predominantly based around materials or commodity components, Unilife was created from the ground up as a developer, manufacturer and supplier of sophisticated injectable drug delivery systems. It has a deep understanding of primary container technologies, and how they must be integrated into the effective production and functionality of a drug delivery system. From a customer perspective, this translates into having a partner that has the expertise, processes and capabilities to take full responsibility for all aspects of the device and its integration within the overall drug-device combination product.

With Unilife also having a broad portfolio of injectable drug delivery systems, it also has the neutrality to help pharmaceutical customers determine whether a particular molecule is best suited for use with a wearable injector, prefilled syringe, auto-injector or a combination of two or more platforms. Unilife is ready to serve pharmaceutical customers under long-term partnerships to enable and enhance the delivery and commercial success of their injectable therapies.



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October	Drug Formulation & Delivery, Services & Solutions	September 15th
November	Pulmonary & Nasal Drug Delivery (OINDP)	October 13th
December	Delivering Biotherapeutics	November 10th
January 2015	Ophthalmic Drug Delivery	December 8th
February 2015	Prefilled Syringes	January 12th
March 2015	Transdermal Patches, Microneedles & Needle-Free Injection	February 3rd
April 2015	Pulmonary & Nasal Drug Delivery	March 2nd
May 2015	Injectable Drug Delivery: Devices Focus	April 13th
June 2015	Novel Oral Delivery Systems	May 4th
July 2015	Wearable Bolus Injectors	June 1st

scPharmaceuticals



SENSILE MEDICAL

LARGE-VOLUME INJECTOR ENABLES ANYTIME ANYWHERE DELIVERY OF PARENTERAL DRUGS

In this piece, Pieter Muntendam, MD, President and CEO, scPharmaceuticals; Gerhard Mayer, PhD, Vice-President, Business Development North America, Sensile Medical USA; and Lars Krinelke, MD, PhD, Head Product Management, Head Medical Affairs, Sensile Medical AG describe how their large-volume injection device allows subcutaneous self-administration, an important part of the “anytime-anywhere” model for drug delivery.

Many important drugs must be administered parenterally because they are not orally active or are insufficiently orally active to remedy a specific condition. With rare exceptions, parenteral administration requires intravenous (IV) or intramuscular (IM) administration by a specially trained clinician. To date, subcutaneous (SC) administration has not been an option for many pharmaceuticals despite the conceptual appeal of a simpler, less invasive drug delivery option. scPharmaceuticals aims to change that – using innovative technology to enable anytime-anywhere treatment options that benefit patients, clinicians, healthcare facilities and payers.

SC administration is appealing in several ways. It provides nearly 100% bioavailability, in most cases offers a preferred pharmacokinetic profile over the standard IV bolus, and does not require special skills. From a patient’s perspective it is also less invasive than IV administration. However, its use for parenteral drugs has been restricted by technology. SC delivery by injection is limited to 1-1.5 ml. Larger volumes of a drug would require a slower rate of administration that is not possible with a syringe and needle. Except for insulin and treatments for certain orphan disorders, none of the commonly used parenteral medications have been developed for slow SC administration.

scPharmaceuticals was formed to develop new SC treatments based on existing and widely used parenteral drugs. The first such therapy will be a novel formulation of the

loop diuretic, furosemide, for heart failure.

Novel technology allows for simple, convenient and comfortable SC administration of parenteral pharmaceuticals in larger volumes than has been possible before. scPharmaceuticals partnered with Sensile Medical to develop an easy-to-use, full-featured patch pump device that permits SC drug administration over durations, rates and volumes that can be tailored to specific drugs.

PART OF THE ANYTIME-ANYWHERE MEDICAL MODEL

SC administration of parenteral drugs, and eventually self-administration of those drugs, is an important part of the emerging anytime-anywhere medical model that seeks to align medical treatments and processes more closely with the fluidity of daily life. Technology enables patients to communicate with clinical staff in real time. Clinical data and even results of blood tests can be transmitted allowing the physician to make informed clinical decisions.

We are at the dawn of a new medical model where time and place are almost irrelevant. In this model physicians can authorise use of more advanced therapies and patients can self-administer medications that previously required visits to a medical facility or home visits from a healthcare professional. SC self-administration of critical medications as envisioned by scPharmaceuticals is a natural component of this new model.



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In the emerging model there are two distinct clinical scenarios or use cases where SC administration offers clear and obvious benefits:

1. Supplementing IV with SC

SC administration offers effective parenteral therapy that bridges current treatments. The use of furosemide in heart failure provides an illustration. Oral furosemide at home and intravenous furosemide in the emergency room or hospital are currently essential in heart failure treatment. SC furosemide for use at home offers an intermediate treatment to prevent the exacerbation of symptoms that now require emergency room or in-hospital treatment, and avert the need for IV treatment. SC furosemide can also be used to continue treatment at home following a patient's discharge so as to extend parenteral treatment without the need to prolong the in-patient stay. In this case SC treatment is not used to replace IV, but to supplement existing options and give patients the kind of therapeutic response that was previously available only in an emergency room or hospital.

2. Substituting SC for IV

Many parenteral antibiotics are administered IV. Instead of daily administration of an antibiotic in a peripherally inserted central line (PIC line or PICC), a patient could receive SC treatment using a patch pump whilst continuing to go about normal daily living. Thus, instead of driving to an infusion centre, for example, the patient can drive to work while the small patch pump on the abdominal wall conveniently and comfortably provides the same dose of the same drug. The benefits are distinct and important – avoidance of the cost and complications of the PIC line, and avoidance of the cost and personal burden of the administration in an infusion centre or doctor's office.

UNTAPPED OPPORTUNITY WITH LARGE POTENTIAL

The safety of most widely used parenteral medications is well established but their use has been restricted to a clinical setting because intravenous or intramuscular administration requires clinical skills and has inherent risks. SC administration of parenteral drugs has simply not been an option with existing technologies, making the benefits of convenient comfortable anytime-anywhere administration of parenteral prescription pharmaceuticals unobtainable.



Figure 1: The heart of SenseCore Technology: Sensile's micropump consisting of two plastic components.

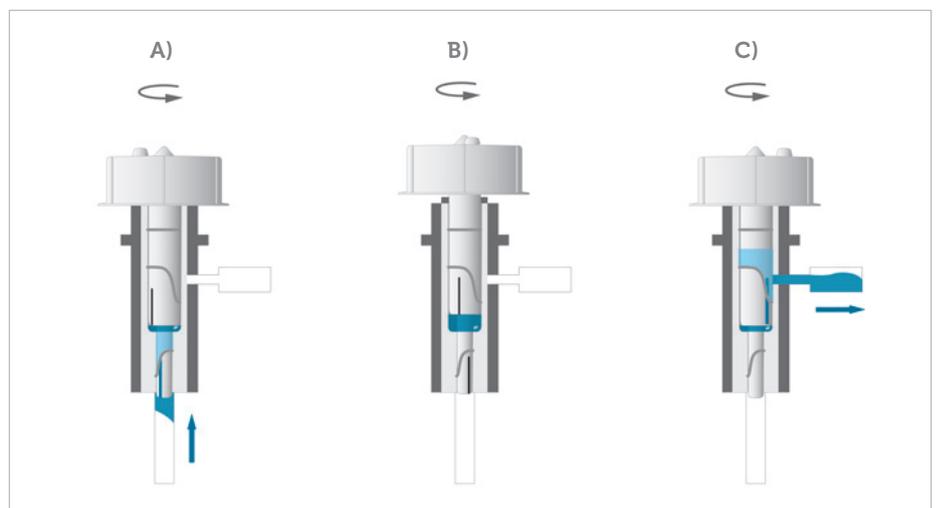


Figure 2: A) As the pump rotates, the upward motion draws in the exact dose. B) The dose resides in the pump with both valves closed, preventing uncontrolled free-flow. C) With continued rotation and the downward stroke, the drug is expelled toward the needle and the patient.

Determined to overcome the technology barrier, scPharmaceuticals explored a range of technologies and options for large volume injectors. After evaluating all available options, scPharmaceuticals selected Sensile Medical's SenseCore technology for its wearable patch pump. SenseCore is a micro piston pump, smaller than the size of a US "quarter" coin, comprising two pieces of precision moulded medical grade plastics (see Figure 1). The piston is rotated by a small electric motor and the rotation provides the pumping force (see Figure 2). The pumping can be bi-directional allowing the device both to fill itself from a standard primary container and to deliver the medication SC.

Until now devices used a single component design wherein the mechanism that provided the force and energy was part of the component that delivered the drug, thus the entire device had to be discarded after use. In most designs this also meant

the device had to contain a filled medication reservoir using non-standard primary containers and closures. These devices were complex, expensive and difficult to manufacture, and thus not suitable for routine widespread use.

The SenseCore technology allows for the development of a small two-component device comprising a single-use disposable unit and a reusable unit (see Figure 3). The disposable unit contains the SenseCore pump, a drug reservoir, the fluid path, needle insertion and retraction mechanism, and the patch that adheres to the skin during drug delivery. The reusable unit consists of a motor, controller and electronics in plastic housing. After inserting the disposable cartridge in the reusable unit, a mechanical drive shaft connects the two to transfer the energy and force.

As mentioned previously, Sensile's technology is being developed to deliver scPharmaceuticals' furosemide heart failure



Figure 3: The Sensile pump is a customised delivery device. In this configuration, it consists of two major parts. In the disposable part, a micropump draws the product out of the reservoir and delivers it through a needle on the underside of the device (not shown). Key high-value components are retained for repeated use in the reusable part. During administration, only the disposable part is in contact with the drug or the patient. After injection, only the disposable is discarded.

treatment. Figure 3 shows an overview of the disposable and reusable components of the furosemide delivery system. In Figure 4, the disposable and reusable components are combined and the drug vial has been attached for automatic transfer of the drug into the internal reservoir. Finally, in Figure 5, the vial has been removed and the furosemide patch is ready for use.



Figure 4: The patient transfers the drug from the vial into the device's internal reservoir. Upon completion of transfer, the vial is removed.

In general, the SenseCore technology offers a number of important benefits:

- **Auto-fill from standard primary container:**

The device for scFurosemide has an auto-fill feature that allows it to fill itself from a standard primary container such as a vial. This eliminated the need to design a new primary container and closure system, and avoided the associated development and regulatory risks. Additionally, it eliminates the need bring the device into the pharmaceutical manufacturing process. The drug and device have separate manufacturing processes and come together in a much simpler kitting process.

- **Controlled Delivery of Large Volume:**

Furosemide and other therapies in the pipeline will require administration of larger volumes than possible with syringes and needles – up to 20 ml. The electromotor and controller allow full control over the delivery. The device has a dynamic range that spans a range from 50 μ l over 24 hours to 5 ml per minute. The electromotor and controller permit every possible required delivery profile, including one that provides multiple distinct administrations – for example it is possible to administer four doses of 5 ml at six-hour intervals. In this case the

device can be filled with multiple doses that, if administered IV, would require multiple resource-intensive drug administrations by a clinician.

- **Platform for Multiple Applications:**

This design includes capability to auto-fill from a standard container and delivery controlled by a pre-programmed computer chip. These features permit a single device to be used across a broad range of therapies by changing only the software programming that controls the fill and delivery.

- **Optimising Pharmacokinetics:**

For some drugs, such as antibiotics, maintaining plasma levels is critical to achieving therapeutic effects. For other drugs, a rapid loading dose is desirable followed by a steady-state delivery. The electronic control allows for optimisation of delivery to achieve the desired therapeutic effects. In many cases the controlled delivery with the patch pump can offer an improved pharmacodynamic response when compared with the same dose administered by the standard once-a-day IV bolus.

- **Cost Efficiency:**

Many of the clinical situations where conversion from IV to SC offers important advantages require frequent drug administration over extended periods. For example, antibiotics usually require daily doses for weeks or even months. This puts pressure on the cost of goods associated with the components that are discarded after each administration. With a two-component design, the reusable component can be used for the entire treatment period and only a low-cost, single-use component is discarded after each drug administration.

- **Advanced Proprietary Features:**

One important feature of the SenseCore technology is the built-in opportunity to monitor its pumping function. As the micro piston pump operates, the piston will make short up-and-down movements with every rotation in the housing. The piston's up-and-down movements can easily be monitored using an electronic sensor in the reusable unit. This enables important safety features typically not possible with other technologies. In case of blockage of the fluid path, for example, the sensor would register impaired piston movement which could trigger a “malfunction” alarm. These features would be complex and expensive to match with most other technologies

since they would require fluid path sensors. Another important feature is that needle insertion and retraction are electronically controlled and do not use a mechanical spring for release. The advanced features of the system are patent protected.

scPHARMACEUTICALS' PIPELINE

The company's lead product is scFurosemide - a novel formulation of furosemide injection optimised for SC delivery. The Affordable Care Act provides unprecedented financial incentives for hospitals to improve management of patients with heart failure and reduce readmission rates following patient discharge. scFurosemide allows physicians to increase diuresis in heart failure patients and reduce fluid overload to prevent the acute form of heart failure known as acute decompensated heart failure. It can also be used to finish a treatment regimen at home that was started in the hospital. The patient would be discharged after a short stay in a medical facility and continue SC furosemide at home for 3-5 days until fluid overload has been resolved.

A second product that scPharmaceuticals plans to bring to market will be the first ever cephalosporin antibiotic for SC administration. This will offer convenient and comfortable administration, and eventually self-administration, that will replace the need for a PIC line, and daily trips to an infusion centre or clinic for intravenous administration. Similarly, it will avoid the costs and complications associated with PIC lines for outpatient parenteral antimicrobial treatment in the home-setting.

scPharmaceuticals expects to file US NDAs for both products in 2015 and to launch the products in 2016.

MEETING HEALTHCARE PROVIDER AND PATIENT NEEDS

Human factor considerations are playing an ever-increasing role, especially as novel drug delivery systems are coming to market. Professionals, patients and caregivers may need to be able to safely prepare, place, activate and remove the device with minimal difficulty. The SenseCore technology allows for single-button operation with visual and audible signals that are easy to understand. The devices are pre-programmed at the time of manufacturing for the drug delivery profile. This eliminates the risk of programming errors by user or clinician.



Figure 5: Now ready for use, the device is placed on the skin and the drug administered. After injection, disposable and reusable parts are separated and only the disposable is discarded.

TIME TO CLINIC OR MARKET

The option to use a standard primary container, combined with the auto fill feature, eliminates the need for development and testing of a novel primary container and a separate fill facility for the container. This can reduce time to clinical use or market by several years, as new primary packaging alone will typically take 4-5 years.. It also removes an important component and risk to the regulatory review.

TRAIL-BLAZING ON A PATH TO THE MARKET

A patch pump straddles the domains between auto-injectors and infusion pumps. It acts as an advanced large form of auto-injector with controls and safety features that are typically absent from auto-injectors. However, structurally it resembles an infusion pump. In the case of the Sensile system it contains a mechanical pump driven by an electromotor controlled by a circuit board. Infusion pumps are subject to increased scrutiny by the regulatory agencies in response to errors and malfunctions that have caused injury or death. Pre-programmed delivery using a patch pump that is easy to use should avoid the problems associated with the programmable pumps.

As is often the case, release of a first-of-its-kind product for use will define a path making it easier for others to follow. The SenseCore technology is well suited to blaze the trail and set the standard because of its combination of precision, controls and advanced safety features.

ABOUT scPHARMACEUTICALS INC

scPharmaceuticals was formed in 2013 to develop innovative pharmaceutical products for SC delivery based on widely-used and proven APIs. scPharmaceuticals is pursuing the largely untapped opportunity of treating patients for serious and life-threatening conditions with convenient anytime-anywhere SC drug administration. scPharmaceuticals is developing a portfolio of innovative drug-device combination products that use the SenseCore micro piston technology for delivery. This technology allows for a cost-effective two-component design. For further information see www.scpharmaceuticals.com.

ABOUT SENSILE MEDICAL AG

Sensile Medical AG is a leading company in the area of advanced micro pump technology developing a broad range of customer-specific delivery and dosing solutions. These pumps are increasingly being used to enable for instance Large-Volume SC delivery of modern pharmaceutical and biotech products for self-administration by patients. Due to Sensile's SenseCore technology the products are highly cost-efficient, accurate, and safe. They are increasingly used in drug delivery, medical and consumer applications. Founded in 2004, Sensile Medical is located in Haegendorf, Switzerland. For further information consult: www.sensile-medical.com.

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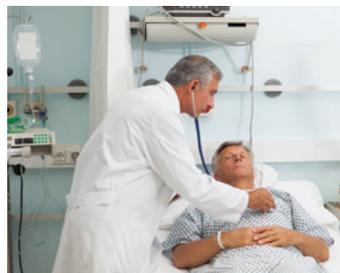
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Home care



Hospital care



Diagnostics



Drug preparation





PATCHPUMP: EXPANDING THE LIMITS OF PARENTERAL ADMINISTRATION

Here, Marylyn Rigby, Director of Business Development & Marketing, SteadyMed Therapeutics, introduces the company's PatchPump device, its design, mechanism of action, steps of use and current status of clinical development.

SteadyMed Therapeutics is a specialty pharmaceutical company redefining the parenteral delivery experience and is committed to expanding the limits of injectable therapeutics to restore freedom, joy, and dignity to patients' lives. The company is actively developing a portfolio of PatchPump™-enabled drug products and intends to submit its first US NDA in the second half of 2015, as further described below.

INTRODUCTION TO PATCHPUMP™

PatchPump is a proprietary system developed by SteadyMed, to enable easier, more convenient and less error-prone drug administration via a single-use, disposable, prefilled (at the site of manufacture under aseptic conditions), pre-programmed drug-device combination product.

PatchPump is highly customisable, and is intended to deliver volumes up to 10 ml, over a period of minutes or a number of days depending on the delivery needs of the particular therapy and disease state.

The core technology inside the PatchPump is the E-Cell, which is comparable to an alkaline battery but with a flexible housing. The key difference between the E-Cell and a conventional alkaline battery is that as the E-Cell discharges, the housing expands. In the PatchPump, the expansion of the E-Cell is precisely controlled by its electrical discharge rate, and as the E-Cell expands against a flexible drug reservoir, the liquid formulation is expelled from the device and delivered either subcutaneously or intravenously.

The PatchPump utilises either an external infusion set as used with insulin infusion pumps (see Figure 1), or an integrated cannula (see Figure 2) to deliver the medication.

In addition to the E-Cell, the other major components of the PatchPump include: a flexible container for the prefilled sterile drug formulation; a programmable circuit board, containing the hardware and software that control the discharge/expansion rate and other device functions; various sensors to assist in flow control and occlusion detec-



Figure 1: PatchPump configured for external subcutaneous infusion set.



Figure 2: The PatchPump together with integrated cannula.



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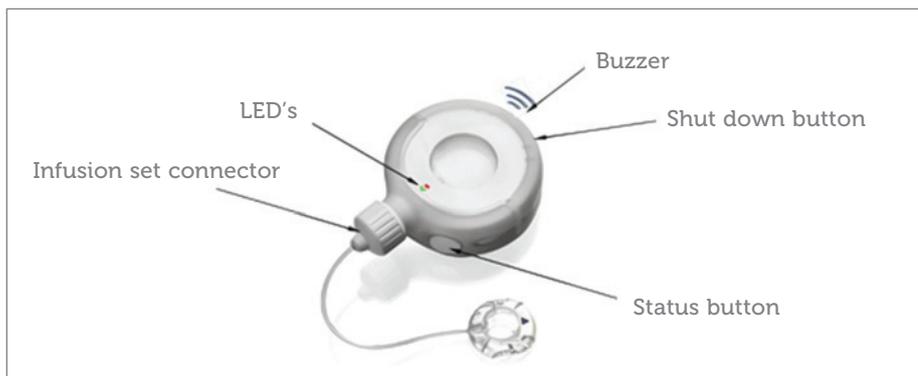


Figure 3: The PatchPump incorporates a number of sensors, and indicators that provide feedback to the patient. (Infusion set configuration shown here.)

tion, and other indicators to tell the patient the status of the drug delivery (Figure 3).

In the configuration developed for SteadyMed's lead internal development programme; treprostinil PatchPump for pulmonary arterial hypertension (PAH), the PatchPump will utilise an external infusion set, and will be programmed to deliver drug continuously for a number of days. At the end of the dosing period, PatchPump will alert the patient that it is out of drug; the patient removes and disposes of the empty device, and replaces it with a new unit to continue the chronic, around-the-clock infusion treatment.

This multi day replacement frequency is consistent with, or better than; the interval currently used for refilling other pumps used for PAH infusion therapy. Further, in contrast to the existing parenteral therapies for this indication, the use of SteadyMed's PatchPump-enabled product will eliminate the need for users to handle or fill the pump with drug, as well as the need for any dose programming.

Future PatchPump configurations for other products may run for shorter or longer periods, and may have the same existing external infusion set or may have an integrated infusion set.

PRINCIPLE OF OPERATION

To activate the treprostinil PatchPump PAH product, the user removes a cap from the discharge port and attaches an infusion set at that location. This action pierces the septum of the primary drug container and simultaneously turns on the product. (For the integrated PatchPump configuration, which may be used to deliver biologic compounds, pressing a small button, which inserts the soft cannula into the subcutaneous tissue, activates the device.) Once activated, the E-Cell begins to expand at

a controlled rate and as it does it displaces the piston, which applies positive pressure to the drug container. The pressure on the container forces drug solution through the delivery channel of the container and into the infusion line at a controlled rate.

The rate of expansion of the E-Cell is related to its discharge current. The movement of the piston is measured using standard sensor technology, and a control circuit in the electronics ensures that the piston moves at the required rate by regulating the discharge current (and hence the rate of expansion) of the E-Cell. If there are any occlusions in the delivery line, or site of infusion, they are detected by a force sensor positioned on the printed circuit board (PCB) underneath the E-Cell (Figure 4). The increase in force produced by an occlusion is sensed by the control system, which triggers an alarm and stops the E-Cell expansion.

During basal delivery the product is silent unless the status button is pressed, in which case the buzzer sounds and the LEDs flash green. Near the end of the delivery period the product will beep and LEDs will be illuminated to instruct the user that delivery will soon end.

It is expected that the PatchPump will usually be positioned on the patient's

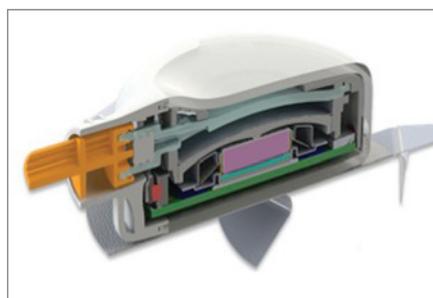


Figure 4: Cross-sectional view showing the components layered within the PatchPump.

abdomen but sites may also include the upper arm, hip, thigh and upper buttocks. The product is intended to be self-administered, and it is intended to be applied, used and worn throughout the course of normal daily activities. Hence the product may experience the environments associated with working, exercising, sleeping and be worn both indoors and outdoors. In addition, PatchPump is designed to be water resistant and can be worn while bathing or swimming.

E-CELL™

The E-Cell is a patented electrochemical actuation unit invented and developed by SteadyMed. The materials of construction of the E-Cell are comparable with a standard alkaline battery cell, with the exception that the cell materials are contained in a flexible polymer housing to allow for expansion. Figure 5, a schematic of the E-Cell, shows the anode and cathode materials contained in a flexible housing that also contains the electrolyte solution. When the product is activated, current is allowed to flow via the electrical connectors to resistors in the control circuit on the PCB. This causes the electrochemical reaction inside the E-Cell to take place, which results in a change in volume of the anode and cathode materials. The geometric design of the anode and cathode along with the flexible housing ensure linear, unidirectional expansion of the E-Cell (in the vertical direction as oriented in Figure 5). The quantities of anode and cathode material ensure that the E-Cell has sufficient capacity to support expansion throughout the entire infusion cycle for the product.

Given the E-Cell acts as its own power source and the driving motor that effects drug delivery the PatchPump can deliver viscous drugs and large volumes from a small compact form factor.

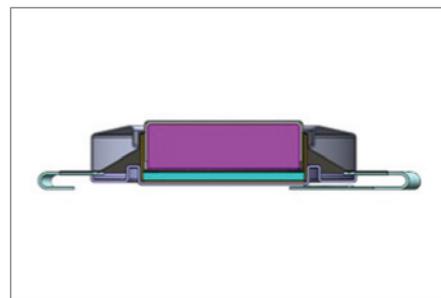


Figure 5: Schematic cross-section of the E-Cell.



Figure 6: The primary drug container comprises a flexible multi-laminate blister heat-sealed to a rigid base plate, with integrated filling/discharge channel, sealed with a butyl rubber septum.

PRIMARY DRUG CONTAINER

The primary drug container is circular in design and made up of several components. A flexible, thermoformed multi-laminate blister is heat-sealed to a rigid, injection-moulded base plate with an integrated filling/discharge channel. The blister and base-plate materials have been used in prior pharmaceutical and medical device applications, and were selected because of their low levels of extractables, and compatibility with biologic drugs. The container is sealed with a butyl rubber septum. An additional cap is fitted

during the aseptic filling process, to maintain the cleanliness of the exterior surface of the septum, up to the point of use of the product.

The container has been tested for drug compatibility, long-term stability and leachable compounds, and results have all been favourable. Additional studies by third party biopharmaceutical companies have been conducted for compatibility with biologic compounds, with favorable results for adsorption and leachables as well as drug stability.

CLINICAL AND HUMAN FACTOR STUDIES

As a part of PatchPump development a series of Human Factors (HF) studies have been completed with physicians, specialist healthcare practitioners (HCPs), patients and healthy volunteers. This empirical work has been informed and supported by an iterative program of design risk assessment activities, including risk reviews of existing devices and Use FMEA studies.

The series of HF studies has provided a foundation of understanding of the users (patients and HCPs), and their current experiences in order to inform device design features and parameters to support safe and effective

use. Several URS and PRS requirements were derived from these studies as well as a deeper understanding of users' acceptance and subjective preferences around the key principles of the drug device combination concept. In addition these studies provided the direction to help develop the PatchPump and Instructions for Use (IFU) design and provided good insight into the potential patient interaction with the design. This series of studies led to further refinement of the user interface and IFU.

SteadyMed has conducted proof-of-concept clinical studies in healthy volunteers in order to evaluate the safety, tolerability and technical aspects of the PatchPump. Data from these studies is undisclosed.

DEVELOPMENT STATUS

SteadyMed's PatchPump is in late-stage development with the supply chain in place to manufacture registration batches of its treprostinil PatchPump product prior to NDA submission in the second half of 2015.

The company is also working with biopharmaceutical companies that are assessing stability and compatibility of certain biologic drugs with the PatchPump as well as the performance of market research studies.



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INTEGRATED SOLUTIONS FOR THE DELIVERY OF HIGH-VOLUME BIOLOGICS

Highlighting the advantages for pharma companies of partnering early in the development process with packaging and delivery device partners, Graham Reynolds, Vice-President, Marketing & Innovation, West Pharmaceutical Services, Inc, introduces the company's wearable bolus injector, SmartDose, in the context of a fully integrated self injection technology platform offering using a standard primary container.

Chronic conditions, such as diabetes and autoimmune diseases, continue to be treated by a variety of therapies, although side-effects and challenges of patient self-administration can affect adherence and therefore effectiveness of these therapies in improving patient outcomes. In fact, according to the World Health Organization, adherence to long-term treatment recommendations for chronic conditions hovers at just 50%.¹ Patients may choose not to follow their healthcare

years. In fact, more than 907 biotechnology medicines were in development as of 2013 – nearly 30% of all drugs in the pipeline.² Medicines derived from biotechnology have aided those suffering from chronic conditions, including cancer, diabetes and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (RA).

Derived from living cells, biologic drugs include genetically engineered proteins known as monoclonal antibodies (mAbs) that can be formulated to target specific components of a disease. For example, biologics designed to treat RA may target components of the immune system that play a role in inflammation. In addition, injectable biologic drugs are being developed for conditions previously treated by non-injectable means, such as asthma and cholesterol-related conditions. When these drugs reach the market, it is likely that the majority will be presented to patients an injectable format, and many will require regular self-injection in a non-clinical environment.

Typically large in size, biologic molecules may require a higher concentration of the drug product for efficacy. In addition, biologic molecules tend to be sensitive to products commonly found in traditional glass prefilled syringe systems, such as metal ions and silicone oil, substances that may impact the drug product's efficacy and a delivery system's performance. The result is a

“Changing a device can be easier than changing the primary containment for a drug, so an understanding of how to create a platform of devices around a single drug container is essential”

providers' recommendations for a variety of reasons, including painful, inconvenient or difficult administration. As chronic conditions continue to rise, and patients take on the responsibility of administration in the home environment, it is increasingly important that delivery and administration systems are designed with the patient in mind.

The success of biologics, which offer patients better long-term outcomes and fewer side-effects than traditional, chemical-based therapies, has led to a rise in the numbers of biologic drugs over the past several



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drug product whose viscosity is significantly higher than currently approved self-injected products. In a traditional system, such high viscosity may require clinical administration, multiple dosing or more frequent injections, which can be less convenient for the patient.

Many biologics in use today are administered via intravenous (IV) infusion in an acute care setting. However, trends toward self-injection and home care have increased the demand for products that are easily injected by patients or caregivers in a home setting. At present there are several approved biologic products intended for self-injection by patients, such as Johnson and Johnson's Simponi® (golimumab), Amgen's Enbrel® (etanercept), and Abbvie's Humira® (adalimumab). These injections are typically designed for delivery into the subcutaneous space, require a relatively low dose for efficacy and have a reduced risk of life-threatening adverse reactions. Both Simponi and Humira are packaged in 1 ml "long" prefilled syringes and dosed on a weekly, semi-monthly or monthly basis, depending on the patient's particular indication. Delivery of the medication can be via manual injection from the prefilled syringe, or by incorporating the syringe into a disposable auto-injector.

As pharmaceutical companies create and clinically test large-molecule antibodies for new therapeutics that may require larger doses given over a longer period of time, packaging and delivery challenges can arise.

DESIGNING A SUCCESSFUL INTEGRATED SYSTEM

While the primary focus of most pharmaceutical companies is on the drug product itself, early collaboration with a packaging and device partner during the lengthy development stages can result in a delivery system that meets the needs of both the drug and the patient. Research and development for a biologic drug product can typically last as long as 15 years and cost as much as US\$1.2 billion (£0.7 billion).³ So, when the product reaches the market, the originator may have only a few years remaining on the patent. Often, the delivery system is considered during the final stages of development. If the drug product cannot be effectively stored or reacts chemically with the containment materials, or if the system does not function well with a high-viscosity drug or is not a good fit for the intended audience, issues may arise that can be costly for the manufacturer.

Since a drug product cannot be effective if the patient does not adhere to therapeutic

recommendations, easy to use, safe and effective integrated delivery systems are an essential part of any drug product. A successful integrated delivery system should combine the following four key elements:

- 1) **The needs of the patient, caregiver and healthcare professional:** Clinical benefit, as well as the ease-of-use and ability to adhere to a treatment schedule, should be considered.
- 2) **The drug:** A drug product must provide effective treatment in an appropriate form that enables effective administration with an optimum delivery rate and frequency.
- 3) **A primary containment system:** The drug must be held in a container that maintains effectiveness, safety and optimum quality over a period of time.
- 4) **A delivery device or system:** The drug should be compatible with the containment system and designed to enhance the drug delivery experience for the patient or caregiver.

By collaborating with a packaging and device partner early in the development process, pharmaceutical and biotech companies can design and develop an integrated system that can help bring the four elements of effective delivery system together sooner. This will help to ensure that the biologic drug product reaches the market in a delivery system that not only helps to protect the drug product's efficacy, but will also help a patient adhere to treatment during any part of the therapeutic lifecycle.

UNDERSTANDING PATIENT NEEDS

To create an effective and easy-to-use delivery system, the patient-use cycle must be considered early in the development process. From initial diagnosis to long-term adherence, the patient passes through a variety of emotional and physical phases. Human factors testing can help establish the emotional and physical needs of patients at each stage of their therapeutic journey. For example, upon initial diagnosis, a patient may be frightened and unsure of the delivery mechanism, and may require guidance from a healthcare professional to deliver the prescribed dose. Delivery systems for a person at this stage should be designed to ease that burden of fear by being simple to use and intuitive in design. It should also provide clear indications that the dose has been delivered successfully.

As the patient learns to cope with the condition, other factors such as accessibility and portability may rise in importance. At this stage, an auto-injector, pen device or

cartridge-based system may offer more convenience. Patients who must be on long-term therapies often find their own level of comfort through varying degrees of drug delivery control. Many may be comfortable determining their own rate or angle of injection with a prefilled syringe system, while others prefer the speed and simplicity of an auto-injector.

Offering delivery choices to the patient may help to ensure adherence at any stage of the patient's therapeutic journey. Currently, Rebif® (interferon beta-1a), a self-injection therapy for relapsing multiple sclerosis from Merck Serono, offers the same drug packaged in a variety of different systems. Such options provide the patient with a choice of delivery methods based on comfort level. Rebif is available as a stand-alone syringe for those comfortable with self-injection. It is also available in either a disposable or reusable auto-injector system.

There is no "one-size-fits-all" device or system for patients suffering from chronic conditions, so a variety of choices for self-injection may soon become the norm for many biologic therapies. Early-stage planning for such choices can help pharmaceutical companies select materials for containment that can be used for multiple options. Changing a device can be easier than changing the primary containment for a drug, so an understanding of how to create a platform of devices around a single drug container is essential.

EVOLVING TECHNOLOGY FOR INTEGRATED DELIVERY SYSTEMS

As the biologic market has grown, so too has the use of prefillable syringe and cartridge systems, moving from 3.1 billion units in 2012 to an expected 4.7 billion in 2016.⁴ Such systems offer convenience and ease of use. Many biologics in the pipeline will require high dose-volumes, and patients who require long-term treatment may prefer options that allow for higher doses to be given over longer periods. Since cyclic olefin polymers can be molded into a variety of shapes and designs, unique systems with larger fill volumes and tighter dimensional tolerance can be used while still remaining compatible with established filling technologies.

Proprietary systems, including West's SmartDose® electronic wearable injector*, are being developed to aid patients with self-administration. The SmartDose system, which features a drug containment system based on a Daikyo Crystal Zenith® cyclic olefin polymer cartridge and Flurotec® plunger, designed specifically to hold high-volume doses of sensitive



Figure 1: West's SmartDose® electronic wearable injector provides a solution for the challenge of delivering a large dose of a drug product.

biologics, offers a subcutaneous, programmable electronic injection system that adheres to the skin and can deliver the drug over time (see Figures 1-3). User interfaces such as electronic indicators optimised through human factors studies can aid in patient adherence and caregiver monitoring.

The SmartDose system is an excellent example of the balance between an effective drug containment system and a user-friendly delivery system. The SmartDose system has been designed for ease of use and patient comfort, while facilitating the delivery of innovative drug products.

The SmartDose system meets a need for high-volume subcutaneous delivery of viscous or sensitive drug products, which may require longer injection times. The use of a Crystal Zenith cartridge offers the ability to deliver a higher dose using an option based on quality, stability and performance considerations. The flexibility of Crystal Zenith

allows it to be optimised for use with the SmartDose system and makes it possible to use this technology for the next generation of self-administered protein-based drugs.

In 2013, West completed a preliminary study of its SmartDose wearable patch injection system, which incorporates a Daikyo Crystal Zenith cartridge. The study evaluated multiple attributes of the technology and subjects' experience with the self-application process.

The June 2013 study, entitled: "First-in-Man, Single Center, Open, Two Periods, Self-Application clinical Study to Evaluate the Safety, performance and tolerability of SmartDose 2.5 using Saline in Healthy Subjects at Two Delivery Rates," was conducted in Israel. This milestone, following extensive scale-up and validation of the system, has helped to confirm the readiness of the system to support customers' clinical studies with their drug product, and will help



Figure 2: SmartDose® uses a Daikyo Crystal Zenith® cartridge that is filled by the pharmaceutical company using conventional filling equipment, and is easily inserted into the injector by the patient.



Figure 3: The SmartDose® electronic wearable injector fulfills a need for high-volume subcutaneous delivery of modern biologics, which may require longer injection times.

ensure the optimum speed to market. West is continuing our "By your side" philosophy by working closely with several pharmaceutical companies that are currently performing drug stability studies in the Crystal Zenith cartridge, and evaluation of the system.

Early collaborations between pharmaceutical manufacturers and packaging experts can help to create a platform of delivery options for patients. While the drug development journey may be long and expensive, the patient journey can last a lifetime. To ensure adherence and brand loyalty throughout that journey, pharmaceutical manufacturers should consider delivery alternatives as early as possible. By working with an integrated packaging and delivery system partner from R&D stages through commercialisation and beyond, the biopharmaceutical manufacturer can present patients with options that will last a lifetime and encourage adherence for as long as the patient requires medication.

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* For investigational use only by our pharmaceutical and biotechnology development partners. West seeks partners for its SmartDose® injector technology platform. This platform is intended to be used as integrated systems with drug filling and final assembly completed by the pharmaceutical/biotechnology company.

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enable injections

PEOPLE POWER: INSPIRING & DELIVERING A UNIQUE WEARABLE BOLUS INJECTOR

In this article we describe the highly customisable wearable bolus injection device developed by Enable Injections to provide the most comfortable, simple and discreet patient experience whilst allowing more biologics, including lyophilised products and previously IV-only therapies, to be brought into the home/self-administration setting earlier for safe SC delivery.

Written by ONdrugDelivery Magazine for and on behalf of Enable Injections

These are exciting times for parenteral drug delivery – an entirely new class of drug delivery device is nearing the market and will soon be out there, improving quality of life for patients suffering from chronic

bolus injectors for high-volume subcutaneous (SC) injection are on their way is not in doubt. The questions remaining are more about which technologies will make it to the market and what will be the final form these technologies take.

“The ability to bring drug mixing and reconstitution into the home self-administration setting in this way brings with it manifold advantages”

There exists a broad variety of device approaches currently in development at different stages, all racing towards the market, all with unique, innovative and clever characteristics in their designs, mechanisms and modes of use. Enable Injections’ wholly mechanical wearable bolus injector (see Figure 1) is no exception. But

diseases. As part of the evolution of self-injection technologies, itself driven by the rise of biologics, the fact that wearable

before going on to describe the device, how it works and how it is used in more detail, it is important to make a point about people.

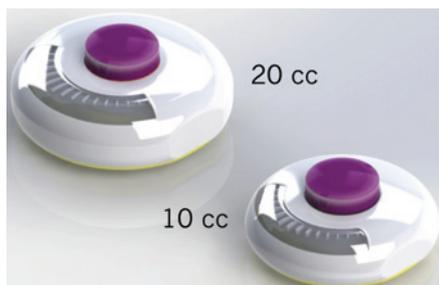


Figure 1: The Enable Injector device in 1-10 ml (right) and 1-20 ml (left) formats. The 10 ml device is about the size of an “Oreo” biscuit.

Enable Injections is all about people. Firstly, let’s consider its own people: the team that President and CEO Michael Hooven has assembled is formidable. Hooven himself is the founder of two previous successful medical device businesses, including the surgical atrial fibrillation treatment firm, AtriCure, in 2000. AtriCure is now a close competitor with global giant Medtronic, and is a publically traded company (NASDAQ: ATRC) with a market capitalisation in excess of US\$500 million. Hooven’s stellar board at Enable Injections includes such



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Figure 2: Fully equipped US manufacturing facilities are already in place.

names as: Mark Collar, former President of Proctor & Gamble's Pharmaceuticals and Personal Health business; Norman Weldon, PhD, founder of and investor in more than 20 medical device companies, who has also served as President and CEO of numerous companies in the field including, amongst others, Cordis Corporation; Karen Robards, former Head of Healthcare Investment Banking at Morgan Stanley; and Don Harrison, MD, former Chief of Cardiology at Stanford University, former Head of the University of Cincinnati Medical School, and former President of the American Heart Association.

Likewise, the design team working on Enable's devices are top-drawer. In total the team has worked on the development of more than 100 products with combined sales topping \$10 billion, they have more than 200 patents between them, and count amongst their ranks a J&J Chairman's Medal Winner. Similarly, the company's clinical, regulatory and human factors teams are of the same experienced, seasoned high calibre.

People. Always uppermost in the thoughts of this top-flight team as they bring Enable's products to fruition are, once again, people. Specifically, they are thinking about the patients who will eventually be using and benefiting from Enable's devices. As one learns more about Enable Injections and begins to examine the device design in-depth, the constant consideration given as the absolute top priority to the detailed wants, concerns and needs (clinical and personal) of the patient becomes apparent. This is the thread that runs through every aspect of what Enable Injections does and the devices it is developing.

Along with a steadfast focus on patients, a clear understanding of the cold, hard science and engineering, plus the capabilities and business acumen to operate in the pharma industry, and the experience and knowledge to navigate the regulatory procedures, are all requirements for successfully bringing a drug delivery device development

project through to market.

As Gary Ansel, MD, Associate Medical Director of the OhioHealth Research and Innovation Institute (Columbus, OH, US) put it: "Having an injector like this, especially one that decreases pain, opens the door to new pharmaceuticals that wouldn't be possible without this revolutionary device. We're talking potential for huge cost savings, reduced hospital stays, and increased patient compliance—all at the push of a button."

The initial technology development for Enable's devices took place at the Children's Hospital Medical Center in Cincinnati, OH, US, and were focused on a painless injection system. Multiple studies showed significant pain reduction and, whilst temperature was found to be one key factor, the deep understanding of all the causes of injection pain gained through Enable's partnership with the hospital means that the Enable Injector addresses all of these causes, delivering the most comfortable injection experience possible.

Enable's admin and finance is still headquartered in Cincinnati with design and manufacturing now taking place at its

"The system automatically warms the drug to room temperature, meaning that instead of waiting the usual 30 minutes ... the dose is ready to inject immediately"

extensive facilities in Franklin, OH, US. Enable plans to continue to manufacture all device components onsite at its US manufacturing facilities (Figure 2), which comprise:

- 5,000 sq ft (465 m²) pilot manufacturing space
- 5,000 sq ft controlled environment manufacturing

- 2,000 sq ft (186 m²) controlled environment injection moulding
- High-volume injection moulding capabilities
- Second manufacturing site identified for occupancy late 2015/early 2016.

THE DEVICE

At the outset, Enable defined its broad goals as follows:

- Development of a bolus injection system
- Utilise the pain-free injection technology
- Deliver very high volumes and viscosities
- Utilise standard vial/cartridge container closure
- Automatically reconstitute lyophilised solutions
- Deliver the highest volume using the smallest possible device.

Since defining those targets just a few years ago, Enable Injections has developed a fully automated, mechanical drug delivery system that allows the user to self-administer any volume of drug from 1 to 20 ml by SC injection. The patient simply inserts the drug vial or cartridge into the system, places the device on the body, and presses a button. The drug is automatically and comfortably delivered at a pre-programmed flow rate into the subcutaneous tissue over a timeframe that can range from minutes to hours. After delivery is complete, the needle is automatically retracted and locked out, and the user is notified with a primarily tactile feedback which is discreet, being only felt and heard by the patient, who can look

at the device for visual confirmation too. The needle is never seen or exposed, and the device is fully recyclable having no electronic components.

From the point of view of the patient using the Enable device, the first thing they are presented with is a small box (approximately 15 cm by 12 cm, and quite flat at only 4.5 cm high). On opening the box (see



Figure 3: Drug transfer process: three simple patient steps.

Figure 3a) the patient sees inside: on the left, a standard vial or cartridge containing their medication; and to the right, the injector device (roughly the size of an “Oreo” biscuit – just over 4cm across) in a plastic housing. One-word instructions with simple graphic illustrations are printed on the inside of the lid. The three simple patient steps for drug transfer are shown in Figure 3a-c.

If the drug needs to be stored in the refrigerator, the vial can be refrigerated as normal and inserted into the transfer system straight from the fridge. During transfer from the vial to the injector, which takes just a few seconds, the system automatically warms the drug to room temperature, meaning that instead of waiting the usual 30 minutes between taking a drug vial out of the fridge and using it, the dose is ready to inject immediately upon completion of drug transfer.

The Enable Injection device can be configured in a dual-vial format too, providing automated mixing of two vials of up to 10 ml each (see Figure 4). The patient is



Figure 4: The Enable Injector in dual-vial configuration requires no additional patient steps.

completely removed from the mixing process and the three-step instructions for the dual-vial system remain exactly the same for the patient as for the single vial system. Enable’s automated mixing system can be pre-configured to mix powder/liquid or liquid/liquid for up to an hour, or more.

The ability to bring drug mixing and reconstitution into the home self-administration setting in this way brings with it manifold advantages. Patient convenience is a key benefit but, in addition, errors due to user mixing are eliminated. Furthermore, treatment and facility cost-savings are likely and, earlier up the line, the ability to release lyophilised formulations earlier brings with it potentially huge commercial advantages.

Once the transfer process is complete, the red retaining tab clicks back to release the loaded injector device and the patient follows the three steps outlined in Figure 5.

PATIENT-OPERATED TRANSFER DEVICE: BENEFITS

Central to the commercial/development advantages that Enable’s system brings is that it requires no change to the primary drug container and, further, that any standard vial or cartridge can be combined with the Enable device at any point in the supply chain, the long-term container and closure material compatibility testing having already been completed with the original container. In fact the device uses only standard IV materials in the entire drug path meaning that any drug already approved for IV administration would be exposed to the same materials, thus minimising short-term material compatibility testing too.

Up against a preloaded device, the patient-loaded device gains several additional wins. In a preloaded wearable bolus

injector, the necessity to incorporate a pre-filled drug container such as a vial or cartridge inside the device, together with plunger and power source (often a spring) to drive the injection, represents a considerable limitation of design options with the addition of bulk being amongst them. Also, the force required to drive the plunger increases as the volume and/or viscosity of drug increases, usually resulting either in an increase in delivery time or an increase in the size of the cannula.

With the Enable device, the force required to deliver the drug does not change with the volume and the delivery rate and cannula size remain the same meaning that the Enable system delivers volumes and viscosities substantially higher than devices that use a cartridge and plunger. Specifically Enable is more than comfortable claiming routinely to be able to achieve effective delivery of 10 ml of 100 cP formulation through a 29g needle at a rate of 1 ml/min, but in most cases needle size can be reduced further to 30g or beyond with obvious advantages with respect to patient comfort.

Very small, ergonomic, low-profile wearable devices capable of delivering volumes of from 1 to 10 ml or from 1 through to 20 ml (Figure 1) become possible because of Enable’s proprietary S.E.T. Drive (details of which are available under a confidentiality agreement only).

PATIENTS FRONT & CENTRE FROM THE BEGINNING

Human Factors Engineering (HFE) has of course been at the heart of every aspect of the development of Enable’s device and the company has put intense efforts into Human Factors studies from the very outset. To date 16 studies have been conducted in different user demographics, following accepted HFE and Usability Engineering standards including:

- ANSI/AAMI HE74:2001 Human factors design process for medical devices
- IEC 60601-1-6, Ed1, Usability
- US FDA Draft Guidance issued June 22, 2011: Applying Human Factors and Usability
- Engineering to Optimise Medical Device Design.

MINIMAL INTERACTION

The HFE studies conducted during the development of the Enable device revealed clearly that users want minimal interaction

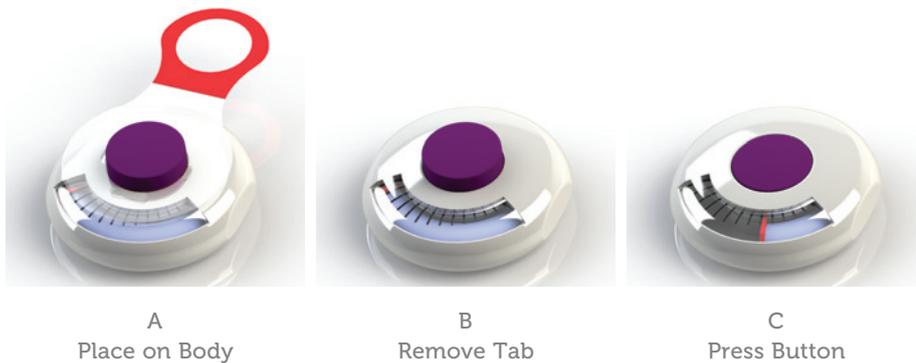


Figure 5: Initiating the injection: three simple patient steps.

with an injection device. In the context of the current trend for numerous programmable devices being brought forward, which provide the user with various functions, indicators, buttons and alarms, it is maybe initially counterintuitive to discover that users prefer not to have to make decisions on programming or about which buttons to press or how many times to press them. Steered by its user study results, Enable's device requires that the patient does one thing after placing the device on their skin – press the central button. On pressing the button the needle is inserted to the right depth and controlled drug flow begins.

In a similar way to the question of “programmability *versus* no programmability”, user studies gave some unequivocal yet possibly unexpected results in the context of refrigerated drugs (i.e. the vast majority of biologics) on the question of “preloaded *versus* patient loaded”. Specifically, every patient surveyed preferred the patient-loaded system. Digging down into some of the most common reasons given reveals that their preference for the patient-loaded device shouldn't be viewed as unexpected at all, but entirely natural.

As mentioned, whilst allowing for the storage of only the vials in the fridge (i.e. not requiring the entire wearable device to be refrigerated), Enable's device also eliminates the need to wait for 30 minutes for the drug to come up to temperature by warming it during the short period of drug transfer process. Among the reasons given by patients for their strong preference for the patient-loaded device were: “The vial

doesn't take up room in the refrigerator”, “The vial is childproof, an injector isn't”, “Once I start something, I want to finish it”, and “If I have to leave it out, I might forget about it.” Also, users wanted a device that is ready when they are.

The user studies also drove Enable towards a clear objective of creating the smallest, flattest, quietest, most unobtrusive possible device. The word “discreet” came up repeatedly throughout the Human Factors studies. We have already mentioned that the Enable device delivers the highest possible volume from the smallest possible device. Additionally, when dosing is completed there is no audible buzzer or alarm ringing out for all to hear like an unwanted mobile phone call. Enable's device makes a subtle click on completion of dosing that only the user can feel and hear, since it is only the user who needs to know. Once aware that the device has finished, the user can then make the decision as to when and where they want to remove and dispose of the device.

The Human Factors studies helped Enable to make additional subtle (yet to users incredibly important) design decisions – the clear one-word instructions being printed on the inside of the lid, for example. Another example is that Enable observed how users with impaired vision or dexterity had difficulty peeling the cover off the adhesive backing with one hand whilst holding an injection device in the other hand. With the Enable Injector, the cover is peeled off the adhesive backing automatically when the user takes the device out of

the box after drug transfer. Even the orientation of the finger gaps either side of the device “front-back” rather than “left-right” as it sits in the packaging has been chosen because Enable found that with this orientation the user intuitively picks up the device with the correct grip to allow them to place it straight onto their skin without further fiddling around.

CONCLUSION

The Enable Injection Device is not only a wearable bolus injector honed for maximum user comfort and satisfaction, for optimal compliance and adherence, but also a unique, highly customisable drug delivery device-offering to the industry featuring:

- Adjustable Volume
 - 1-10 ml – Standard Device
 - 1-20 ml – High-Volume Device
 - Up to 50 cc – Very High-Volume Device
- Adjustable Flow Rate
 - From 0.1 cc/min to 100 cc/min
- Adjustable Needle Size
 - 27-33g
- Unlimited Viscosity
 - 100 cP of 10 ml volume through 29g needle at 1 ml/min
- Automated Mixing
 - Vials of up to 2 x 10 ml volume
 - Liquid/Liquid or Lyophilised/Liquid.

To conclude, a message direct from Enable for formulations teams who are spending millions of dollars and pounds and euros striving to adjust concentrations to make biologics injectable or otherwise deliverable: “There's no longer a need to worry about that. The Enable Device can mix and deliver the drugs as formulated, with potential cost-savings and quicker time to market. IV is no longer the only alternative!”

From the stellar line-up of board members to the attention to every fine detail of numerous rigorous HFE and user studies, every aspect of the Enable Injections wearable device has been defined with people front and centre, from the very earliest stages and throughout.



IN WHICH EDITION COULD YOUR COMPANY APPEAR?

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GERRESHEIMER

SAFE & RELIABLE PRIMARY DRUG CONTAINER MANUFACTURING

All wearable bolus injection devices must use a primary drug container at some stage. Some are used in conjunction with standard primary drug containers, from which the patient transfers the drug into the device at the point of use. Other wearable bolus injectors incorporate prefilled primary drug containers – standard or customised – into the device body itself. Here, Gerresheimer, a global leader in the manufacture of parenteral drug delivery systems and primary packaging, including standard and customised glass vials, ampoules and cartridges, provides a brief overview of the manufacturing process.

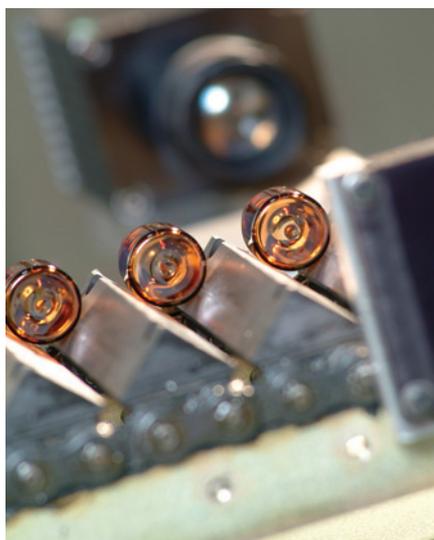


Figure 1: Vials are inspected for cosmetic defects.

Like syringes, ampoules and cartridges, vials are made of glass tubing. Vertical or horizontal production technology is used to make them, depending on whether the glass tubes are positioned vertically or horizontally in the machine.

On a horizontal forming machine, a thermal-shock process is used to cut the glass tube to the required length when it has been fed into the machine. One length of cut tube is then used to make two vials. Tiny glass splinters or dust are sometimes created when the tube is cut, which are immediately removed with pressurised air. After the tube cutter, the tube sections are transported on a conveyor belt along flames where both ends of the tube are heated and converted to create the shoulder, neck and lip in the required geometry.

In the next step, the tube is heated at the centre, pulled apart, and the two ends are formed to create the bottom. During the entire converting process, the tube sections are transported horizontally orientated, hence the name of the procedure.

In vertical manufacturing, the glass tubes are positioned vertically into chucks of the forming machine. Unlike the conveyor belt in the horizontal process, the forming machine has a rotary design like a carousel. The end of the glass tube is heated and the shoulder, neck and lip are formed by using forming tools. Then, the glass tube is heated and pulled apart. To finalise the conversion of the new vial from the short section, the other end is heated to form the bottom. During the process, glass tubes and sections are located in a vertical position, hence the name of the procedure.

After the converting process, each vial is precisely measured. If even one measurement is outside the defined tolerance limits, the vial is rejected. Then the vials go into the annealing oven to eliminate any stress in the glass caused by the converting process. This is particularly important because stress in the glass can cause cracks at a later time and render the content of the vial unusable.

When the vials have come out of the annealing oven they are inspected for cosmetic defects (Figure 1). These include cracks and scratches, as well as impurities or bubbles. After an initial camera inspection they are also inspected visually by a member of staff. Defective vials are rejected. The good vials are sealed in shrink wrap and stacked onto pallets. Geometric and cosmetic inspections of each individual vial are also performed in process (100% inline control), as well as additional random quality checks. Polarised light is used to show whether all the stress has been eliminated from the glass.

Chemical tests are used to assess the glass's hydrolytic resistance and at times a pressure test is used to measure the vial's mechanical resistance. All these quality inspections are very important to ensure that the vials don't interact with the medication, that they don't cause any problems on our customers' machines and that they don't break during transportation.



Figure 2: Traditionally vials are the storage container for parenteral drugs that are ultimately transferred into a syringe at the point of use but increasingly vials are used to transfer parenteral formulations into new-generation self-injection devices.

Gerresheimer ensures that the vials make safe packaging and that the medications arrive intact at the pharmacy, doctor's office, hospital and ultimately at the patient. Whilst traditionally vials have been used as the storage container for parenteral drugs that would ultimately be transferred into a syringe by a medical professional at the point of use (as shown in Figure 2), increasingly vials are used to transfer parenteral formulations into new-generation injection devices such as wearable bolus injectors. Similarly, drug cartridges commonly used in pens and auto-injectors are now also being incorporated into wearable injection devices. Whatever the intended end-use, patient safety is the highest priority in every single stage of the primary container production process.

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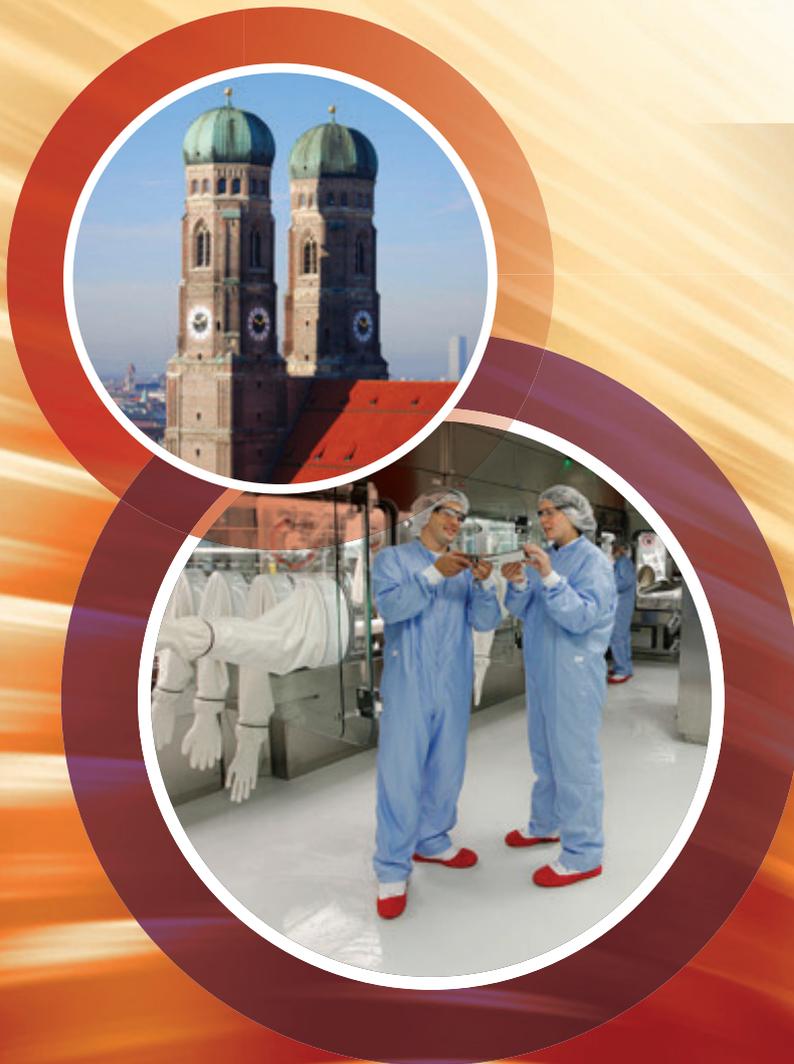
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