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 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

Alan Shortall
Chief Executive Officer

Unilife Corporation
250 Cross Farm Lane
York
PA 17406
United States
T: +1 717 384 3400
E: info@unilife.com

www.unilife.com

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

a)

b)

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 handheld 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-

fortable 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 prefilled 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.

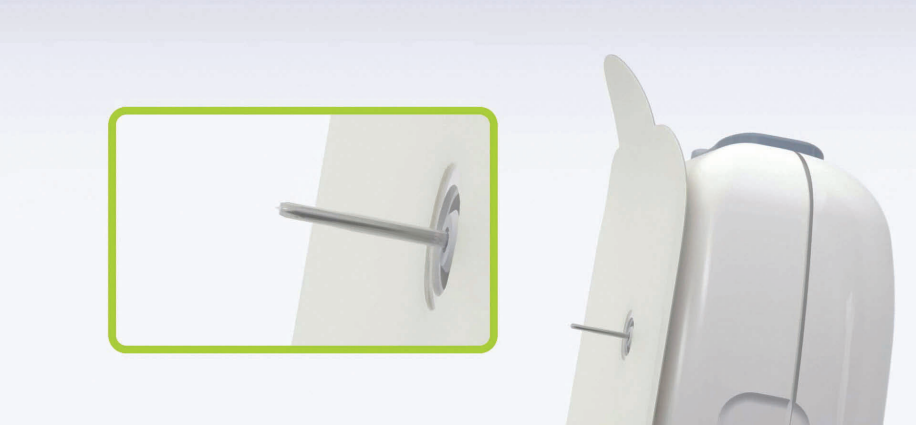

Figure 3: A metal needle automatically retracts into the device after insertion of the FlexWear comfort catheter to maximise patient comfort during the injection.

USER STUDIES

Usability and human factors represent a strong area of focus for pharmaceutical companies evaluating wearable injector technologies. Common criteria for pharma 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 variety 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.

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 opportunities 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

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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, 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 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 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 awareness. 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.

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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.

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.


Pre-filled,
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Peel,
Stick,
Click.
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These products have not yet been evaluated by the FDA