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

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

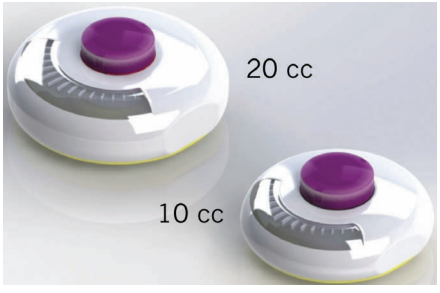

Figure 1: The Enable Injector device in 1-10 ml (right) and 1-20 ml (left) formats. The 10 ml device is about the size of an "Oreo" biscuit.

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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 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 m^2) pilot manufacturing space
- 5,000 sq ft controlled environment manufacturing
- 2,000 sq ft (186 m^2) 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.

> "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"

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

A
Remove Vial Flip Cap

B
Insert Vial

C
Remove Injector

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 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.

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

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 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

A
Place on Body

B
Remove Tab

C
Press Button

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.