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Wearable Bolus Injectors - A New Class of Patient-Friendly Drug Delivery Systems

By: Michael D. Hooven, MSME

Injectable drugs are projected to be the largest growth category of drug delivery throughout the next decade. The majority of the new injectables are biologics, which now account for $161 billion in sales and are predicted to gain market share, growing to $215 billion in sales throughout the next 5 years, according to a Roots Analysis. The analysts further predict that approximately 50% of the top 100 drugs will be biologics by 2016.

Biologics hold tremendous promise for advancing treatment of numerous cancers, various immunologic disorders, such as Rheumatoid Arthritis and MS, and a number of other disease categories, including rare genetic disorders.

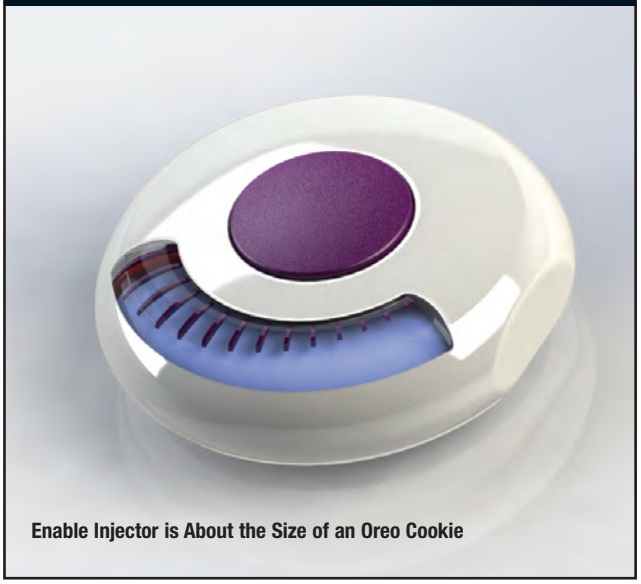
Many of these drugs (biologics, monoclonal antibodies, and immunoglobulins) are characterized by large molecules that cannot be absorbed into the digestive tract. Because they require direct injection into the tissue or bloodstream, they raise multiple drug delivery issues that cannot be addressed with today's injectable systems.

ADDRESSING THE CHALLENGES OF DELIVERING LARGE DOSE OR VISCOUS DRUGS

Biologic drugs are often viscous or high volume formulations and are thus developed primarily as intravenous formulations or, in some instances, as intramuscular or subcutaneous formulations. Such parenteral drugs, however, require specialized training to administer, which often necessitates a patient visit to a hospital, outpatient clinic, or specialty pharmacy solely for drug therapy. Not only do these issues raise health care costs, but also decrease patient satisfaction and compliance.

Further, a significant number of large-dose drugs currently on the market or in development require more than 1 mL per dose,

FIGURE 1



Enable Injector is About the Size of an Oreo Cookie

which is generally considered near the upper limit for subcutaneous administration using a syringe or autoinjector. The subcutaneous tissue cannot comfortably handle a bolus injection of more than 1 mL delivered in this way.

Pharmaceutical companies have attempted to address these various issues by decreasing the frequency of dosing, converting intravenous to subcutaneous administration, and most recently, by rapidly adopting (and adapting) drugs to more patient-friendly drug delivery systems.

One of the most promising drug administration systems is the Bolus Injector, a new class of drug delivery device that can be customized to subcutaneously inject doses far larger than today's syringes or autoinjectors. Bolus injectors are wearable injectors that have the capability to deliver more than 1 ml of a drug subcutaneously in a simple, reliable, and inexpensive manner.

BOLUS INJECTORS MAY REVOLUTIONIZE TREATMENT REGIMENS FOR CHRONIC CONDITIONS

There is a compelling need for this simple-to-use, low-cost disposable device that allows at-home self-administration of high-volume drugs. Minimizing the need for patients to travel to a healthcare facility, these new injectors could potentially revolutionize treatment regimens for many of the most prevalent chronic conditions, from cancer to autoimmune disorders to blood diseases and others that now require multiple, repeated doses of drug at frequent intervals.

Bolus injectors allow patients to easily and comfortably self-administer injectable drugs. In addition, drug delivery with bolus injectors may enable additional treatment advances by making it possible to safely, conveniently, and cost effectively deliver many of the more than 900 biologics and biosimilars in development today.

WHAT IS DRIVING ADOPTION OF BOLUS INJECTORS?

There are several drivers for adoption of the new bolus injectors, including the following:

- FDA regulations requiring the use of a device in drug clinical trials
- New safety and needle-stick standards
- Lifecycle management
- Brand differentiation
- The overall drive to lower healthcare costs by moving therapy from office and healthcare professional to home self-administration
- Patient convenience
- Increased patient comfort for greater compliance
- Cost containment

A SOPHISTICATED, PATIENT-FRIENDLY BOLUS DRUG DELIVERY SYSTEM

Enable Injections has developed a fully automated drug delivery system that allows the user to self-administer any volume of drug from 1 to 20 mL. 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 audible, visual, and tactile feedback. The needle is never seen or exposed, and the device is fully recyclable with no electronic components.

FIGURE 2

A Single-Vial Enable System

THE PRIMARY CONTAINER: NO CHANGE REQUIRED

In developing any drug/device combination, the greatest development challenge and risk is validation that the drug is stable and compatible with the primary container for the storage life of the drug. Modifying a primary container involves long-term stability testing with the drug, as well as extensive manufacturing process development and validation designed to incorporate the drug and primary container into the device. Any material compatibility issues or processes that affect the stability or integrity of the drug or container must be addressed.

Enable's system is unique in that it requires no change to the primary container and can utilize any standard vial or cartridge. This minimizes the risk, cost, and time associated with development of a new delivery system because the long-term container closure testing and manufacturing process and equipment changes have been validated with the original container. The vial or cartridge can then be

FIGURE 3

A Dual-Vial Enable System

combined with the Enable system at any point in the supply chain.

COMPATIBLE DRUG PATH

In addition, short-term material compatibility testing must be performed with all materials in contact with the drug during delivery. The Enable system minimizes the risk, time, and cost of this testing by using only standard IV materials in the drug path. Therefore, any drug that is approved for IV administration should be exposed to the same materials, minimizing the short-term material compatibility risk.

HUMAN FACTORS ENGINEERING – DELIVERING WHAT PATIENTS WANT

The FDA is placing an ever-increasing emphasis on Human Factors testing for drug-device combinations. The agency recognizes that it is not enough to simply ensure that the device is safe and efficacious if used properly, particularly as home self-injection has become more prevalent. This emphasis on patient self-administration of injections challenges drug and device manufactures to show that the device delivers the proper dose of the drug when used by the patient in a home environment. A device that is shown to be highly reliable in laboratory bench testing may be prone to user confusion or errors, and as a result, may not perform reliably in actual use. Devices must be designed with the assumption that the user is one of the primary variables. To address these concerns, Enable has put intense effort into Human Factors, from the earliest concept through the final design.

Enable's primary emphasis during design was to focus on a safe, reliable device that minimizes user error and confusion.

To address the fact that few users read instructions, the entire Enable injection process is printed on the inside cover of the box in six simple, consecutive, numbered steps with single-word descriptions and accompanying pictures.

In testing, those users with compromised dexterity or eyesight had difficulty "peeling" the cover off the adhesive backing. Holding the device in one hand while pulling at the adhesive cover with the other created the opportunity to drop the device on a hard floor, potentially damaging it. The Enable system was designed to eliminate this step with automatic removal of the adhesive cover on the tape as the injector is being removed from the package.

COUNTERINTUITIVE RESULTS: PATIENTS PREFER ONE-BUTTON FUNCTIONALITY – NO PROGRAMMING

"Programmability" is a buzzword that most would assume is a benefit in an injection device. It turns out to be the opposite. Rather than having a number of features, indicators, functions, alarms etc., users wanted minimal interaction with the device. They did not want to have to make decisions on programming or which button they needed to push. Consequently, the Enable Injector gives them one thing to do after inserting the vial - press the central button. With one press of the button, the needle is automatically inserted to the proper depth, and a controlled flow of the drug begins.

DISCRETION IS KEY FOR PATIENTS

Another issue encountered again and again throughout 15 Human Factor studies was the word "discreet" - the user did not want to see, feel, or hear the device. So Enable designed a small, low-profile device about the size of an Oreo cookie that makes a subtle click that only the user can feel, hear, and see when the dosing is completed. The patient then makes the decision when and where to remove and dispose of the device.

PRELOADED VERSUS PATIENT LOADED: PATIENT PREFERENCES

When presented with the alternative "preloaded" or "patient-loaded," most people's initial reaction is that a preloaded device is

preferable. With a non-refrigerated drug, this may be true. However in the case of a refrigerated drug, encompassing the vast majority of biologics, every patient surveyed preferred the patient-loaded system for a number of reasons. For every injector that uses a refrigerated drug, the patient must wait 30 minutes or more for the drug/device to warm to room temperature. At colder temperatures, the drug viscosity can increase by more than threefold, and a cold drug is more painful to inject. Additionally, an electronic system requires a battery. As everyone knows from starting their car in the winter, both battery life and power are significantly decreased when cold. Battery-powered devices are designed for room temperature use.

With the non-electronic Enable system, patients need only refrigerate the drug vial or cartridge and when ready, insert it into the Enable system. The system automatically warms the drug during the transfer to the injector, and the injector is ready to use immediately upon transfer, eliminating the 30-minute wait and saving patients valuable time. When given a choice of a preloaded or patient-loaded Enable Injector, all of those surveyed chose the patient-loaded system. Among the reasons given 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." And of course, patients want an injector that is ready when they are.

ENABLE'S S.E.T. DRIVE SYSTEM ELIMINATES DRAWBACKS OF CARTRIDGE/PLUNGER INJECTORS

In a wearable injector, the drug primary container, specifically a cartridge or vial, is not the ideal container for use in delivering the drug, and this can result in some significant compromises in design. A typical system using a cartridge with a plunger driven by a motor or spring has two major drawbacks - it is relatively large, and the force required to drive the plunger increases as the volume of the drug increases. This increase in force means either an increase in delivery time or an increase in the cannula size as the volume of drug increases.

For example, take a standard 1cc syringe, fill it with water, and attach a small-gauge needle. Push the plunger as hard as you can and time how long it takes to deliver the 1 cc. Then take a 10-cc syringe with that same needle. Pushing just as hard on the plunger, it will take 10 times longer to deliver that 1 cc of water.

To eliminate these significant technical challenges, the Enable Injector uses a proprietary S.E.T. drive system that is optimized for wearable injectors. The force required to deliver the drug does not change with the volume, and the delivery rate and cannula size remain the same.

The Enable system is, consequently, unique in its ability to deliver volumes and viscosities significantly higher than cartridge/plunger-based systems (10 mL of 100 cP through a 29-g needle at 1 mL/min). In most cases, the needle size can be reduced to 30 g or less for patient comfort. The S.E.T. system allows for devices with volumes of 1 to 10 mL and 1 to 20 mL with a very small size and low profile.

Having the same device for volumes ranging from 1 to 10 mL provides for great flexibility in studies where the dosing may not yet be determined. Having a small device with volumes of 20 mL or more could allow subcutaneous delivery of currently approved IV drugs without a change to the formulation. This unique capability to deliver higher volumes and viscosities in a very small size enables patient-focused, reliable delivery of new and existing drugs.

MINIMIZING INJECTION PAIN YIELDS THE MOST COMFORTABLE PATIENT EXPERIENCE

One of the primary challenges of delivering a high-volume drug through a wearable injector is making the experience comfortable for the patient. If the injection is painful, or even uncomfortable, the patient will be resistant to use of the product or might attempt to remove it during the injection. This could have a major impact on patient compliance and affect the device's ability to consistently deliver the proper dose.

Enable Injections was founded with a focus on painless injection technology, a concept originally developed and evaluated in multiple clinical studies at Children's Hospital in Cincinnati. Enable has partnered with CHMC to gain a deep understanding of the causes of injection pain. The Enable Injector addresses each of these causes, resulting in the most comfortable possible injection experience.

AUTOMATED MIXING PROVIDES CONSISTENT, RELIABLE THERAPY

Many drugs are first introduced in lyophilized form because of increased stability and quicker time to market. Enable has developed an automated mixing system that provides fully automated mixing of two vials of up to 10 mL each. The system can be customized to mix powder/liquid or liquid/liquid for up to 1 hour or more.

The mixing capability of the Enable Injector completely removes the user from the mixing process and provides consistent, reliable results that could allow for therapies to be moved from the clinic or hospital to in-home administration. Not only is this a great

convenience for patients, but it can also help reduce treatment and facility costs. The entire mixing and injection process is completed using the same six simple user steps as with a standard liquid vial.

ENVIRONMENTALLY FRIENDLY

Since its inception, the Enable system has been designed to be compatible with the ennvironment and integrate easily into the recycling process. The system uses only standard IV component materials, and contains no electronics or batteries that must be removed for recycling. The total volume of the material and packaging is less than what would be used in an IV system.

SUMMARY

Bolus Injectors represent one of the most exciting new opportunities in the field of medical devices. Enable injections' focus on developing innovative technology in combination with an intense emphasis on Human Factors has resulted in a system that is unique in a number of ways. It is the only Bolus Injector that utilizes a standard container closure. It has very high volume and viscosity capability and can be customized to automatically mix lyophilized solutions. Additionally, it provides the patient with a product that is small and low profile, simple, environmentally friendly, and ready to be used immediately. With this unique technology, a highly experienced Board and staff, manufacturing facilities in place, and agreements in negotiation with major Pharma/Biotech companies, Enable Injections is poised to help pharmaceutical and biotech companies develop and market exciting new therapies that benefit and delight patients while lowering the cost of drug administration. ◆

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BIOGRAPHY

Mike Hooven is President and CEO, Enable Injections, LLC. Mike has over 30 years of experience in the medical device industry in a broad variety of business, technical, and clinical areas. He is the Founder of five medical device companies and holds over 100 issued and pending US patents. Mr. Hooven is the Founder, and a Director of AtriCure, Inc. (NASDAQ:ATRC), where he previously held positions as the Chairman and CEO. He is also Founder and Chairman of Enable Medical, a surgical device manufacturer that was acquired by AtriCure in August of 2005. Prior to Enable Medical, he was Director of Product Development at Ethicon Endo-Surgery from 1988 to 1994, where he had responsibility for all in-house product development and supervised a staff of 200 engineers. He held Engineering positions in pacemaker and lead development at Siemens/Pacesetter from 1986 to 1988 and at Cordis Corporation in neurosurgical products from 1981 to 1986. In addition, he is Director and past Chairman of BioOhio, a state-funded organization to accelerate life-science startups in Ohio. He earned a Bachelor of Science in Physics and a Master of Science in Mechanical Engineering from the University of Michigan. Mr. Hooven was recently appointed by the Governor to the Third Frontier Advisory Board, a $2.1-Billion initiative to create new technology-based companies and jobs in Ohio.