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

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

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

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

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

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

INNOVATION PROPELS PRODUCT LEADERSHIP

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

Dr Jeannie Joughin
Vice-President, Corporate Development
T: +1 781 639 1910
E: info@enableinjections.com

Enable Injections
2863 E Sharon Road
Cincinnati
OH 45241
United States

www.enableinjections.com

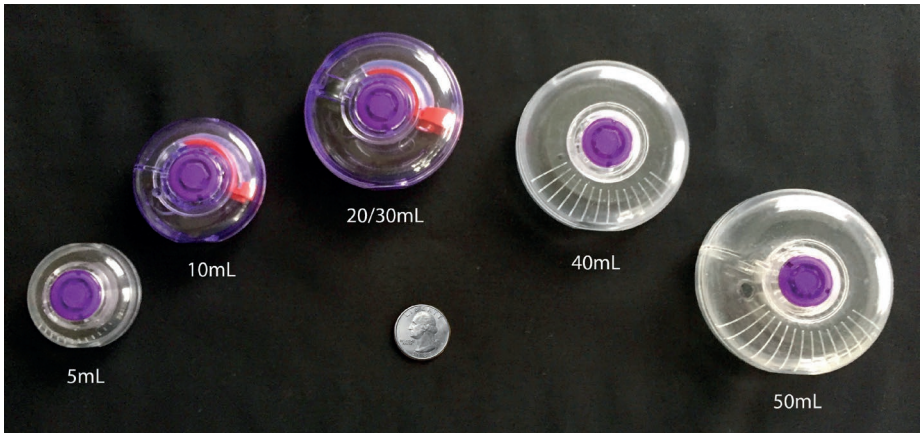

Figure 1: Enable Injections' OBDS: Self-administration of subcutaneous delivery volumes of 5-50 mL. The 10 mL and 20/30 mL injectors with syringe-transfer are ready for clinical application.

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

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

IMPROVING BIOLOGICS' BIOAVAILABILITY, ENABLING SC INJECTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONSIDERATIONS IN CHOOSING A HIGH VOLUME DELIVERY DEVICE

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

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

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

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

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

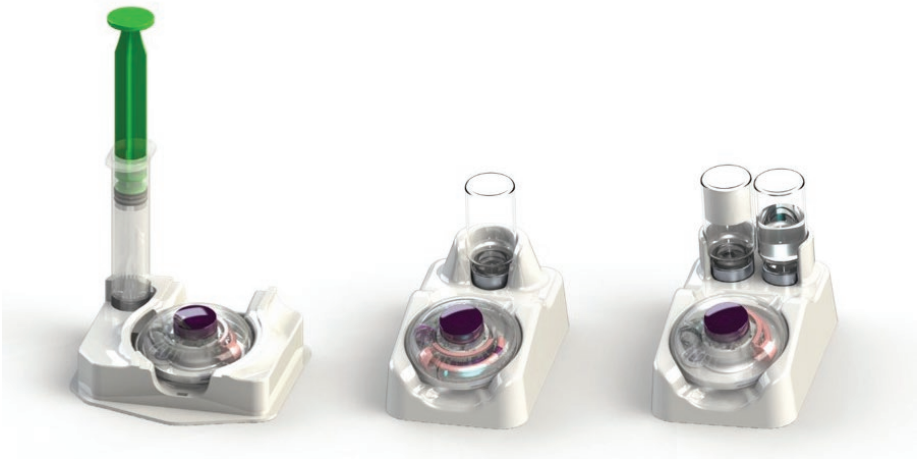

Figure 2: Platform technology that utilises standard vials or syringes and offers automated mixing and reconstitution.

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

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

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

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

ELIMINATE PATIENT CONFUSION & ERRORS WITH DOSING SIMPLICITY, FLEXIBILITY

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

EARLY CLINICAL USE DETERMINES OPTIMAL DOSING, FLOW RATE, COMPLIANCE

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

STUDIES: PROVEN USER ACCEPTANCE OF ENABLE INJECTIONS' OBDS

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

BESTING THE COMPETITION

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

EASIER CLINICAL TRIAL RECRUITMENT – READY TO PARTNER

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

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

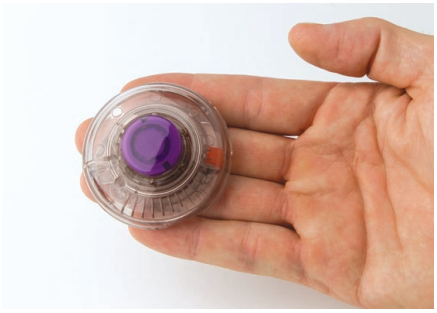

Figure 4: Enable Injections' technology is designed to have a friendly appearance with a low profile that can be discreetly worn on the body to also allow for greater freedom and mobility.

……..Enable their Day!

REFERENCES

1. *Innovation Tracking Factbook 2016, "An Assessment of the Pharmaceutical Pipeline". GBI Research Report, Jun 2016.*
2. *Collins, M. "Here's What's Important About Alder Biopharmaceuticals' Latest Release". Market Exclusive, July 26, 2016.*
3. *Burgess, BE, "Optimizing Drug Delivery for Modern Biologics". BioPharm Int, 2012, Vol 25 (5).*
4. *Doughty D, Clawson CZ, Lambert W, et al, "Understanding subcutaneous tissue pressure for engineering injection devices for large-volume protein delivery". J Pharm Sci, 2016, Vol 105, pp 2105-2113.*
5. *Rule S et al, "Subcutaneous vs intravenous rituximab in patients with non-Hodgkin lymphoma: a time and motion study in the United Kingdom". J Med Econ, 2014, Vol 17(7), pp 459-468.*
6. *Palm T, Sahin E, Gandi R, et al, "The Importance of the Concentration-Temperature-Viscosity Relationship for the Development of Biologics". BioProcess Int, March 10, 2015.*
7. *Škalko-Basnet N, "Biologics: the role of delivery systems in improved therapy". Biologics, 2014, Vol 8, pp 107-114.*
8. *Cilliza C, "The price of EpiPens has gone up 450 percent since 2004. That's ridiculous". Washington Post, August 5, 2016.*

Treatment developed by you. The future delivered by us.

Enable their day!

enable injections

*OBDS - ON BODY DELIVERY SYSTEM
FOR INVESTIGATIONAL USE ONLY