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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 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.

> "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"

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 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 prefillable 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

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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 at 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 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

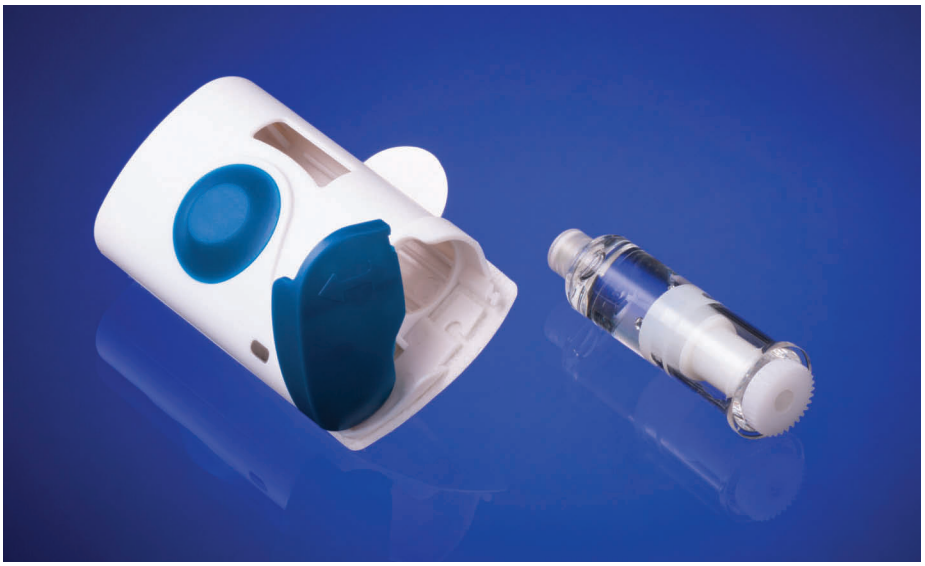

Figure 1: West's SmartDose® electronic wearable injector provides a solution for the challenge of delivering a large dose of a drug product.

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 injections 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 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.

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.

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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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