

# Collaborative Development: Finding Solutions for the Packaging Challenges of Modern Injectable Biologics



For the past 20 years, biotechnology medicines have aided those suffering from chronic conditions, including cancer, diabetes and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. Derived from living cells, biologic drugs are 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 rheumatoid arthritis may target components of the immune system that play a role in inflammation.

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 biological drugs over the past several years. In fact, more than 900 biotechnology medicines were in development as of 2011 – nearly 30 per cent of all drugs in the pipeline.<sup>1</sup> When these drugs reach the market, it is likely that the majority will be presented to patients in an injectable format.

Unlike traditional, chemical-based drug products, biologic molecules tend to be sensitive to products commonly found in 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. In addition, biologic molecules are typically large in size, which may require a higher concentration of the drug product for efficacy. The result is a 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.

Of the biologics in use today, many 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®, Amgen's Enbrel® and Abbvie's Humira®. These injections are typically designed for delivery into the subcutaneous space, require a relatively low dose (< 100 mg) for efficacy and have a reduced risk of life-threatening adverse reactions. Both Simponi and Humira are packaged in 1mL long pre-filled syringes and dosed on a weekly, semi-monthly or monthly basis, depending on the patient's particular indication.

However, 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.

As patients take an even greater role in decisions regarding their treatment, easy to use, safe and effective integrated delivery systems will be essential. Novel materials, unique devices and enhanced administration systems, as well as partnerships between pharmaceutical and packaging manufacturers that help to ensure patient needs for safety and efficacy are built into the

drug product's packaging from early-stage development, may improve the overall effectiveness of biologic therapy, and ultimately, the health, safety and comfort of the patient.

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 delivery 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 to bring the four elements of an effective delivery system together sooner. This will help to ensure that the biologic drug product reaches the market in an effective and safe 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.

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### Ensuring Patient Adherence Begins with Early Collaborations

Even the most innovative drug can provide the appropriate therapeutic benefit to the patient only if it can be delivered effectively, and the patient adheres to the necessary treatment regimen. In addition, drug therapies must deliver the appropriate clinical value to ensure payor acceptance.

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 as 15 years and cost as much as \$1.2 billion<sup>2</sup>. So when the drug product reaches the market, the originator may have only a few years remaining on the patent. Often, the delivery system is only thought of during the final stages of development. If the drug product cannot be effectively stored within, 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, it can be a costly disaster for the manufacturer. Considerations relating to dosing volume, delivery technique and frequency should also be taken into account at an earlier stage to ensure optimum speed to market and chance of success.

Collaborating with a packaging and device partner early in the drug process can help at a variety of stages. For example, packaging manufacturers who also provide analytical laboratory services may be able to provide stability work early in the process to ensure that the containment materials do not react with the drug product. Many biologics, by their very nature, do not respond well to glass containment, which can result in higher levels of extractables and leachables, protein aggregation, or the risk of glass delamination. Cyclic olefin polymers (COPs) offer an alternative to traditional glass and, since COPs can be moulded to a variety of shapes, they can provide containment throughout the drug

product's lifecycle. Such choices early in development may also aid decisions later in the manufacturing cycle. COPs also offer improved dimensional tolerance and design flexibility, so innovative container/device combinations can be considered to help optimise overall system design based on the needs of the patient.

### Understanding Patient Needs

As the drug product progresses through its own lifecycle, the patient-use cycle should also be considered. Understanding the needs of the patient can be critical to designing a delivery system that is both easy to use and effective for the patient. From initial diagnosis to long-term adherence, the patient passes through a variety of emotional and physical phases. Human factors testing can help to 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.

Further along in the patient journey, as the patient learns to cope with the condition, other factors such as accessibility and portability may rise in importance. At this stage, a patient may not want to publicise the fact that he is sick, so 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. Another option might be a more expensive electronic system that fits into a person's pocket and aids with compliance.

As pharmaceutical companies recognise that there is no "one-size-fits-all" device or system, patients suffering from chronic conditions may be offered more choices for self-injection. Early stage planning for such choices can help pharmaceutical companies select materials for containment that can be used for a variety of 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

By combining the four key elements with expertise in container closure systems and design technology early in the development process, and by collaborating with a partner whose knowledge includes a thorough understanding of the pharmaceutical manufacturer's filling requirements, pharmaceutical companies may be able to better meet the needs of the end-users while improving overall value and reducing time to market.

As the biologic market has grown, so too has the use of prefilled syringe and cartridge systems, moving from 3.1 billion units in 2012 to an expected 4.7 billion in 2016<sup>3</sup>. Such systems offer convenience and ease of use, as well as precision filling and reduced risk of breakage or other issues such as glass delamination. Prefillable systems can also be combined easily with auto-injectors and other safety systems to create an integrated device.

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However, many of the 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 of time.

New designs are evolving around the needs of biopharmaceuticals and alternative forms of delivery. Higher molecular weight biologics require delivery devices and systems that are designed to accommodate higher dose volume and reduced dosing frequency. Since cyclic olefin polymers can be moulded 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 patch injector technology platform\*, are being developed to aid patients with self-administration. The SmartDose system, which features a Daikyo Crystal Zenith® cyclic olefin polymer cartridge designed specifically to hold high-volume doses of sensitive biologics, offers a subcutaneous, programmable electronic injection system that adheres to the skin and can deliver the drug over time. User interfaces optimised through human factors studies, including electronic indicators, 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. In spite of the internal system complexity, the SmartDose system has been designed for simplicity and patient comfort, while facilitating the delivery of innovative drug products.

Other options include designs that centre on more traditional containers, such as vials or prefillable syringes. Auto-injectors have long been recognised as a convenient method for delivering drug products, especially for patients who may have dexterity or needle phobia issues. However, many sophisticated delivery systems are still based around conventional glass syringes designed primarily for manual injection. Costly recalls caused by broken syringes, or slow

or incomplete delivery of a drug in an auto-injector system, have pushed manufacturers to develop safer systems for use in every healthcare setting.

Auto-injector systems such as West's ConfiDose® auto-injector technology platform\* can be combined with the Daikyo Crystal Zenith 1mL insert needle syringe to help prevent breakage and other issues associated with glass prefillable syringes. The ConfiDose auto-injector system is designed to minimise the force an auto-injector places on a syringe system's weakest areas, so the system can overcome many of the issues that may occur when glass systems are combined with viscous products. In addition, customised cyclic olefin polymer syringes have the potential to contain a higher volume of drug than a conventional glass syringe. The combination of West's ConfiDose technology platform with a customised larger capacity (1.5mL) Daikyo Crystal Zenith syringe offers the opportunity for a smaller, more patient-friendly injection system, capable of delivering a higher dose volume than from a conventional 1mL long syringe.

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 research and development 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.

### References:

1. *Adis R&D Insight Database and PhRMA*
2. *PhRMA slide pack "Biopharmaceuticals in Perspective"*

3. *"Injectable Drug Delivery through 2016", Greystone Research Associates*

\* For investigational use only by our pharmaceutical and biotechnology development partners.

West seeks partners for its ConfiDose® and SmartDose® injector technology platforms. These platforms are intended to be used as integrated systems with drug filling and final assembly completed by the pharmaceutical/biotechnology company.

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