In recent years, there has been a shift in the pharmaceutical industry toward a Quality by Design (QbD) philosophy. To maximise a drug product’s safety and efficacy, pharmaceutical companies and their drug packaging and delivery partners are building new quality principles into the entire manufacturing process, from design and development to commercialisation and administration. This scientific, risk-based QbD approach is fast becoming an essential strategy for bringing high-quality therapeutics to market quickly and efficiently.

One area where pharmaceutical packaging and device delivery companies are successfully applying QbD principles is the manufacturing of high-quality components for prefillable syringes. The quality, safety and efficacy of a drug product can be linked to the suitability of its container closure system (Figure 1). Understanding how drug container closure systems and their various components impact a drug’s safety and efficacy is fundamental to the QbD approach.

Market trends toward home-use and patient self-administration of drugs used to treat chronic conditions (e.g. multiple sclerosis and rheumatoid arthritis) have made prefilled syringe systems an ideal choice for single-dose drugs (Figure 2). Prefilled syringe systems for pharmaceuticals and biopharmaceuticals offer convenient, fixed dosing and are adaptable to automated injection devices.

For patients, use of a prefilled syringe system has the potential to minimise microbial contamination and reduce medication dosing errors. The syringe systems offer ease of use and enhanced convenience for those who require frequent dosing, and when combined with an auto-injector system, can provide a more portable drug delivery system.

Pharmaceutical and biopharmaceutical manufacturers who select a prefillable syringe system for their drug product may be able to reduce therapy and injection costs, as well as signifi-
cantly reduce overfill when compared with single-dose vials. The system may also optimise the number of doses from the existing drug supply, while offering a delivery option that will help to differentiate the system in a crowded market and potentially increase patient preference.

Strategies employed in early phases of drug development that consider delivery devices such as prefllable syringes and their components can mitigate risk to quality, and position the product to meet needs of the ongoing drug product lifecycle. The return on investment can be realised once a drug product is commercialised and has gained patient loyalty through ease of use, therapeutic benefit and high confidence in the delivery device. While it is not easy to meet these challenges, a drug product manufacturer can benefit from early investment in the right drug delivery system and high-quality components.

**MITIGATING RISK IN PREFILLABLE SYRINGE COMPONENTS**

Prefillable syringes are an ideal choice for single-dose drugs, especially those used to treat chronic conditions such as multiple sclerosis, rheumatoid arthritis and other autoimmune diseases. Often medications used to treat these conditions can be self-administered by patients. Prefillable syringes offer convenient, fixed dosing, are easy to use and can be combined with an auto-injector system. In addition, prefillable syringes have the potential to minimise microbial contamination and reduce medication dosing errors.

With prefillable syringe systems becoming more widely used, it is essential that the components used to contain and deliver the drug be of the highest quality in order to minimise impact on the drug product. A critical component in a prefillable syringe system is an elastomeric plunger – also known as a piston or stopper – which expels the contents of the barrel to deliver the drug to the patient. The plunger serves as the primary seal for container closure integrity and helps maintain the purity of the drug throughout its shelf life. It is important for drug packaging and delivery manufacturers to ensure plungers from the elastomers into the drug product is known as leaching, but the reverse process of the drug product adsorbing or absorbing onto the plunger can also occur. The impact of extractables and leachables, and adsorption/absorption can be significantly reduced with a barrier film.

To streamline the manufacturing process and handling of prefillable syringe components, the pharmaceutical industry has moved toward ready-to-use (RU) plungers. RU plungers are washed and sterilised prior to delivery to the drug manufacturer with specifications for particulates and endotoxins, reducing the risk of microbiological contamination to the drug product during final packaging. There are several methods for sterilisation of plungers and an increase in extractable breakdown products has been observed under gamma radiation; therefore, autoclave steam sterilisation of these components is a preferred, low-risk choice.

![Figure 2: Trends toward home-use and self-administration for chronic conditions have made prefilled syringe systems an ideal choice for single-dose drugs.](image-url)
**APPLYING QBD TO PREFILLABLE SYRINGES**

When designing and developing a component using QbD principles, manufacturers must define desired product performance and identify critical quality attributes (CQAs). The component and process are then designed to meet those product attributes, which leads to understanding the impact of material attributes and process parameters on the CQAs and identification and control of sources of variability. As a result of this knowledge, a company can continually monitor, update and improve its manufacturing process to assure consistent product quality.

Since prefilled syringes are considered a combination product, consisting of a drug and a device, two US federal quality regulations apply: cGMP Finished Pharmaceuticals part 21 CFR 210-211 and QSR Regulation for Devices 21 CFR 820. To meet these regulations, pharmaceutical manufacturers must comply with several areas including management responsibility, purchasing controls, corrective and preventive action, design controls and a design history file. As part of the industrialisation of plungers using the QbD approach, these aspects were considered and elements incorporated into the manufacturing process and product.

Most subcutaneous drug product injections use a staked needle in a 1mL long prefilled syringe format that can retain a fill volume ±1.0mL. The plungers that fit 1mL long staked needle syringes were originally developed for a manual injection action. As industry requirements for higher quality and patient needs for self-injection with auto-injectors have evolved, the demand for plungers with improved functionality has grown.

To meet growing demand for high-quality components, it is important that drug manufacturers look for prefillable syringe components that have the following attributes:

- **Dose Accuracy and Injection Time Reliability** – Variations in the quality of the glass barrel/plunger interface may cause inconsistent break-loose and glide forces. This can be compensated for by the force applied to the plunger by the patient or caregiver during manual injection. However, when an auto-injector is used this variability may cause incomplete injections or stall the plunger’s movement, resulting in variable delivered dose volumes.

- **Low Levels of Particulates and Visual Defects** – The US FDA is continually spurring the pharmaceutical industry to reduce patient risk and improve safety and compliance. As part of this process, continuous improvements are needed for loose and embedded particulates, including visible and sub-visible, to minimise drug interactions and patient harm.

By designing with these attributes in mind, prefillable syringe components can help maximize a drug product’s efficacy and safety profile while enhancing product manufacturability. QbD philosophy and principles can help to optimise break-loose and glide force and significantly reduce plunger variation from part-to-part. Following a QbD approach throughout the product design and development process can help manufacturers ensure that components are developed based on science and data-driven decisions and meet critical specification for defects, visible and sub-visible particulate and extractables consistently.

### **THE WEST SOLUTION: NOVAPURE® HIGH-QUALITY COMPONENTS**

Using QbD principles, West developed NovaPure components for prefillable syringe systems to provide high reliability for break-loose and glide force, dimensional accuracy and consistency, sub-visible and visible particulate control, and low parts per million (ppm) defect attributes.

The optimised functional and dimensional performance for NovaPure plungers provides predictable injection times and statistical consistency when used in conjunction with 1mL long staked-needle syringes and an auto-injector system.

The 1mL long NovaPure plunger followed a development framework, which used a Quality Target Product Profile (QTPP) to establish CQAs for control of break-loose and glide forces. As the product – which included risk-based design inputs, Finite Element Analysis (FEA) modelling, data generation on multiple concepts, and final product performance verification with glass barrels from multiple suppliers of a 1mL long staked-needle syringe – was developed, the QTPP served as a guideline to assure that targeted specification values for break-loose and glide force were met.

In order to achieve a high-quality product, QbD components are washed and steam sterilised for optimised material compatibility and the knowledge gained throughout the process used on an ongoing basis to maintain continuous improvement by the manufacturer. Selecting a manufacturing partner like West early in the development process can help pharmaceutical companies choose a high-quality component for use in prefillable syringe systems that will meet demands for high quality, improved total cost, and increased safety and security for the drug product.

**CONCLUSION**

With so many different elements involved in bringing a drug product to market, it is increasingly important to incorporate QbD principles into the manufacturing of both the drug product and its container closure system. Quality should be built into all of these components with a thorough understanding of the process by which it is developed and manufactured and knowledge of the risks involved.

The selection and quality of components used in prefillable syringes are important parameters in pharmaceutical development and throughout the drug product lifecycle – from the design and manufacturing process, to transport and storage, through to administration. Prefillable syringe components pose a potential risk to a drug’s efficacy, but if developed and manufactured with consistent QbD principles in mind, they can play a critical role in ensuring a drug product’s integrity and efficacy.

Additionally, the use of high-quality components, such as NovaPure plungers, in prefillable syringe systems can help facilitate efficient manufacturing processes and support a reliable supply of drug products. The knowledge gained throughout the QbD process can be used on an ongoing basis to maintain continuous improvement by the manufacturer and meet demands for high quality, improved total cost, and increased safety and security for the drug product. The return on investment can be realised once a drug product is commercialised and has gained patient loyalty through ease of use, therapeutic benefit and high confidence in the delivery device.

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Cartridge-based drug delivery systems are playing a prominent role in the injectable market. Simplify your drug development strategy, streamline manufacturing and help assure patient safety with West cartridge plungers and lined seals by choosing Westar® ready-to-use components. With West, you have a partner by your side every step of the way, from discovery to the patient.

Ease of manufacturing with no component processing

Optimized for functionality and performance

Validated to enhance regulatory compliance

Visit us at Parenteral Pharma Technica/Pharma Congress, March 25-26, 2014, booth #51.