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## PFS COMPONENT SELECTION STRATEGIES – RISK MITIGATION, PERFORMANCE, & LARGER VOLUMES DRIVE INNOVATION

With a focus on the company's Novapure® brand, Christa Janssen-Otten, Director, Product Management Prefillable Solutions & Delivery, West Pharmaceutical Services, discusses the application of quality-by-design principles in the development of plungers for prefillable syringes and auto injectors. The selection of optimally designed and developed delivery system components, such as plungers, is presented as an essential part of a pharmaceutical company's risk mitigation strategy.

The market for prefillable systems is still growing. In fact, two-thirds of the world's blockbuster drugs are now delivered via a prefilled syringe system or auto injector, and auto injectors are one of the fastest growing delivery segments. To ensure effective delivery and patient safety, manufacturers need high-quality components that are designed and manufactured to reduce particulates, ensure consistency of delivery and fit the changing needs of higher-volume delivery systems.

As new sensitive pharmaceuticals and biopharmaceuticals are prepared for market, regulatory agencies have asked manufacturers to build quality in from the start and ensure consistent quality throughout the product lifecycle. To make sure drug products maintain safety and efficacy from concept to commercialisation, and to reduce the total cost of ownership, packaging materials must evolve.

Because biologics are typically more viscous, can require larger volume doses, and are often paired with auto injectors and other self-administration systems, they present unique challenges in drug containment and administration. Such new characteristics require high-quality

packaging to help maintain drug purity and efficacy, as well as more customised containers and the ability to accommodate larger dose volumes.

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Of course, every product that pharmaceutical companies and their drug delivery partners develop focuses on one priority: patient safety. West leads the industry in risk mitigation in its components, creating best practices that facilitate better quality and ensure regulatory compliance – all for the benefit of patients.



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Figure 1: NovaPure® components are a crucial part of West's drug delivery systems offering.

### NOVAPURE: MITIGATING RISKS WITH QUALITY DESIGN

NovaPure® components (Figure 1) from West are a crucial part of the company's drug delivery systems offering. NovaPure components, including the 1-3 mL and 1 mL long NovaPure plungers and 13 mm and 20 mm NovaPure lyo and serum stoppers, utilise quality-by-design (QbD) principles to help ensure superior quality and function, and addresses the evolving needs of patients who need these injectable biologics in higher doses.

The plunger is a critical element of the prefillable syringe because it serves as the primary seal for container/closure integrity, maintaining drug purity during shelf life, and its function is central to the delivery of the drug to the patient. It is essential to understand and assess the plunger during the QbD process.

Plungers are typically made from butyl rubber and can be coated with a fluoropolymer film that can increase lubricity and serve as a barrier between the drug and the elastomer, reducing the potential for extractables and leachables. Evolving industry demands for higher-quality components have increased the need for plungers developed using QbD processes.

The ICH Technical Requirements for Registration of Pharmaceuticals for Human Use define QbD as, "A systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management."

With a QbD approach, components are manufactured in a manner that helps to ensure reliability and, most importantly,

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patient safety. By considering the impact of prefillable syringe systems and their components on a particular drug product early in the development process – and employing QbD strategies to overcome development challenges – manufacturers can minimise potential quality risks and position the product to meet lifecycle needs.

The QbD approach promotes a holistic understanding of the product, its integrated delivery system and the manufacturing process. As a first step in initiating QbD processes, it is critical to understand the unique traits of the product that is to be developed. To this end, a quality target product profile (QTPP), which forms the basis for drug product formulation and process development in a QbD framework, must first be constructed.

The QTPP consists of a series of considerations that will uphold the highest standards. Such standards may include: the desired product performance based on the intended clinical setting, dosage strength and delivery mode, pharmacokinetic characteristics, drug product quality criteria, as well as sterility and the drug's container closure system.

Critical quality attributes (CQAs) and ultimately the critical process parameters (CPPs) for a given product and process, respectively, are developed in support of

achieving the QTPP. The information generated to determine the CQAs and CPPs will help to:

- Develop a meaningful control strategy
- Ensure product quality throughout the product lifecycle
- Increase product and process knowledge to support decisions
- Increase transparency and understanding for regulators and industry
- Enhance information needed for identifying and evaluating potential changes
- Monitor and track critical data for continuous improvement.

As a result of this knowledge, a company can continually monitor and improve its manufacturing process to ensure consistent product quality – and mitigate risks by designing and verifying machinability, testing sterilisation methods, and honing manufacturing methods to reduce particulates in the production environment.

### DESIGN INTENT

West Pharmaceutical Services developed and commercialised the FluroTec® barrier film laminated NovaPure plungers in

bromobutyl rubber formulation 4023/50 Gray with B2 coating using QbD principles. NovaPure plungers are intended for prefilled delivery systems and designed to reduce particulate, ensure consistency of delivery and fit also the changing needs of higher-volume injectable drug delivery systems.

West NovaPure plungers were developed using a QTPP that ensures dimensional control and consistency, sub-visible and visible particulate control, and low parts per million (ppm) defect attributes. In addition, the break-loose and glide force profile has been optimised to deliver consistent functional performance for auto injector applications across various injection volumes, such as the increasingly common 2.25 mL injectable drug delivery systems.

West developed FluroTec barrier film laminated plungers to minimise risk associated with leachables migrating from the elastomeric plunger in prefilled syringes, which can potentially compromise the quality of the drug and the safety of patients. Such contamination can also impact a drug manufacturer's bottom line via increased costs, lost batches and manufacturing inefficiencies. Further, product recalls can have a negative impact on patient confidence, shareholder value and market share.

The FluroTec film provides a barrier between the drug and elastomer, thus mitigating the risk of interaction over the product's shelf life. In addition to the improved compatibility with the drug formulation, plungers with FluroTec help to ensure container closure integrity in ISO standard glass barrels. Further, FluroTec barrier films in combination with B2-coating provide lubricity without the need for free silicone oil, and reduce stopper clumping during autoclave sterilisation.



Figure 2: West 1 mL Long NovaPure plunger.

NovaPure plungers also have improved control strategies and release specifications and have been optimised through exhaustive studies to ensure the best overall performance. The dimensions of NovaPure plungers not only need to be within specification, but four dimensions are assessed at the release of each lot to ensure a predetermined process capability is achieved.

#### CCI, BREAK-LOOSE & GLIDE FORCE STUDIES

Container closure integrity (CCI) of the syringe system is critical to ensure the sterility, stability and efficacy of a drug product. Our CCI test – which is ongoing – includes four types of samples:

1. Bulk plungers stored in bags at ambient conditions then filled with water before testing (simulate customer storage before assembly)
2. Bulk plungers stored in bags at 5°C then filled with water before testing (simulate customer cold storage before assembly)

3. Assembled, water-filled syringes stored at ambient conditions (simulate customer product storage)

4. Assembled, water-filled syringes stored at 5°C (simulate customer cold product storage).

The study results up to 12 months show that, in both ambient conditions and 5°C storage, the system remains integral.

Legacy FluroTec plungers were developed for intent to be used for manual injection. As a result, their performance is not optimised for use in auto injector applications. As the market has been evolving from manual to auto injector device applications, a FluroTec barrier film faced plunger with consistent performance became imperative. In order to address that need, NovaPure plungers were developed. To demonstrate the high quality and reliable performance of NovaPure plungers, a co-operative study of break-loose and glide forces was performed alongside legacy FluroTec plungers. The study results showed that, under every test condition, NovaPure

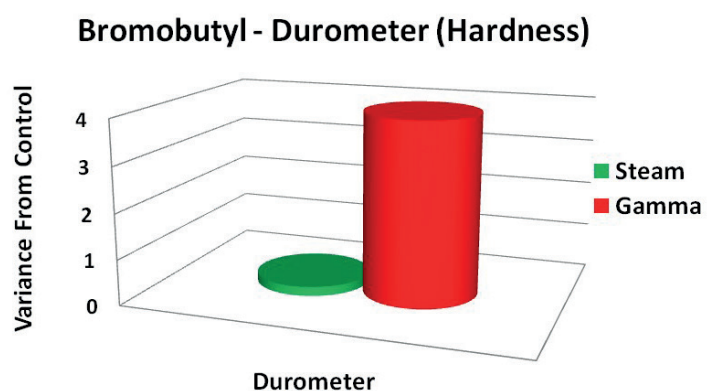
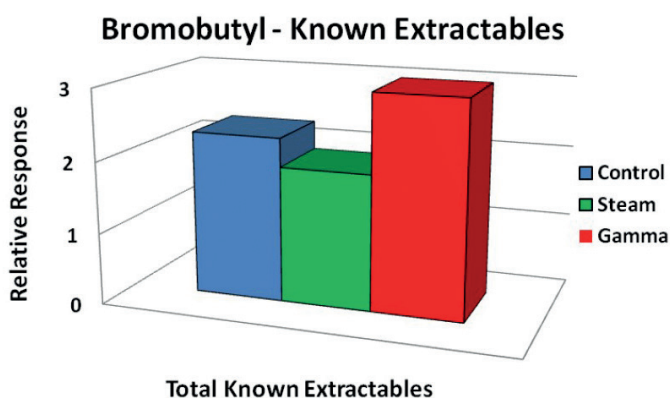


Figure 3: Influence of different sterilisation methods on rubber components. Steam sterilisation: exposure of 122°C for 60 min; Gamma sterilisation: irradiation exposure of 40.7 kGy (target range 36-44 kGy).

plungers had lower break-loose and glide forces, as well as more consistent force profiles, throughout the extrusion within the glass syringe barrel, compared with the legacy FluroTec plungers.

### STEAM: PREFERRED STERILISATION METHOD FOR ELASTOMERIC COMPONENTS

The washing and sterilising of parenteral packaging components is required for aseptic pharmaceutical manufacturing in order to ensure the particulate, bioburden, and endotoxin levels are within acceptable limits. The most common methods for sterilising elastomers are gamma irradiation and steam sterilisation.

Some elastomeric components from other manufacturers utilise gamma processing. Because of the complex nature of rubber, the effects of gamma irradiation are immediate, cumulative, more damaging to the polymer, and they continue over time well after the radiation exposure is over. In studies on steam sterilised and gamma-irradiated halobutyl elastomers, gamma-irradiated samples showed higher levels of extractables, mainly degradation products of ingredients and the polymer. These extractables could become leachables in a drug product and cause unpredictable issues for the drug. Additionally, results indicate that gamma processing has a potential for a

higher rate of degradation of the elastomeric formulation, ultimately affecting the shelf life of the component.

Steam processed elastomer formulations exhibit less degradation and lower levels of extractables. As such, NovaPure plungers are only available in a steam sterilised format, and we educate our pharma partners on best practices for implementing these processes during the drug packaging process to maintain sterility on their lines, too.

### MACHINABILITY IS KEY FOR PHARMA PARTNERS

The machinability of parenteral packaging components – or how components perform and process on a drug manufacturer’s filling line – is recognised to have a significant influence on productivity. As such, fill/finish equipment and machining assessments were conducted with the NovaPure plunger to ensure that effective machinability could be achieved on the small, medium and large sized machine lines our customers employ.

The assessments have verified reliable performance of NovaPure plunger on high-speed filling lines. Additionally, NovaPure components were designed with both vent-tube and vacuum filling processes in mind to accommodate the different machines that our partners use. Our exhaustive testing on both types of processing is just one facet of the customer support we provide.

### CONCLUSION

A robust and dependable risk management or mitigation strategy is fundamentally critical to the success of a drug manufacturer, and inherently a drug product. Selecting the appropriate parenteral packaging components is one of many factors that should be considered within this strategy.

West developed the NovaPure components using QbD principles specifically to address the industry need for a risk-mitigating, optimally performing plunger for auto injector applications. The design, as well as the dimensional control, of the steam-sterilised and FluroTec laminated NovaPure plungers ensure low part-to-part variability, low and consistent break-loose and glide forces, optimal machinability performance and reliable container closure integrity.

Why employ such rigid risk mitigation in every phase of drug development, including the plungers and other components of a drug delivery system? The process starts and ends with helping our pharmaceutical partners to achieve its most critical goal: providing safe, effective drug products for patients.

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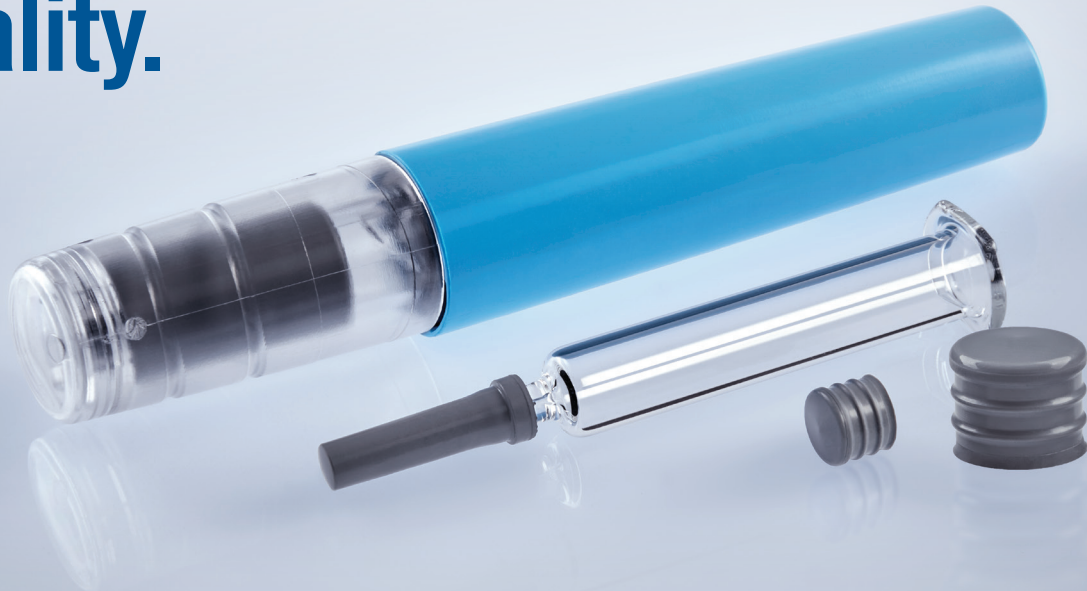
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## High-Quality NovaPure® Plungers Fit Your Needs

The 1mL and 1-3mL NovaPure plungers are manufactured with Quality by Design principles to help ensure efficacy and purity of the drug product. The NovaPure plungers' design incorporates high-quality processes and features, including FluroTec® barrier film, B2 coating, validated wash and sterilization processes, 100% vision verification, and a comprehensive extractable profile. NovaPure plungers are designed to reduce particulate, ensure consistency of delivery and fit the changing needs of higher volume injectable drug delivery systems. By choosing NovaPure syringe plungers, you can help ensure drug product compatibility with components designed specifically for optimized performance and consistency in delivery systems.

VISIT US AT CPHI/INNOPACK IN BARCELONA OCTOBER 4-6, 2016, HALL 2, BOOTH #2M22



Contact West today to learn more about how NovaPure syringe plungers, offered in multiple sizes, can meet your needs.

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