Responding to Market Trends in Prefilled Delivery

A Review of Component Assessment and Selection

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Preface

For many years, most injectable products were marketed in vial format with the drug administered by a caregiver using multiple steps to withdraw the medicine using a disposable plastic syringe that was also used for final administration. According to Roots Analysis, glass prefilled syringes are now the preferred drug delivery format thanks to high market acceptance and strong global growth rates continue to be reported at 10% during foretasted period 2016-2021. A prefilled syringe (PFS) has significant benefits over a vial format, including ease-of-use due to fewer steps, less over-fill volume for reduced unit cost, and a more precise therapeutic dose as the required drug volume can be filled during syringe filling.

There are several factors driving the growth of the global market for prefilled syringes. The rapid growth in the biologics market, technical advances in the sector, and the rising preference for self-administration using prefilled syringes, auto-injectors, and pen injectors are all contributing to PFS growth. According to Pharmacircle, currently more than 60% of the drugs under clinical development are biologics and are likely to be approved for parenteral administration. This is because most biologics, including monoclonal antibodies (mAb), vaccines and anticoagulants, are large molecules that need to be administered via parenteral route to achieve the desired therapeutic effect. The most common PFS sizes are 1mL long and 2.25mL staked needle format. To make injections more convenient and more acceptable to patients, injection devices are being used to automate some or all the parenteral delivery steps. These injection devices, primarily an auto-injector, provide additional ease-of-use, needle safety protection and lifestyle preference for the patient. Drug manufacturers have also implemented the use of devices to aid in product and brand differentiation.

Table of Contents

Drug Delivery Challenges and Needs | 2

A New Generation of Plungers for Syringe Applications | 2

West-Drug Manufacturer Partnership:
The Journey to Select and Qualify the 1mL Long NovaPure® Plunger | 3

Conclusions | 15

About the Authors | 15

Drug Delivery Challenges and Needs

As drug delivery systems have evolved, a common mistake is to simply apply plunger components approved for legacy drug products that may not meet the current regulatory expectations for quality. More importantly, these legacy components are not fit for applications where the drug will be delivered using an auto-injector. Plungers designed traditionally for manual injection can pose problems for auto-injectors, primarily in the form of variability.

The selection of plunger technology to fit auto-injector systems is important since it will help to avoid potential incompatibility that may lead to delays in development. As drug product viscosities increase, as with biologics, the design factors of the complete delivery system need to be understood. Currently, Pharma and Biotech companies are spending valuable resources to ensure they select the right plunger/syringe barrel/device combination.

Top Variations to Overcome:

- Dimensional
- Silicone oil
- Breakloose and glide variability
- Sterilization method
- Visual quality
- Device reliability – injection time/rate

A New Generation of Plungers for Syringe Applications

In response to the market need for plunger technology designed specifically for auto-injectors, West developed a new generation plunger with FluroTec® film. The NovaPure® plunger was industrialized to provide a quality target product profile (QTPP) for modern drug products.

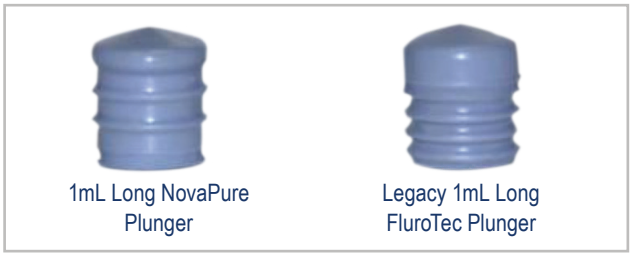
To achieve the QTTP's outlined above, West adopted a Quality by Design (QbD) approach, embracing product and process understanding, process control and continuous improvement as part of the design space. This approach succeeded in meeting the market requirements for plunger quality and performance, as well as enabling West to build an extensive data package to support customer development programs.

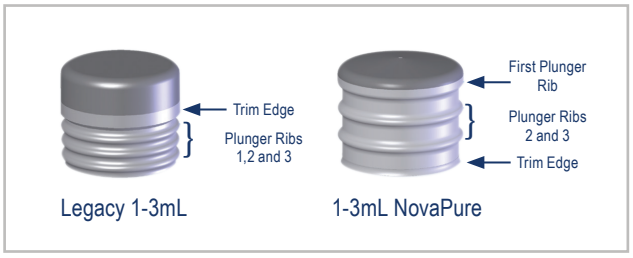
A New Generation of Plungers for Syringe Applications:

- Injection time reliability and delivered dose accuracy
- A FluroTec plunger that does not exhibit film wrinkling in a prefilled syringe
- Components with lower levels of loose particulate and visual defect levels

The 1mL long and 1-3mL NovaPure plungers were industrialized with statistically low part-to-part variability, and optimized breakloose and glide forces without the need for additional siliconization. They were designed to mitigate film wrinkles and meet the highest quality standards. Critical quality attributes (CQAs) of NovaPure plungers and control strategy focus includes the following:

- 4023/50 Gray elastomer formulation
- FluroTec film on the drug contact surfaces
- B2 coating on the plunger ribs for lubricity
  - Meets global pharmacopeia standards for USP/ Ph. Eur./ JP
  - 100% automated vision verification for attributes
  - Steam-sterilized and ready to use
  - Extractables profile on every lot
  - Process quality (CpK) analysis for critical dimensions
  - Specifications in ppm (part per million)
  - Specifications for sub-visible and visible particles

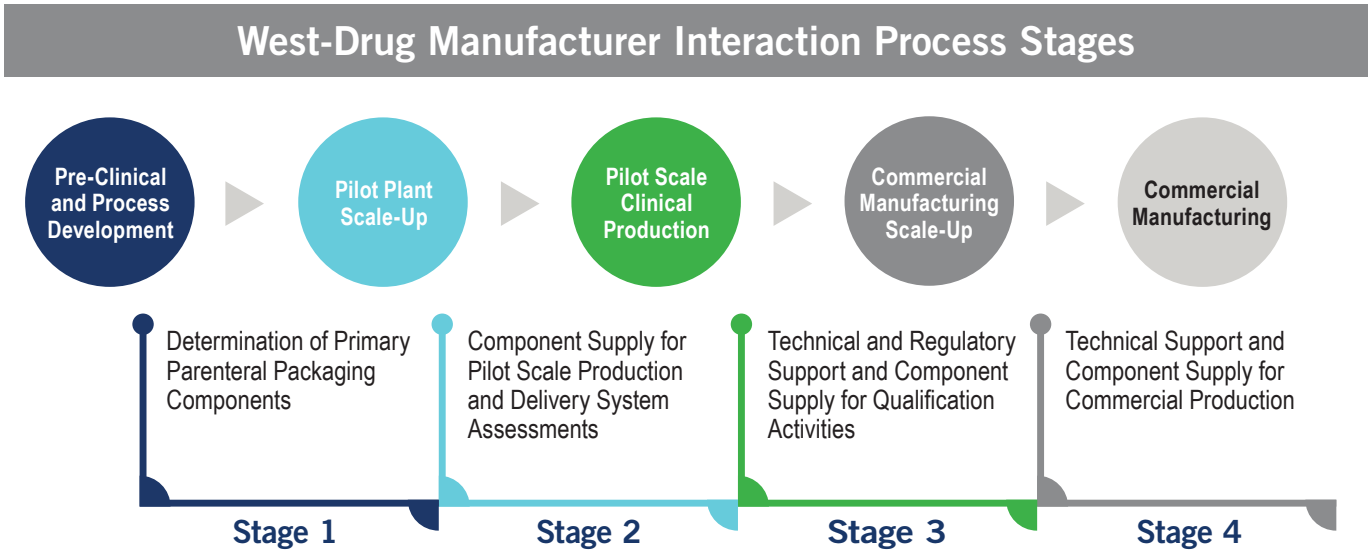




West-Drug Manufacturer Partnership: The Journey to Select and Qualify the 1mL Long NovaPure Plunger

West actively engages drug manufacturers throughout the pharmaceutical development and commercialization process. Depending on the drug manufacturer and the stage of the drug product, the interactions with West can vary greatly. The following section will review the typical recommended interaction process stages between West and the drug manufacturer, as depicted in Figure X.

Figure X: West-Drug Manufacturer Interaction Process Stages



Stage 1: Preliminary Assessment

As a drug manufacturer initiates pre-clinical and process development activities, the need to select, assess and procure parenteral packaging components is a critical step. When West is approached to provide recommendations or guidance on the packaging components, the request is typically directed to West's Technical Customer Support (TCS) department. The TCS representative will lead the discussion with the drug manufacturer to determine the best fit for the drug product and delivery system. Often a Product Requirement Questionnaire (PRQ) is used to help facilitate this activity (the questionnaire can be found online: **http://www.westpharma.com/support/product-recommendation-form**).

The PRQ requests detailed information regarding the drug product and formulation, as well as requirements for the intended delivery system and packaging components. The information on the PRQ is critical to ensure that the TCS representative recommends the appropriate packaging components. Based on the drug manufacturer's input, West will make recommendations regarding component or combination of components that will most effectively achieve the detailed requirements. Understanding the type of drug product (such as whether it is a protein, mAb, small molecule or diluent) and the drug formulation characteristics (pH, viscosity or other known incompatibilities) will influence the recommendation.

In the case of NovaPure plungers, the 1mL Long NovaPure plunger is commonly recommended for biologic/protein based therapies needing a FluroTec barrier film (a proprietary fluoropolymer film) and/or for drug products targeted for use in medical devices and auto-injectors that require low and consistent breakloose and glide (BLG) forces, and use an ISO standard 1mL long syringe.

Following the introduction/recommendation of the 1mL Long NovaPure plunger to the drug manufacturer, West will provide several fundamental documents to assist with the drug manufacturer's assessment and consideration of the NovaPure plunger. The following documents are typically provided, and the figures or tables represented below are examples of what information is contained within these documents. Note, that in addition to these highlighted reports West is currently generating data (and ultimately reports) associated with container closure integrity (CCI) using High Voltage Leak Detection (HVLD), as well as auto-injector simulation testing focused on dose delivery and time of injection as it pertains to plunger design and formulation viscosity.

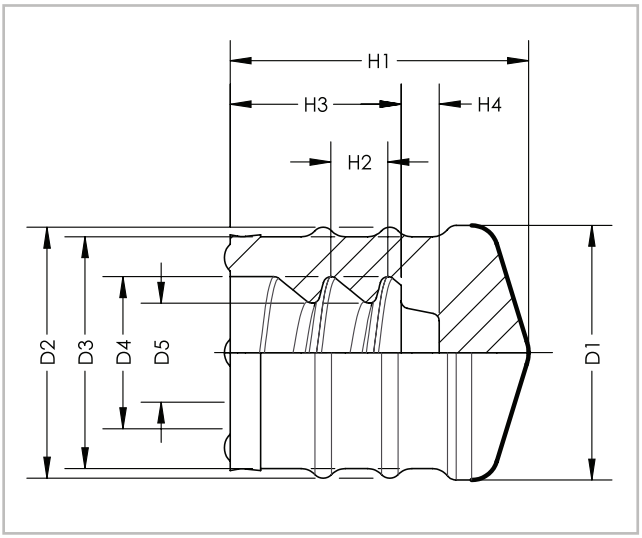
Documents provided may include:

1) 1mL Long NovaPure® Plunger Technical Drawing

The technical drawing is required for the:

- drug product history file
- theoretical assessments of interference fit
- understanding and assessments of the design
- evaluations associated with fabrication of change parts for the filling lines
- determination of the appropriate plunger rod

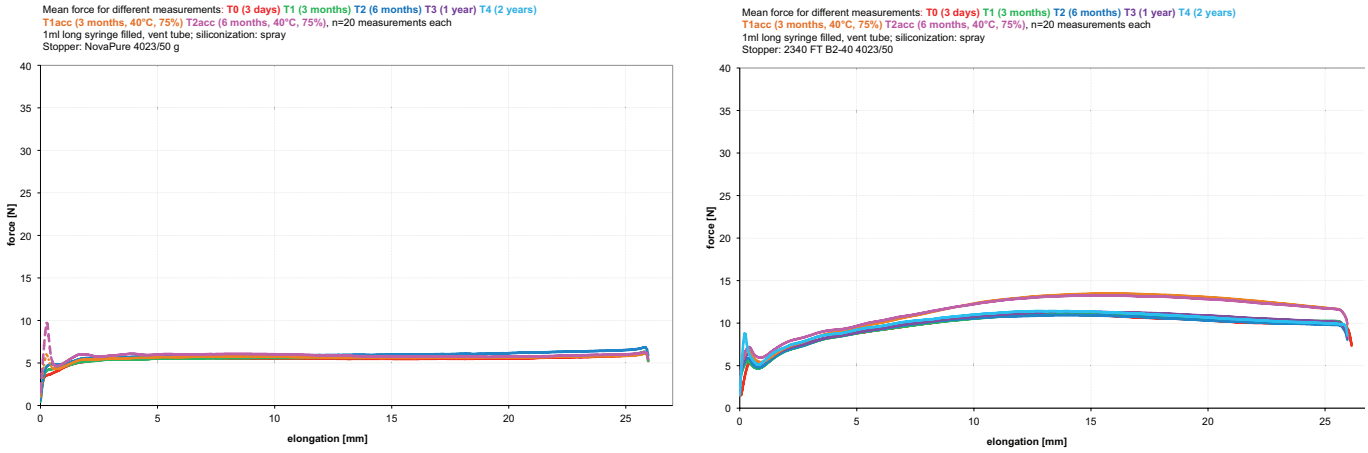
1mL Long NovaPure® Plunger Technical Drawings



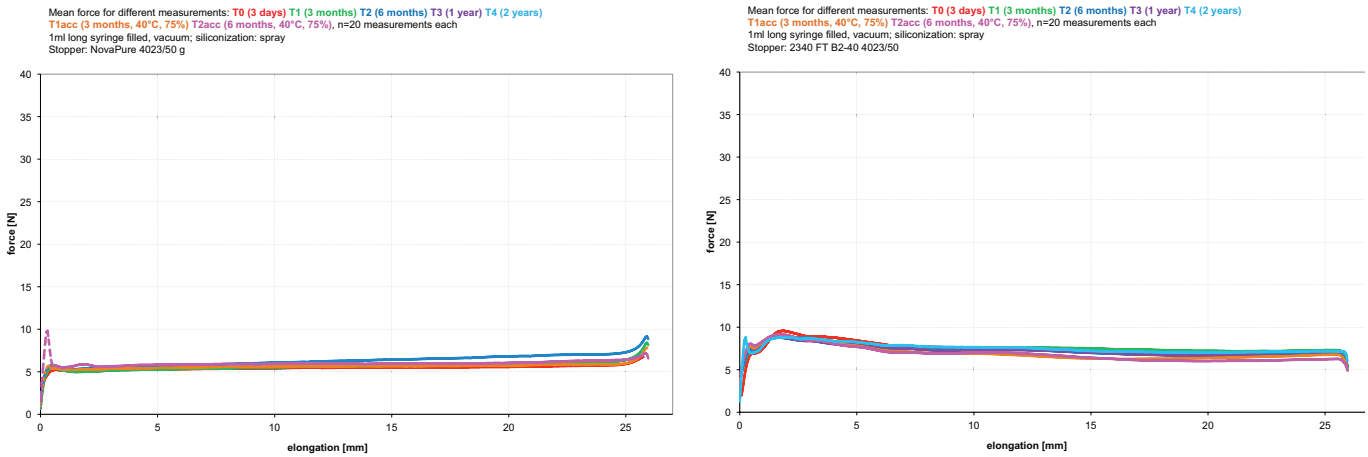
2) Prefillable Syringes Functionality Study – 1mL Long NovaPure® Plunger vs. 1mL Long FluroTec® Plunger (Article 2340)

- An overview of the breakloose and glide force performance improvements compared to the legacy FluroTec plunger, as well as correlates the performance as it pertains to plunger placement method.
- Focuses on the reduction of performance variability as required for auto-injectors or medical devices.

Vent Tube Placement



Vacuum Placement



Mean force for different measurements (n=20 measurements each):
T0 (3 days), T1 (3 months), T2 (6 months), T3 (1 year), T4 (2 years)
T1acc (3 months, 40°C, 75 RH), T2acc (6 months, 40°C, 75 RH)

Figure 2: Comparison of plunger placement methods for FILLED Syringes

Graphs courtesy of Gerresheimer.

3) West's 1mL Long NovaPure® Plunger in West Formulation 4023/50 Gray Design Intent and Dimensional Fit with ISO 1mL Long Glass Syringes

Table 1: Components, Dimensional Values, Tolerances and Process Capabilities

Component	Dimension	Dimension Description	Nominal Value (mm)	Tolerance (mm)	μ (mm)	Ó (mm)	C_{pK} Specification	C_{pK} Current Manufacturing
1mL Long NovaPure Plunger	D1	First Rib	6.70	0.15 -0.15	6.68	0.015	1.33	2.96*
	D2	Secondary Rib	6.60	0.15 -0.15	6.59	0.012	1.33	4.01*
Syringe Barrel[1]	Barrel Inner Diameter	Inner Diameter of Barrel	6.35	0.10 -0.10	N/A	N/A	N/A	N/A

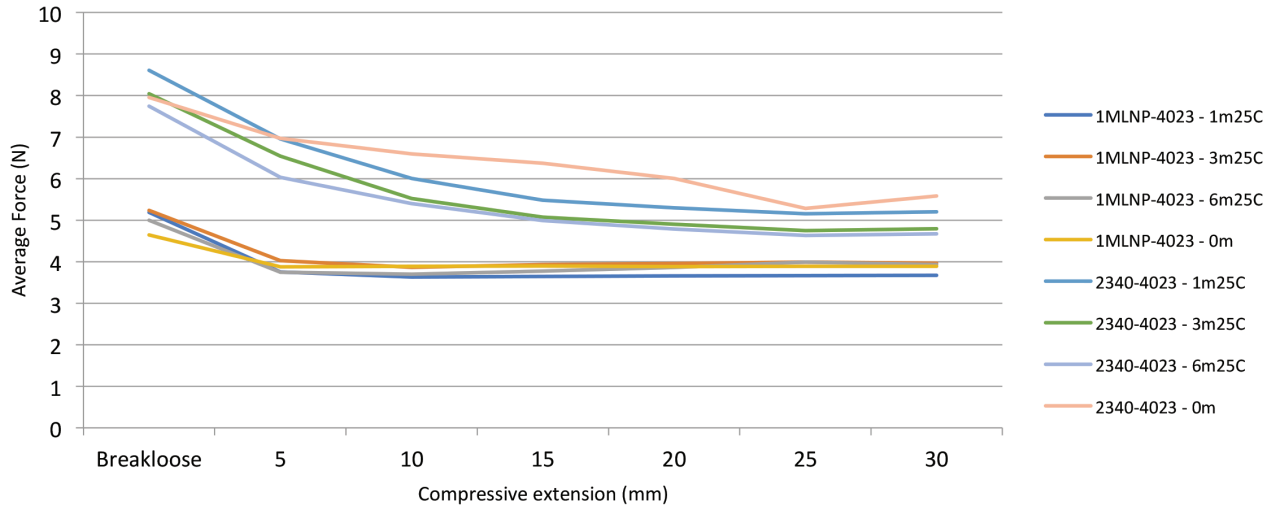
[1] *Barrel Dimension as indicated in ISO 11040-4:2007(E)*
* *Current manufacturing capabilities are based on a minimum of 10 batches.*

4) NovaPure® 1mL Long 4023/50 Gray Plunger Container Closure Integrity Assessment

- An overview of the container closure integrity testing that was conducted on the 1mL Long NovaPure plunger, and concludes that the NovaPure plunger conforms to the acceptance criteria.

5) NovaPure® 1mL Long 4023/50 Gray Plunger vs. Article 2340 4023/50 Gray Plunger Breakloose and Extrusion Performance Comparison

- An overview of the breakloose and glide force performance improvements compared the legacy FluroTec plunger as it relates to varying storage conditions.
- As captured in the previous study report, this report also highlights the reduction of performance variability as required for auto-injectors.



6) 1mL Long NovaPure® Plunger 4023/50 Gray Breakloose and Gliding Force Performance Evaluation in Multiple Vendor Syringe Barrels

- An overview of the breakloose and glide force performance within several different vendors' glass syringe barrels.
- The report highlights the consistent (and low variability) performance in each barrel type as required for auto-injectors, thus providing the customer the confidence that consistent performance will be achieved for any industry standard barrel.

Based on the review of the technical documentation on the 1mL Long NovaPure Plunger, the drug manufacturer typically will initiate additional component assessments. West ensures that samples will be readily available in inventory to support these assessments. The samples are fully processed and ready to use, and are typically packaged within a bulk sterilizable bag. Within stage 1 typically 5,000 or less 1mL Long NovaPure plungers are required to complete these tests. As an example, a drug manufacturer will often focus on the following tests:

- Container closure integrity (CCI) testing
- Breakloose and glide forces (BLG) testing
- Drug product compatibility and stability testing (including extractable and leachable testing)
- Component specification/incoming testing evaluations

The background and importance of these tests for prefilled syringe systems will be highlighted in the following section.

Container closure integrity (CCI) testing

The plunger provides a seal on the interior of the barrel between filling and drug administration. This seal reduces the likelihood that microbes will enter the syringe, thereby preserving the sterility of the syringe contents. At the same time, the seal prevents the syringe contents from leaking.

The plunger stopper may have more than one sealing rib. The function of the sealing rib(s) is to preserve sterility. To enter the syringe, microbes must pass all barriers formed by the sealing ribs, starting with the rib that is farthest from the drug product and ending with the rib that is closest to the drug product. Each rib acts independently as a seal, and the redundancy of ribs increases the robustness of the system.

Care must be taken with respect to transitional movement of the plunger resulting from pressure fluctuations such as those that can occur during air transport. In this case, the plunger first moves in the direction of the lower pressure (the cargo space), and then in the opposite direction when pressure is equalized again. Movement must be controlled to protect the syringe content from microbial contamination.

To preserve sterility and syringe content, the plunger stopper and barrel must have an appropriate interference fit. This implies that the sealing-rib diameters (of the plunger stopper) before assembly into the barrel are sufficiently large compared to the internal diameter of the barrel. At placement of the plunger stopper into the barrel, the sealing ribs are compressed and forced to adopt the dimension of the inside of the glass barrel, thereby forming sealing "rings" on the barrel. It is important to note, a higher number of sealing ribs and a higher interference fit not only leads to a greater system robustness in terms of seal integrity, but also commonly entails a less favorable breakloose and glide force profile. Additionally, the uniformity and consistency of coatings and dimensions of the components (syringe and plunger) are critical for ensuring CCI.

When testing the system (including the 1mL Long NovaPure Plunger) for CCI, samples may be tested on empty syringes and/or on placebo or water filled syringes. At this stage, samples are typically generated using manual or semi-automated bench-top units, but samples also can be generated using small-scale filling lines. The acceptance criteria may vary depending on the test method or laboratory conducting the testing, but typically for an effective integral system, no leakers or integrity breaches per predetermined acceptance criteria can occur. There are a range of test methods that may be used to assess CCI (as examples):

- Vacuum decay
- Helium Leak
- High Voltage Leak Detection (HVLD)
- Headspace analysis
- Methylene blue dye ingress (qualitative method)

Breakloose and glide forces (BLG) testing

The delivery performance of the drug product within prefilled systems is dictated by the characteristics and attributes of the components and drug product formulation within that delivery system. Specific to the 1mL Long NovaPure Plunger, the dimensions, design and lubricity of the plunger are critical factors affecting the delivery performance. The 1mL Long NovaPure Plunger was developed with the requirement of an optimal/low and consistent BLG profile to effectively achieve the force requirements for spring or motor driven medical devices and auto-injectors. However, for prefilled syringes intended for manual injections, there is typically less impact due to variability within the BLG profile given the ability of the caregiver or patient to inherently overcome such variation.

Assessing the 1mL Long NovaPure Plunger performance in each respective delivery system is recommended to ensure that the delivery system and components effectively deliver the drug product in the targeted dose and time. When testing the system (including the 1mL Long NovaPure Plunger) for BLG, samples initially may be tested on empty syringes; however, testing on placebo or water filled syringes will be required during later stage assessments. Samples are typically generated using semi-automated bench-top plunger placement units, but samples also can be generated using small scale filling lines. The samples for BLG testing are often assessed using a material test machine, such as an Instron or Zwick, at a predetermined extrusion/compression rate (reference ISO 11040-8 for further guidance). Preferred performance results are a low breakloose force and a consistent glide force.

Drug product compatibility and stability testing

The drug manufacturer should perform compatibility and stability testing, as well as extractables and leachables assessments, on the drug product within the targeted delivery systems. The glass or polymer syringe or cartridge and elastomeric components, such as the plunger, are in direct contact with the drug product. As a result, leachables from packaging components potentially can extract from the components into the drug product, directly impacting the efficacy, stability and safety of the drug. Typically, a series of tests are conducted to determine the interactions of the packaging components and drug product.

I. Extractables testing of the parenteral packaging components should be conducted to determine the chemical constituents that potentially could migrate into the drug product. It assists in identifying any high-risk chemical constituents that could impact the drug or patient.

II. Leachables testing provides an overview of what chemical migrants will extract from the packaging components into the drug product during intended use. Leachables testing should be conducted using the target drug product and formulation, as well as the intended primary packaging components.

III. Biocompatibility testing of the parenteral packaging components is typically executed per ISO 10993-1 or USP <87> and <88>. Compatibility assessments between the drug product and packaging components should also be conducted to determine if packaging leachables or interactions result in the deactivation or denaturing of the drug product. Samples should be aseptically prepared within a Grade A environment using manual or semi-automated bench-top units, or using small-scale filling lines.

IV. Stability testing of the drug product and packaging components is a time-based study that is required to ensure the efficacy and safety of the drug product is maintained over the target life cycle of the drug product. Samples should be prepared aseptically within a Grade A environment using manual or semi-automated bench-top units, or using small-scale filling lines.

Ideally there is no or minimal impact from the packaging components on the drug product; however, if there are any changes to the drug product due to the packaging components, the drug manufacturer may be forced to change the intended packaging components, drug product formulation, drug product concentration or drug product dose. In addition, it is critical that the chemical profile of the packaging components is controlled, and the extractable and leachable profiles do not change lot to lot, thus impacting the drug product biocompatibility or stability.

The 1mL Long NovaPure Plunger is tested for extractables at the completion of each lot as a release criteria. The results of the extractables testing is compared to a standard extractable profile to ensure that the product and process are in control. The standard "finger print" of the extractables profile can be provided within the supplemental documentation associated with the 1mL Long NovaPure Plunger.

Component specification/incoming testing

At the receipt of a lot of packaging components, the drug manufacturer will commonly review the supplemental documentation that accompanies the packaging components, and the drug manufacturer will perform incoming inspection testing to verify that components are within the component specifications. The drug manufacturer typically performs identification, particle, dimensional and compliance testing at the receipt of each lot. During the assessment of a new component, the incoming inspection test method and acceptance criteria needs to be established. West has an overall component specification document and a reference document of the extractables standard "finger print" available upon request,. which can be used to assist with these efforts. West also provides a Certificate of Analysis (CoA) with each lot of 1mL long NovaPure Plungers that overviews the test methods and corresponding specification limits.

ANALYSIS SECTION

Test/Method	Spec Limit
BIO-05: Bacterial Endotoxin [EU/mL/10 stoppers]	<=0.10
Bio-15: Biological Indicator [Positives]	<=0
AA-29: B2 Level Post Sterilization [ug/part]	4 – 50
CG-44: Extractable Profile	Reference to Chromatogram
Particl-21: >=5.0 µm but <10.0 µm [Particles/10cm2]	<= 100.0
Particl-21: >=10.0 µm but <25.0 µm [Particles/10cm2]	<= 60.0
Particl-21: >=25.0 µm but <50.0 µm [Particles/10cm2]	<= 10.0
Particl-21: >=50.0 µm but <100.0 µm [Particles/10cm2]	<= 1.0
Particl-21: >=100.0 µm [Particles/10cm2]	<= 0.2
AQL 0.010 (Critical)	Ac-0 / Re-1
AQL 0.015 (Major)	Ac-0 / Re-1
AQL 0.040 (Major)	Ac-0 / Re-1
AQL 0.10 (Major)	Ac-1 / Re-2
AQL 0.25 (Major)	Ac-3 / Re-4
AQL 2.5 (Major)	Ac-21 / Re-22
Overall Height (H1) cpk	<= 1.33
Lead Rib Diameter (D1) cpk	<= 1.33
Second Rib Diameter (D2) cpk	<= 1.33
Third Rib Diameter (D2) cpk	<= 1.33

Stage 2: Verification

Following the drug manufacturer's initial assessment of the 1mL Long NovaPure Plunger and approval of the packaging components for a respective drug product, the drug product process development and pilot scale clinical supply manufacturing typically begins. West can support inventory requirements for 1mL Long NovaPure Plungers for use during process development and clinical supply manufacturing. The 1mL Long NovaPure Plungers will be fully processed and ready-to-use, and are typically packaged within the West STERILIZABLEBAG™ packaging system; however, the plungers can be packaged in Getinge-La Calhene (GLC) or Sartorius Stedim Biotech (SSB) ported bags for use in Restricted Access Barrier Systems (RABS) or Isolators. Within Stage 2, typically 10,000 to 100,000 1mL Long NovaPure plungers are required to complete these activities and to support clinical supply. During this stage, there are several activities and assessments that need to be conducted.

For example:

- Machinability assessments and change parts fabrication of pilot scale filling lines
- Establishing and optimizing process parameters on the pilot scale filling line, inspection machines and plunger rod insertion machines
- Determination of acceptance criteria for in-process and off-line testing
- Evaluation and determination of the target delivery system

The background and importance of these activities for prefilled syringe systems will be highlighted in the following section.

Machinability assessments and change parts fabrication for pilot scale filling lines

As fill and finish (fill/finish) activities are initiated using the pilot scale filling equipment, an assessment of the packaging components with regard to the change parts on the filling line should be conducted. The feeder bowl, sorting and orienting tracks, feeder tracks, push rods, transfer bars, insertion tubes or vacuum tooling, and insertion rods are common change parts that need to be assessed when introducing a new plunger, such as the 1mL Long NovaPure Plunger, on a syringe filling machine.

Often the first assessment is a theoretical dimensional analysis in which the dimensions associated with the pre-existing change parts of the filling machine and the 1mL Long NovaPure Plunger are considered to determine the feasibility of machinability. (In such a case, the pre-existing change parts would need to be designed for a 1mL long plunger, but if no 1mL long plunger change parts exist, then change parts will need to be fabricated.) If the theoretical assessment determines that change parts are required, the technical drawing and samples of the 1mL Long NovaPure Plunger will need to be provided to the fill/finish equipment manufacturer to fabricate the necessary change parts. If the theoretical assessment indicates that the pre-existing change parts may be acceptable (as may be the case if the pre-existing change parts are designed for West's Article 2340 1mL Long plunger), a low-speed line trial should be conducted to assess machinability.

Dependent on the performance of the plungers during the low-speed line trial, the speed of the consecutive line trials should be increased until the required processing speeds are achieved. At any stage that the plungers do not process well on the filling line, modifications to the processing parameters and possibly new change parts are required. If new change parts are required and are fabricated, a series of line trials will need to be conducted to ensure and verify optimal machinability. To support these activities, West can work with the drug manufacturer to ensure that samples will be readily available that are fully processed and ready to use within bulk bags and ported bags.

Establishing and optimizing process parameters on the pilot scale filling line, inspection machines, and plunger rod insertion machines

The optimization of the processing parameters throughout fill/finish operations typically occurs during process development. Variations in the plunger, syringe, plunger rod, fill volume, head space requirements, drug product properties, plunger placement methods and rate of throughput will all directly impact the parameters associated with the filling line, inspection machines and plunger rod insertion machines (labeling and secondary packaging machines also may be impacted).

Machinability performance assessments used for determining process parameters for a plunger typically focus on several criteria, such as the presence of missing or wrongly oriented plungers in the syringe, plunger placement depth in the syringe, consistency of the flow on the tracks and in the bowl, number of stoppages or interventions required, and maximum achievable flow rates. Determining parameters such as the feeder bowl or track vibration settings (percent power to the vibratory solenoids), filling needles insertion and retraction profile, vacuum pressure setting (for vacuum plunger placement), and plunger insertion depth will all impact a plunger's machinability performance and therefore need to be assessed and optimized.

In addition to establishing the filling line process parameters, the automated inspection and plunger rod insertion operations need to be assessed and optimized. The automated inspection is impacted by factors such as the fill volume, drug product appearance, plunger depth and plunger rib design. These factors may impact sample rotation speed, camera angle, lighting profiles and acceptance criteria. The plunger rod insertion is impacted by factors such as the plunger thread design, plunger core depth, plunger thread lubricity and plunger static breakloose forces within the syringe barrel. The rotation parameters, torque and plunger movement criteria, as well as the speed, radial force and downward force of plunger rod insertion, can all be impacted by these factors.

Determination of acceptance criteria for in-process and offline testing

Critical performance and release criteria govern the quality of fill/finish activities as well as the delivery system. The use of in-process and off-line testing during manufacturing also help to ensure the processes remain in control, and ensure appropriate modifications to the process parameters can be made if needed. For instance, weight checks are a common in-process control (IPC) employed by most all drug manufacturers to ensure that the intended drug delivery volume is achieved throughout the manufacturing.

The plunger placement depth within the syringe is also commonly used as an indicator of operation and plunger performance, and therefore plunger depth measurements are often incorporated into the process development, as well as into IPC or off-line testing during operations. The plunger depth within a syringe, and any variability associated plunger placement, can impact the headspace within a syringe (potential plunger movement concern during transit), plunger rod insertion processes (plunger position could vary such that poor insertion or over insertion could occur), and performance of a medical delivery device (may result in incomplete or inaccurate delivery of drug product).

There are numerous other types of IPC or offline test methods that are used during operations, such as vision systems that focus on ensuring a plunger is present at the end of the track or that a plunger has been inserted into the syringe. Each of these process checks/tests can be directly impacted by the performance and design of the plunger, and it is recommended that these checks/tests be evaluated to determine potential new settings or criteria.

Evaluation and determination of the target delivery system

During early stage clinical trials, the evaluation of future delivery systems is typically initiated. There are numerous factors that need to be considered when designing a delivery system, such as an auto-injector. The human factors, target patient population, frequency of dosing, volume of dosing, drug product pharmacokinetics, drug product viscosity and market/branding considerations are just some of the aspects that need to be thoroughly assessed to ensure the efficacy, safety and overall industry acceptance of the drug product. The method of assessing all the critical factors will not be captured here. However, the role the plunger plays in the overall performance of the delivery system will be reviewed.

The design and ultimately the performance of the plunger is directly correlated to the outcome and effectiveness of the auto-injector. The typical auto-injector uses a spring associated with a plunger rod to push the plunger down the syringe barrel and consequentially deliver the drug product. As the spring elongates, the applied force will decrease, so it is critical that the appropriate spring is used in conjunction with an optimized plunger with a low and consistent force profile. It is recommended the delivery system developers conduct auto-injector simulation tests to ensure the intended delivery profile is achieved. As noted previously, the NovaPure 1mL Long Plunger was designed to ensure a low and consistent force profile necessary to accommodate use within spring-based auto-injectors.

West technical and regulatory support

Throughout the process development and clinical trials, West's technical customer support (TCS), quality assurance (QA), and regulatory affairs (RA) teams actively support the drug manufacturer. TCS will ensure the appropriate technical support is provided in terms of documentation and product understanding, such as details on the 1mL Long NovaPure Plunger Design History File (DHF) or control strategies. TCS is also the conduit for voice of the customer, and for enabling a feedback loop for continuously improving current and future parenteral packaging components, such as the 1mL Long NovaPure Plunger. QA engages with the drug manufacturer if support is needed for any complaint or non-conformance that may occur. RA actively provides regulatory support in the form of Letters of Authorization (LoAs), Drug Master Files (DMFs), and electronic Common Technical Documents (eCTDs) to assist with interactions with international regulatory agencies. In addition, West also welcomes drug manufacturers to audit the West manufacturing sites and to support evaluations associated with supply chain risk management.

Stage 3: Implementation

Based on the completion of the early stage clinical trials and the anticipation of a successful approval of the drug product and delivery system using the 1mL Long NovaPure Plunger, the commercial manufacturing scale-up activities typically begin. As highlighted in Stage 2, there are a number of activities and assessments that need to be conducted.

For example:

- Machinability assessments and change parts fabrication of commercial scale filling lines
- Process transfer, verification and validation of process parameters on the commercial scale filling line, inspection machines and plunger rod insertion machines, as well as the in-process and off-line testing
- Verification of delivery system performance

West can support inventory requirements for 1mL Long NovaPure Plungers for use during process development and clinical supply manufacturing. As noted previously, the 1mL Long NovaPure Plungers will be fully processed and ready to use, and are typically packaged within a bulk bag. However, the plungers can be packaged in GLC or SSB ported bags for use in RABS or Isolators. The inventory requirements for Stage 3 can vary greatly, so it is critical that strategic inventory planning is conducted for scale-up activities, as well as the initiation of commercial scale manufacturing. Often during verification and validation activities, three or more different lots of plungers are requested, and incorporated into the activities to support diversity validation practices.

Machinability assessments and change parts fabrication for commercial scale filling lines

As fill/finish activities are initiated using the commercial scale filling equipment, an assessment of the packaging components with regards to the change parts on the filling line should be conducted. As conducted in Stage 2, the various change parts will need to be assessed when introducing a new plunger, such as the 1mL Long NovaPure Plunger, on a syringe filling machine.

If the commercial-scale filling line is from the same filling equipment vendor as the pilot-scale filling line, then commonly the required change parts already will be known and can be proactively fabricated. However, if the commercial-scale filling line is from a different filling equipment vendor than the pilot-scale filling line, then the steps highlighted in the Stage 2 should be followed again for the commercial-scale filling line.

Process transfer, verification and validation of process parameters on the commercial scale filling line, inspection machines, and plunger rod insertion machines, as well as the in-process and off-line testing

During process development, typically the optimal parameters and required acceptance criteria are established for the filling line, inspection machines and plunger rod insertion machines. This is also typically true for all IPC and off-line testing that is required. A considerable amount of the processing parameters and control strategies will be scalable and translatable to commercial scale production from the pilot scale production. There will be some variances in settings and criteria depending on whether there is a significant change in the technologies being used. In those cases additional assessments will be required to solidify the necessary parameters. Once all processing parameters are solidified, engineering studies are typically conducted to verify process, components and equipment are performing as intended and required. Lastly, the equipment qualification and process validation occurs to provide assurance that a robust drug manufacturing process has been successfully implemented. As noted previously, multiple lots of components, such as the 1mL Long NovaPure Plunger, are used for the qualification and validation activities to further support and assure a robust processing range and design space.

Verification of delivery system performance

Typically, during Phase III of the clinical trials the dosing regimen of the drug product has been determined. Often during this phase, the intended drug delivery system also has been solidified, and may be used during the final phase clinical trials. This is, however, dependent on the timing associated with the “speed to market.” As a life cycle management, many drug product manufacturers will move to commercialize a drug while still in a prefilled syringe format to be “first to market,” but will subsequently proceed with establishing the device once the drug product has been sufficiently accepted within the market. In either case, as noted before, the performance of the plunger is critical to ensure the intended delivery profile is achieved. Follow-up evaluations with the delivery system commonly will be conducted to ensure that dose delivery and time are established and non-varying during patient or caregiver use.

Stage 4: Ongoing Support

Within this stage, West's primary focus is on ensuring the drug manufacturer's commercial manufacturing is uninterrupted by supply of parenteral packaging components, such as the 1mL Long NovaPure Plunger. Strategic planning of inventory becomes critical, and it is critical that the appropriate component packaging (bulk bags or ported bag options) has been solidified and incorporated into the inventory planning. The requirement for supply stock, especially as a drug approaches commercial launch and the need to understand and communicate forecast expectations to the various suppliers is particularly important. TCS and QA remain engaged with the drug manufacturer during this stage; however, those interactions typically are on an as need basis. There is also ongoing Regulatory support in the form of managing agency requests for West DMFs and responding to agency questions on NovaPure products and processes.

Conclusions

As the industry continues to see significant growth for drug products developed in PFS, there is a trend for pharmaceutical companies to evaluate more complex drug molecules that require delivery systems. These biologics are typically intended for self-administration by the patient and integrate a PFS with an auto-injector to optimize safety, dose accuracy and ease of use. The challenge is that existing plunger technology for PFS was developed for manual injection and does not meet the evolving requirements for drug delivery especially for consistency of injection rate.

West has reviewed these current trends for PFS and self-injection, and developed the 1mL Long NovaPure plungers to meet the needs of advancement in injectable technology. Through the West-Drug Manufacturer Process Stages, West has shown that an experienced partner can help new – or advanced – drug companies move a product to a new plunger or syringe system by actively collaborating during key activities and decisions during primary container selection, component implementation, and commercial scale up. With proper testing, including plunger functionality, container closure integrity, system compatibility and machinability performance, companies can move forward with the right system for their drug product – helping to ensure a safe and efficient move to market.

About the Authors

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Simon Cote is a Principal Engineer within West's Technical Customer Services organization. Simon supports both the Commercialization and Research and Development teams as a technology lead/expert associated with fill/finish processes, component packaging (ported bags, etc), seals (plastic and aluminum), and up until just recently as the technology lead for PFS components. He has been with West since March 2012. Prior to that, he worked approximately 10 years within the pharmaceutical industry, split between Centocor (J&J) and Merck. Simon has a Bachelor of Science in Bioprocessing Chemical Engineer from Penn State University.

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