# All about Pre-filled Syringe Systems

## From Initial Development to Final Fill Finish

**Plunger, Needle Shield, Tip Cap**

Christa Jansen-Otten

*Copenhagen, 25th and 26th April 2024*


PDA Parenteral Drug Association

PDA TRAINING

# Customer Impact - Demands on Packaging Components are Increasing

**Vial Components**

- Particulate reduction/foreign matter
- Concerns regarding extractables/leachables
  - Ultra-clean components needed
  - New ways to deliver medicine
- Functional performance of components
  - High-speed lines
  - Complex devices
- Moisture Vapor Transmission Rate

**PFS Components**

- Container closure integrity (CCI)
- New manufacturing approach
  - Flexibility
  - Time to market
  - Total cost of ownership (TCO) focused
- Functional performance of components
  - High-speed lines
  - Complex devices

**Cartridge Components**

# Considerations in Selection of PFS Components

| COMPATIBILITY WITH DRUG | APPLICATION – MANUAL OR AUTO SYSTEM | CONTAINER CLOSURE INTEGRIETY (CCI) | QUALITY SPECIFICATIONS | FINISHIING |
|---|---|---|---|---|
| • Type of drug<br>• pH<br>• Viscosity<br>• Excipients | • Break loose & glide force requirements<br>• Accuracy of delivery volume | • Interference fit of plunger with barrel<br>• Sealing ribs and their function<br>• Preservation of drug potency and sterility | • Particulate level – visible & sub-visible<br>• Dimensional control<br>• Endotoxin level<br>• Bioburden level<br>• Visual defects | • Mode of sterilization<br>• Lubricity<br>• Consistency |

# Rubber material

# Why Use a Rubber Material?

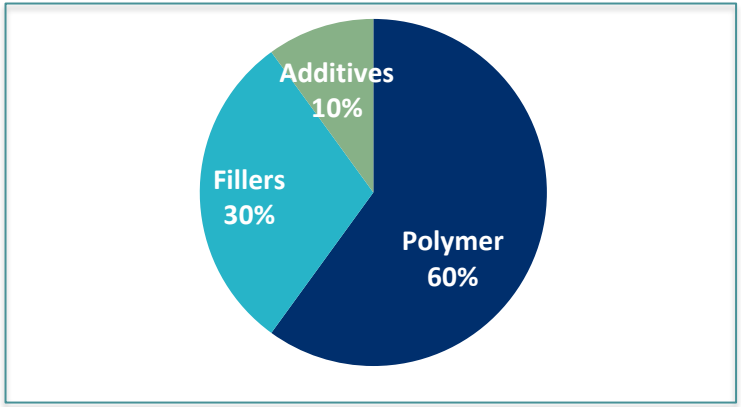
- Sealing properties that maintain container – closure seal integrity over time.
- Physically and chemically compatible with different sterilization methods.
- Different range of material permeability.
- Compatible in long-term contact with drugs.
- Wide range of product designs

# Main Elastomer Types Used for Parenteral Applications

- Natural Rubber (NR) – from Hevea Brasiliensis
- **Isoprene Rubber (IR)** – synthetic equivalent to NR
- Styrene-Butadiene-Rubber (SBR)
- Butadiene Rubber (BR)
- Nitrile Rubber (NBR)
- Ethylene-Propylene Rubber (EPM/EPDM)
- **Isobutylene Isoprene Rubber** (IIR, Butyl Rubber)
- **Halogenated Butyl Rubber** (XIIR) – Br, Cl

# Elastomers Closures General Composition

*Approximate Composition of an Elastomer Component*




**Additives**

can be curing agents, antioxidants, accelerators, activators, protective agents, colorants, plasticizers, acid scavengers, light and heat stabilizers, lubricants, anti-static agents, etc.

**Fillers**

are mainly defining the physical properties

→ "Ask your supplier for potential extractable lists"

# Elastomeric Formulations for Pharmaceutical Use - Properties Butyls/Halobutyls

1. Application: stoppers, plungers, cartridge seals and tip caps
2. High elasticity
3. Low potential E&L[1] for good drug compatibility
4. Low moisture and gas permeation rates
5. Steam and gamma sterilizable
6. JP, USP, EP compliant[2]
7. Low fragmentation / corning
8. Optimal penetrability/good resealing properties

[1]extractables & leachables [2]design dependent

# Elastomeric Formulations for Pharmaceutical Use - Properties synthetic Polyisoprene

1. Application: needle shields/rigid needle shields, tip caps plungers, cartridge seals (laminates)
2. High elasticity
3. Low potential E&L[1] for good drug compatibility
4. Good permeability rates towards moisture and gases (ETO[2])
5. Steam, gamma and EtO[2] sterilizable
6. USP, EP compliant
7. Low fragmentation / corning
8. Ozone resistance (low cracking), no blooming, no frosting

[1]extractables & leachables
[2]Ethylene oxide

# Potential Issues: Needle Shields and Tip Caps

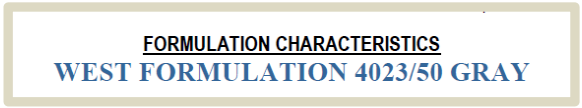
## Ozone Cracking

## Frosting (Bloom)

# Supporting Documents

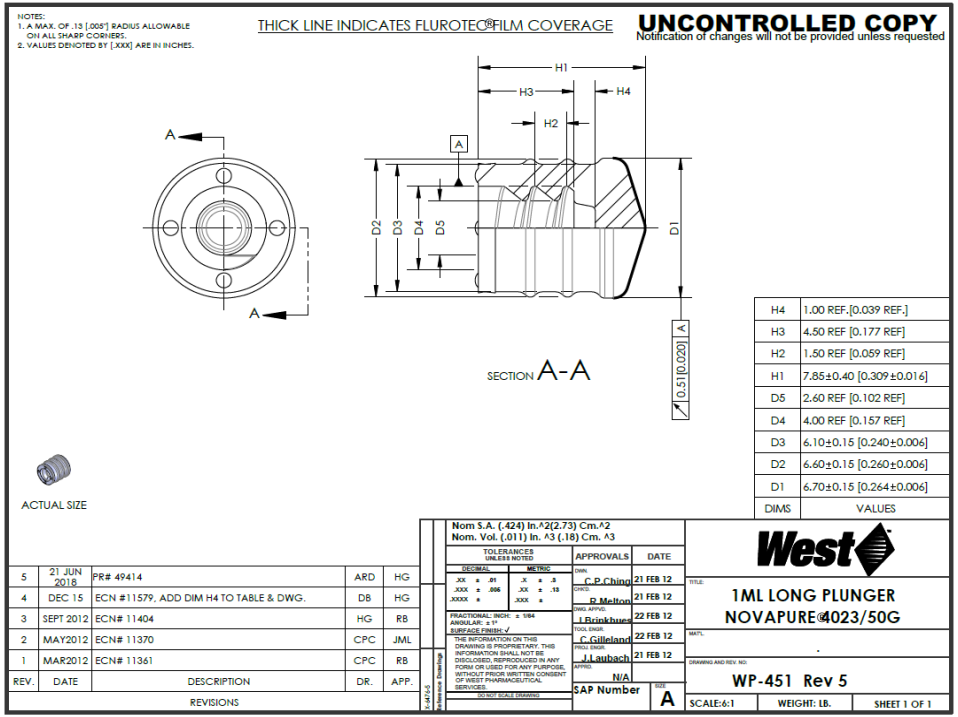
# Supporting Documents: Example

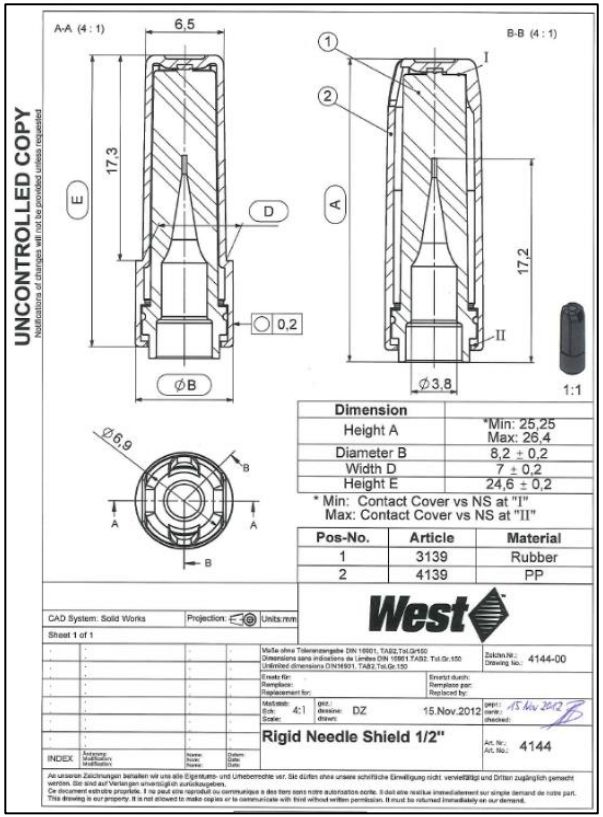
- Technical drawings
- Formulation Characteristics
- Elastomer Formulation Biocompatibility
- Technical Bulletins and Reports
- Theoretical Material Extractable List
- VeriSure® Extractable Technical Package
- Material Characterization Package
- Regulatory Compliance Bulletins
- Product Specifications
- DMF
- Certificates

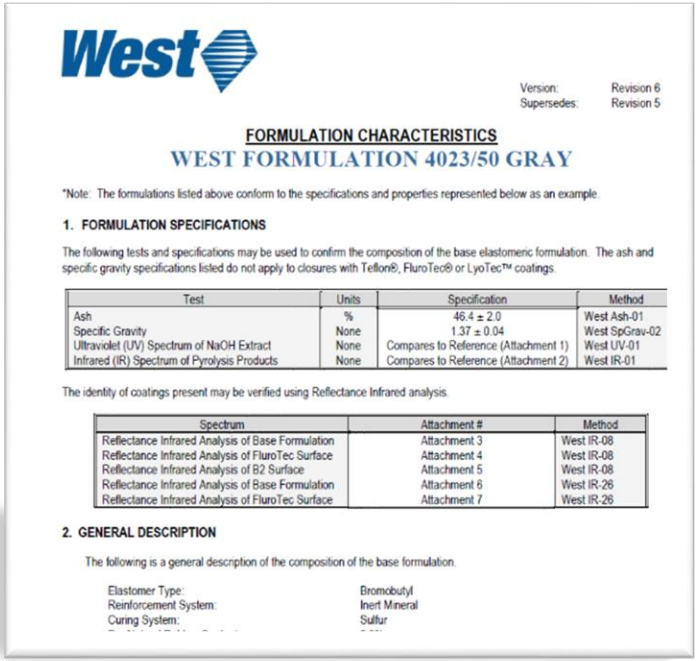


# Uncontrolled Drawings: Example



# Formulation Documents: Example



West

Version: Revision 6
Supersedes: Revision 5

**FORMULATION CHARACTERISTICS**

**WEST FORMULATION 4023/50 GRAY**

*Note: The formulations listed above conform to the specifications and properties represented below as an example.

**1. FORMULATION SPECIFICATIONS**

The following tests and specifications may be used to confirm the composition of the base elastomeric formulation. The ash and specific gravity specifications listed do not apply to closures with Teflon®, FluroTec® or LyoTec™ coatings.

| Test | Units | Specification | Method |
|---|---|---|---|
| Ash | % | 46.4 ± 2.0 | West Ash-01 |
| Specific Gravity | None | 1.37 ± 0.04 | West SpGrav-02 |
| Ultraviolet (UV) Spectrum of NaOH Extract | None | Compares to Reference (Attachment 1) | West UV-01 |
| Infrared (IR) Spectrum of Pyrolysis Products | None | Compares to Reference (Attachment 2) | West IR-01 |

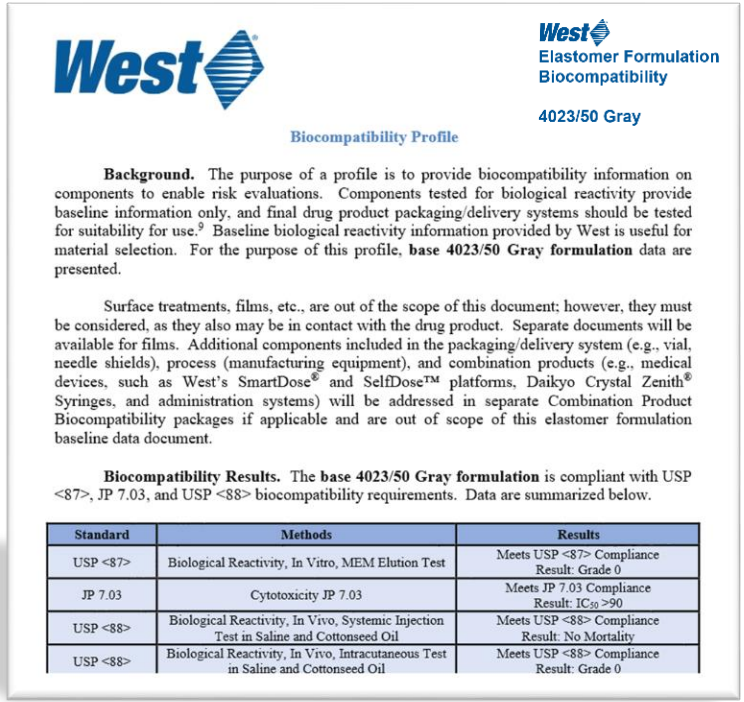
The identity of coatings present may be verified using Reflectance Infrared analysis.

| Spectrum | Attachment # | Method |
|---|---|---|
| Reflectance Infrared Analysis of Base Formulation | Attachment 3 | West IR-08 |
| Reflectance Infrared Analysis of FluroTec Surface | Attachment 4 | West IR-08 |
| Reflectance Infrared Analysis of B2 Surface | Attachment 5 | West IR-08 |
| Reflectance Infrared Analysis of Base Formulation | Attachment 6 | West IR-26 |
| Reflectance Infrared Analysis of FluroTec Surface | Attachment 7 | West IR-26 |

**2. GENERAL DESCRIPTION**

The following is a general description of the composition of the base formulation.

| | |
|---|---|
| Elastomer Type: | Bromobutyl |
| Reinforcement System: | Inert Mineral |
| Curing System: | Sulfur |



West

West
Elastomer Formulation
Biocompatibility

4023/50 Gray

**Biocompatibility Profile**

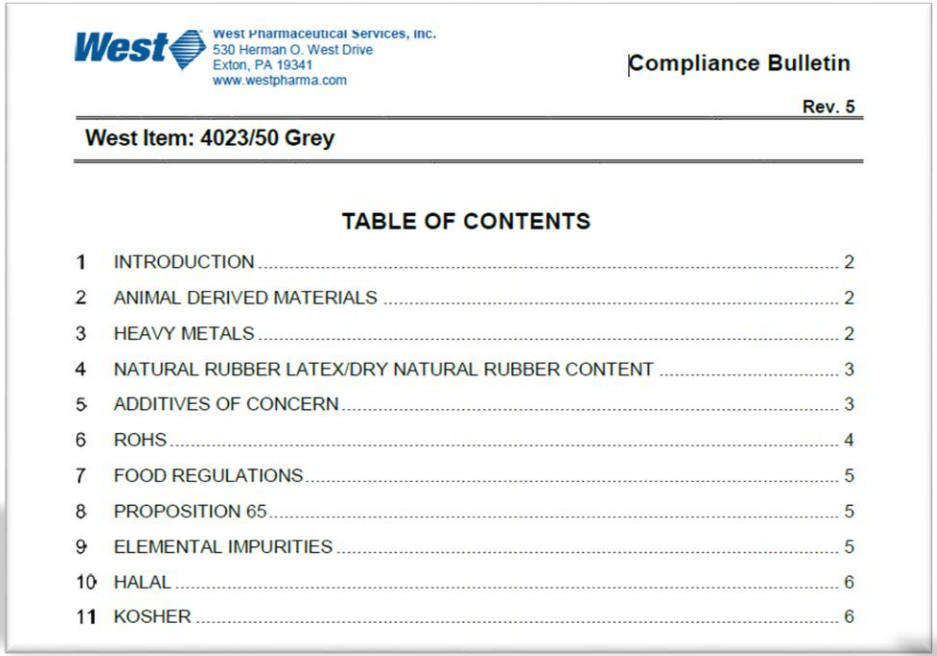
**Background.** The purpose of a profile is to provide biocompatibility information on components to enable risk evaluations. Components tested for biological reactivity provide baseline information only, and final drug product packaging/delivery systems should be tested for suitability for use.[9] Baseline biological reactivity information provided by West is useful for material selection. For the purpose of this profile, **base 4023/50 Gray formulation** data are presented.

Surface treatments, films, etc., are out of the scope of this document; however, they must be considered, as they also may be in contact with the drug product. Separate documents will be available for films. Additional components included in the packaging/delivery system (e.g., vial, needle shields), process (manufacturing equipment), and combination products (e.g., medical devices, such as West's SmartDose® and SelfDose™ platforms, Daikyo Crystal Zenith® Syringes, and administration systems) will be addressed in separate Combination Product Biocompatibility packages if applicable and are out of scope of this elastomer formulation baseline data document.

**Biocompatibility Results.** The **base 4023/50 Gray formulation** is compliant with USP <87>, JP 7.03, and USP <88> biocompatibility requirements. Data are summarized below.

| Standard | Methods | Results |
|---|---|---|
| USP <87> | Biological Reactivity, In Vitro, MEM Elution Test | Meets USP <87> Compliance Result: Grade 0 |
| JP 7.03 | Cytotoxicity JP 7.03 | Meets JP 7.03 Compliance Result: $IC_{50}$ >90 |
| USP <88> | Biological Reactivity, In Vivo, Systemic Injection Test in Saline and Cottonseed Oil | Meets USP <88> Compliance Result: No Mortality |
| USP <88> | Biological Reactivity, In Vivo, Intracutaneous Test in Saline and Cottonseed Oil | Meets USP <88> Compliance Result: Grade 0 |

# Formulation Documents: Example



West Pharmaceutical Services, Inc.
530 Herman O. West Drive
Exton, PA 19341
www.westpharma.com

**Compliance Bulletin**

Rev. 5

**West Item: 4023/50 Grey**

**TABLE OF CONTENTS**



West — By your side for a healthier world™

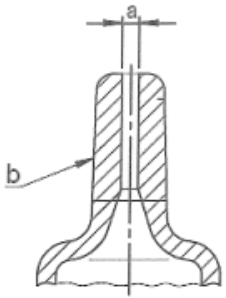
530 Herman O. West Drive • Exton, PA 19341
T: 610 594 2900
www.westpharma.com

**Theoretical Material Extractables List: 4023/50 Gray**

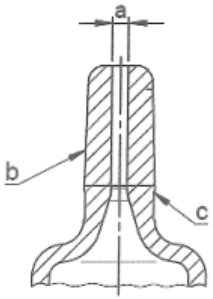
Below is a summary of the potential chemical entities that could be extracted from West elastomer formulation 4023/50 Gray based on the materials that are used in the formulation. Since each drug application is unique, it is possible to form new reaction products from the closure or from a combination of the closure and the drug product components.

# Rigid Needle Shields and Tip Cap

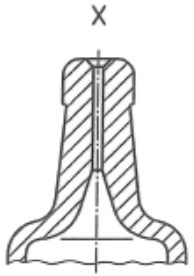
# Pre-filled Head Designs ISO 11040-4 require different closure design solutions



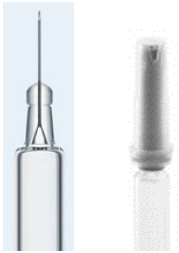

Head design of glass barrel with a 6% Luer cone




Head design of glass barrel with a 6% Luer cone for Luer Lock (LL)




Head design of glass barrel with staked needle



# West Rigid Needle Shields

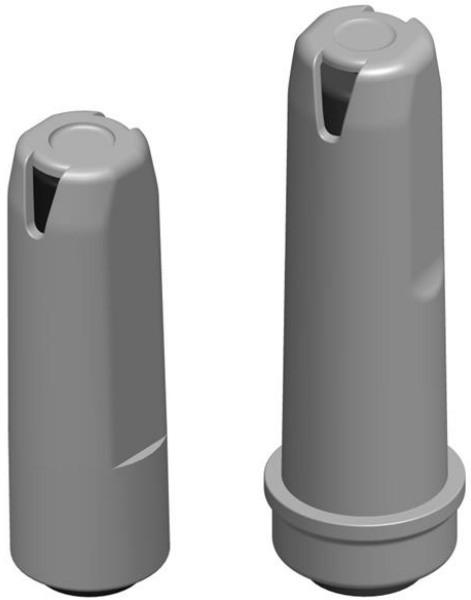
| Rigid PP Shell | | Soft Rubber Part | | Assembled RNS |
|---|---|---|---|---|
|  | + |  | = |  |

**Rigid Needle Shields [RNS] are a safe & efficient closuring system for Prefilled Syringes with staked needles**

# Design examples of Rigid Needle Shields

**RNS ½'' [13 mm]**

*Needle length used for subcutaneous drug injection (into the tissue layer between the skin and the muscle)*



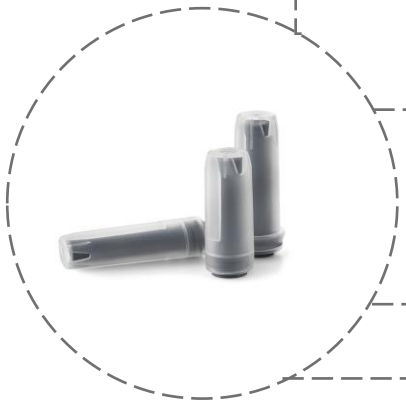
**RNS ⅝'' [16 mm]**

*Needle length used for intramuscular drug injection (deep into the muscles)*

# Solution

- Designed for existing assembly machine and filling equipment.
- Fits to ISO Norm 11040-4 glass syringe with staked needle
- Suitable also for polymer (e.g. COP) syringe
- Compatible with safety devices
- High gas permeation rubber formulation combined with sterilization windows of the rigid shell allowing effective sterilization by ethylene oxide or steam

# Advantages of Rigid Needle Shields vs Soft Needle Shields



**Process**

- Easier distribution & orientation on syringe assembly equipment
- Compatible with safety devices

**Protection**

- Reduces risk of needle tip damage and deformation, the rigidity helps straight removal, no compression during removal

**Handling Final Use**

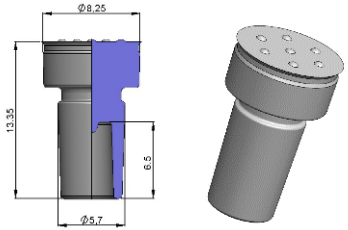
- Easier and safer de-shielding through its optimized design and comfortable haptic for health care professionals and patients
- Considered as more user friendly by Health Care Professionals
- Easier to de-shield when used with auto-injectors

**Appearance**

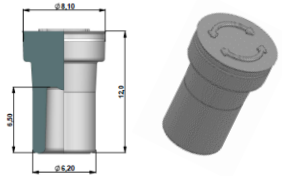
- More valuable appearance, no visible defects of soft NS e.g., “banana” effect

Rigid Needle Shields are the preferred closure for staked needle syringes

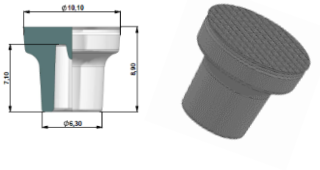
# Example of various Tip Caps for Luer and Luer Lock Syringe




Tip Cap to be inserted  a rigid plastic cap # 3155



Easy Turn Tip Cap # 3131



Mushroom Rip Cap # 3379

**Multiple rubber formulation options (halobutyl and synthetic isoprenes)**

# Barrier Film & Coatings

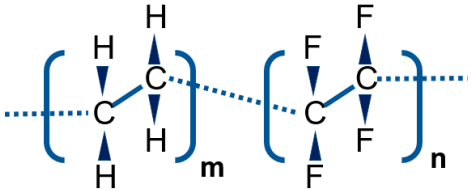
# Films and Coating Technologies

- **Film** – sheet (e.g., PTFE, ETFE) that is laminated to elastomeric component during the molding process
  - – - Barrier function, e.g., FluroTec™ film

- **Coating** – liquid or vapor that is sprayed, tumbled or vapor deposited onto the elastomeric component
  - Lubricity, e.g., B2-Coating
  - Lubricity and barrier function

# Film properties

*The blue color indicates FluroTec™ film*




*Structure of Poly(ethylene tetrafluoroethylene) (ETFE)*

**FluroTec™ film is**

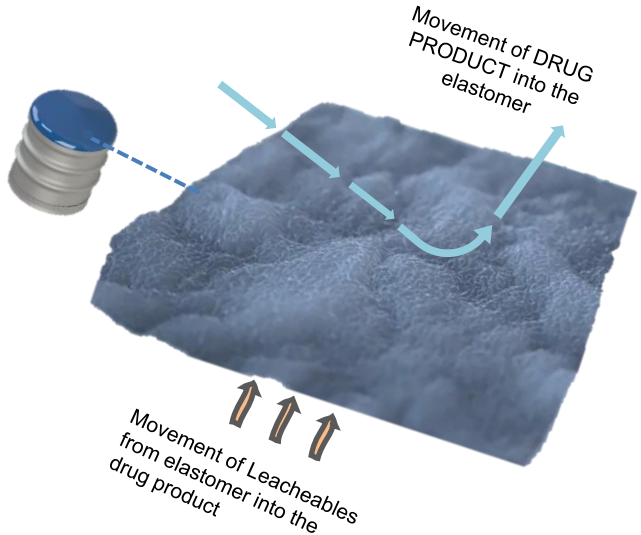
- based on poly(ethylene tetrafluoroethylene)
- smooth surface
- very adherent to elastomers (either bromo- or chloro-butyl)
- translucent
- compatible with sterilization by either:
  - autoclave
  - gamma irradiation
- Applied during the compression molding process



COPYRIGHT © PDA 2018

# Film has a low level of Interaction

ETFE acting as a barrier reduces transport in two directions

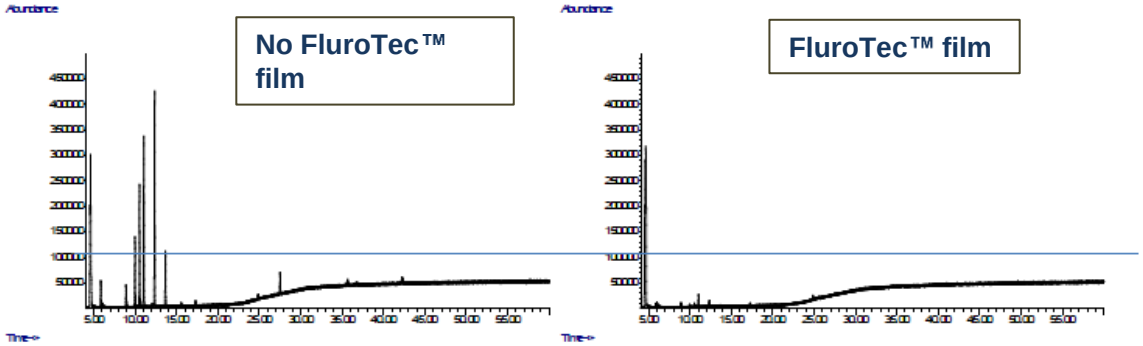



**FluroTec™ film**

- No reactive functional groups
- chemically inert – mitigates chemical migration
- resistant to degradation
- supports reduction in absorbance

**Very Low Surface Energy → Very Low Level of Interaction!**

# Fluoropolymer film coating Significantly Reduce Leachables

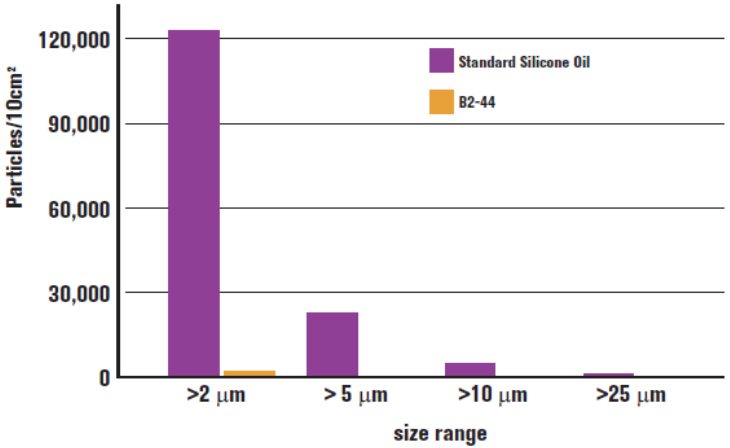



- The drawn blue line indicates an estimated identification threshold of 0.5 µg/unit, which is below the Product Quality Research Institute recommended safety concern threshold for parenteral drug products
- Non-laminated elastomers showed approximately eight volatile organic compound (VOC) peaks estimated to be > 0.5 µg/unit
- Elastomers with FluroTec™ film did not show any peaks > 0.5 µg/unit [blue line]

**Most marketed biopharmaceuticals use fluorpolymer-coated component technology (FluroTec® film)**

# Lubricity coating


## B2-coating vs. Traditional Silicone Oil
## - Sub visible Particles -




### B2-Coating

- Cross-linkable high and low molecular weight polydimethylsiloxane coating
- Applied to the surface of rubber stoppers and syringe components
- Low levels of extractable silicone oil
- Reduced particulate count
- Does not alter chemical and biological stopper/plunger properties
- Enhanced machinability




*Study extract from Technical Report TR 2000/026 B2-Coating Quantitative Particle Analysis*

# Lubricity Coating: Classical Silicone Oil

Polydimethylsiloxane *DuPont ™Liveo ™ 360 Medical Fluid** added during washing operation into the washing drum:

- 350 centistokes → USA
- 1000 centistokes → Europe

| ADVANTAGES | DISADVANTAGES |
|---|---|
| • Commonly used<br>• Applied during wash cycle<br>• Low cost | • Particles/droplets may be found in drug product<br>• Silicone level may be inconsistent if process is not validated |

* *Example of silicone oil used by West*

# Plungers

# Facilitating Life Cycle: Seamless Transition from Vial to Prefilled Syringe format

Multi Dose Vial
[MDVs]



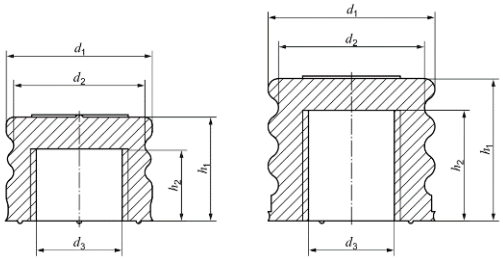
Single Dose
PFS

- **The Same** Rubber Formulation
- **The Same** Lubricant [B2-coating]
- **The Same** Fluoropolymer Film lamination
- **The Same** Manufacturing Technology
- **The Same** Quality

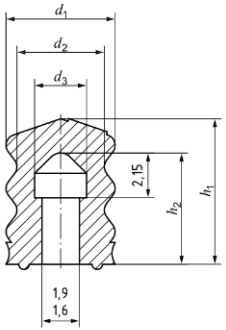
# Main requirements for Prefillable Syringes Plungers

- Delivers a smooth injection profile [break loose & glide forces profile]
- Compatibility with the drug product
- Compatible with gamma-irradiation and final steam sterilization treatment
- Compatible with glass and plastic (COC/COP) barrels
- Good compression set properties
- Maintains Container closure Integrity
- Well performance on fill-finish equipment
- Optimized Break Loose & Extrusion Profile
- Low Part-to-Part Variability

# Plunger ISO 11040-5




b) Plunger stopper with thread (PST)




a) Plunger stopper with snap lid (PSL)

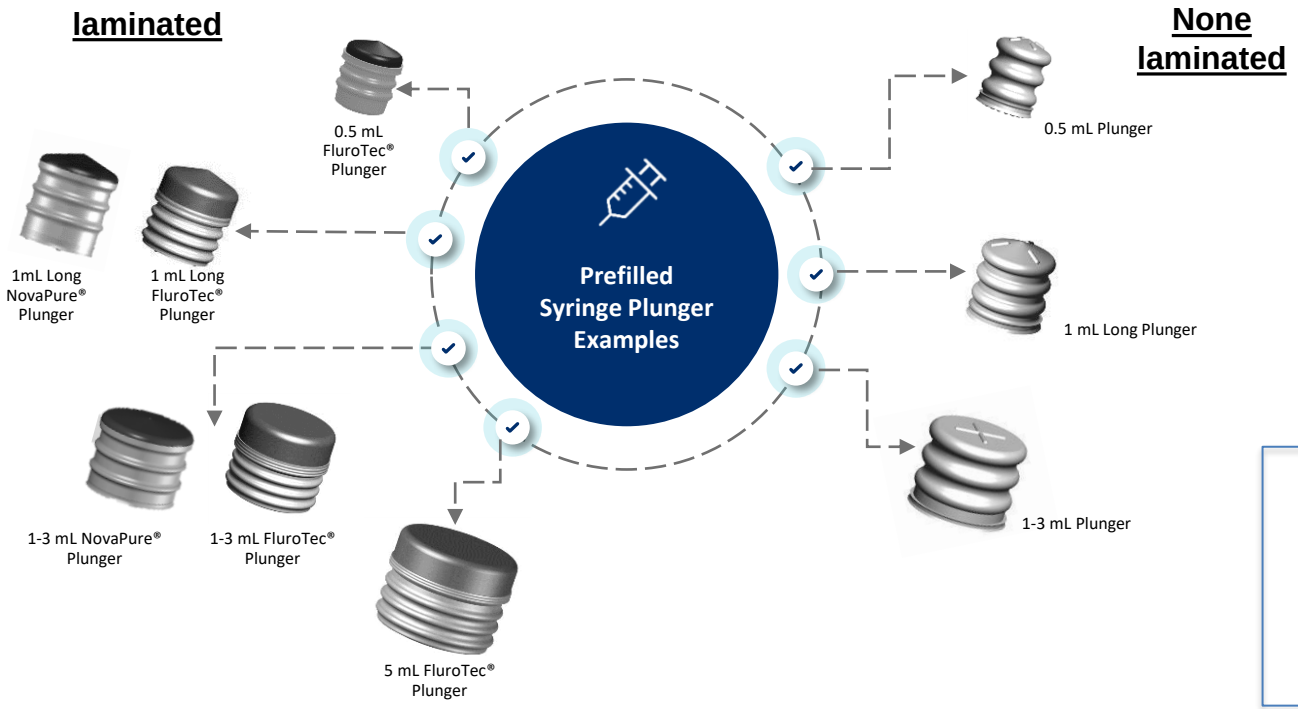
| Nominal inner diameter $d_2$[b] | Nominal volume | Type | $d_1$[a] | | $d_2$[a] | | $d_3$[a] | | $h_1$[a] | | $h_2$[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ml | | nom. | tol. | nom. | tol. | nom. | tol. | nom. | tol. | nom. | tol. |
| 4,65 ± 0,1 | 0,5 | PSL | 5,2 to 5,3 | ±0,1 | 4,1 to 4,2 | ±0,15 | 2,5 | ±0,2 | 6,85 to 7,0 | ±0,4 | 5,3 | ±0,35 |
| 6,35 ± 0,1 | 1 (long) | PST | 6,8 to 7 | | 5,9 to 6 | | 2,6 | | 7,65 to 7,85 | | 4,5 | ±0,3 |
| 8,65 ± 0,2 | 1 to 3 | | 9,05 to 9,25 | | 7,6 to 8 | | 4,7 | | 7,7 to 7,85 | | 4 | |
| 11,85 ± 0,2 | 5 | | 12,5 to 12,7 | | 10,5 to 11,15 | | 5,2 to 5,6 | ±0,25 | 8,5 | | 6,0 | |
| 14,25 ± 0,2 | 10 | | 15 to 15,3 | | 13,5 to 13,75 | | 7,4 to 7,6 | | 8,5 to 10 | | 6 to 6,2 | |
| 19,05 ± 0,2 | 20 | | 19,9 to 20,1 | ±0,15 | 18,4 to 18,6 | | 10,7 | | 13,45 to 13,50 | | 7 | |

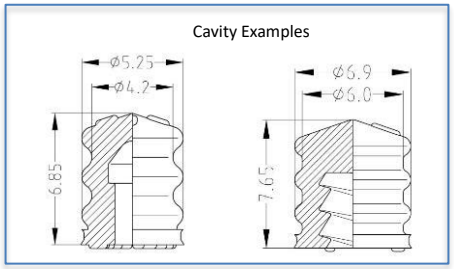
[a] The nominal diameter shall be agreed upon between the manufacturer and the user within the given range.

[b] In accordance with ISO 11040-4.

West standard components are compatible with ISO glass barrels

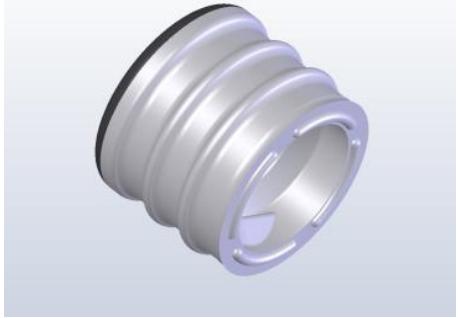
# Example of Prefillable Syringe Plungers - Portfolio at West

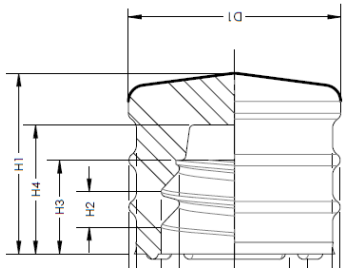


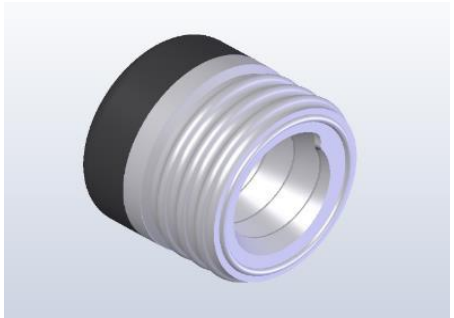
# Examples of Prefilled Syringe plunger designs

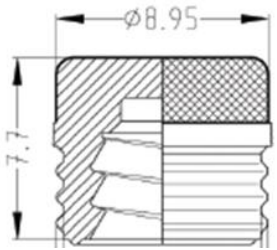
## 1-3 mL NovaPure® Plunger



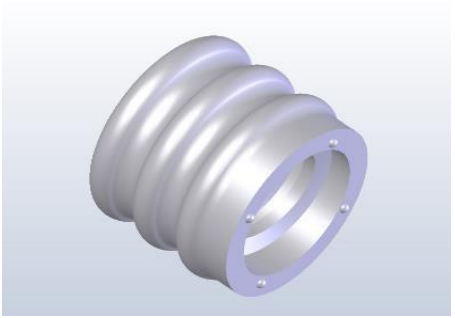


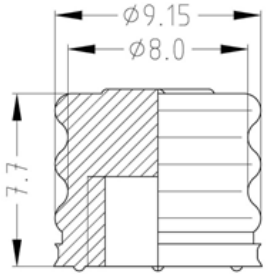

## 1-3 ml FluroTec® Plunger






## 1-3 ml Plunger

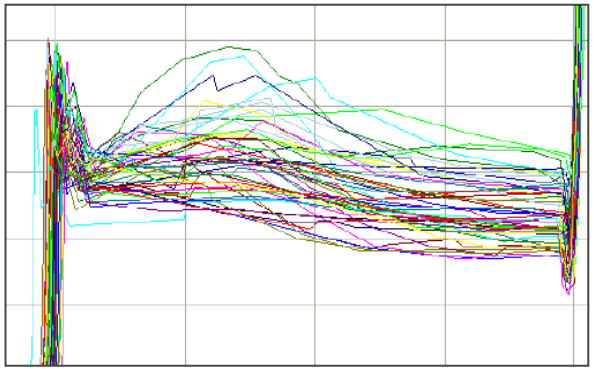




# Manual PFS to Auto-injector Challenges

## Challenges

- Complex container closure
- Designed for manual injection
- Top variations to overcome
  - Dimensional
  - Silicone oil
  - Break loose and gliding force



Syringe functionality with high variability

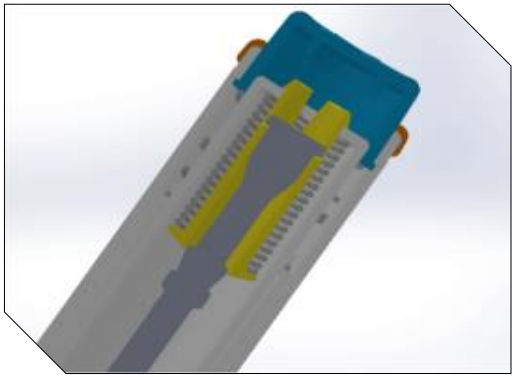
# Auto-injector Reliability Risks

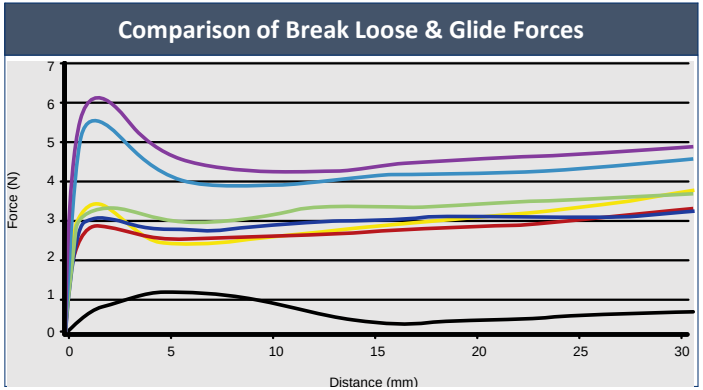
**If injection times vary between doses with an auto-injector:**

- Patient may stop dose if too long
- Patient may question quality of the product

**Critical design factors must be considered, especially functional compatibility**

- Break lose and glide forces (max/min)
- Spring falling rate forces (max/min)



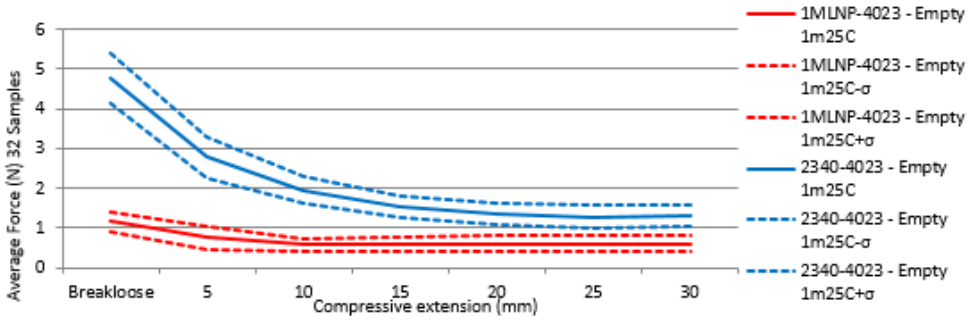




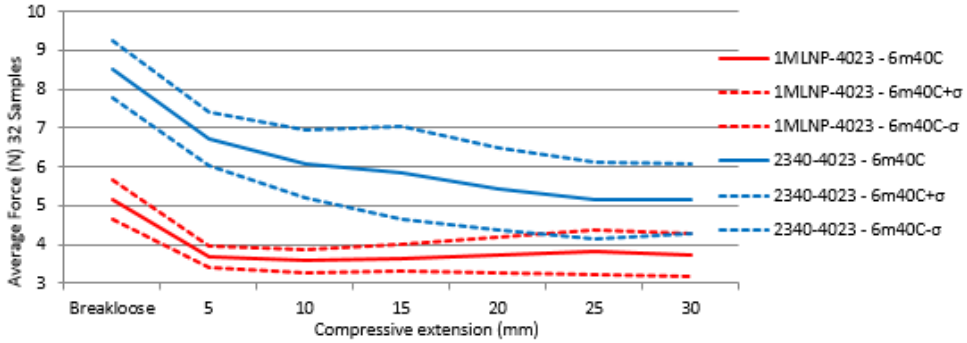

COPYRIGHT © PDA 2018

# Performance: two different laminated 1 ml long Plungers

Empty

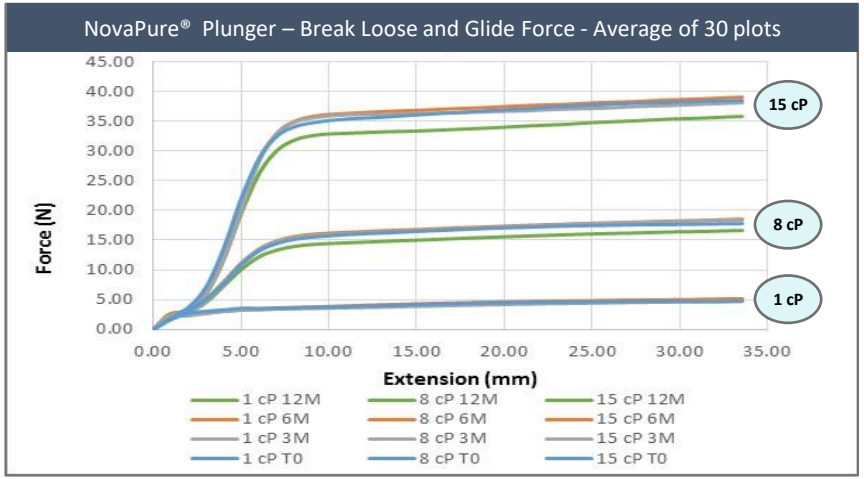


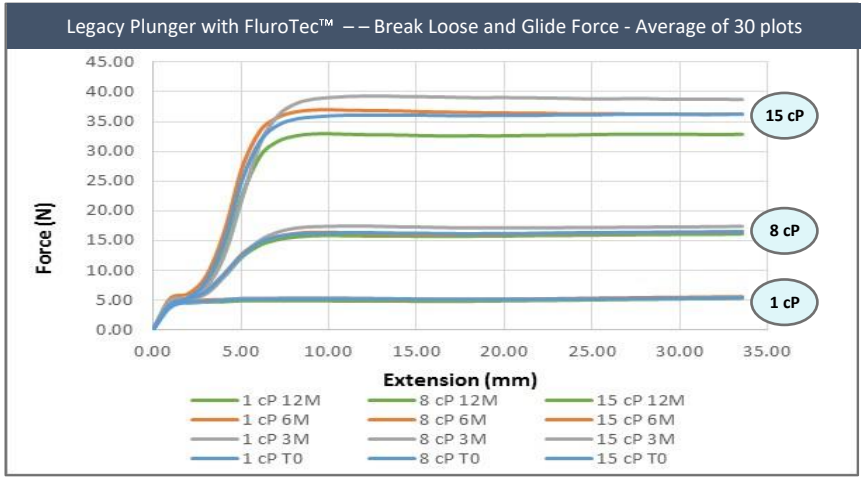

Water Filled




*Source: West TR 2013/147*

# Break-loose and Glide Force - 1 ml Long Plungers
# - Curves represent averages of 30 plots – Example -




- Break-loose forces are on average 50% lower for NovaPure® plungers at all viscosities and all timepoints
- Less variability over time with NovaPure® plungers especially for high viscosities

*Study Extract: TR 2018/191*

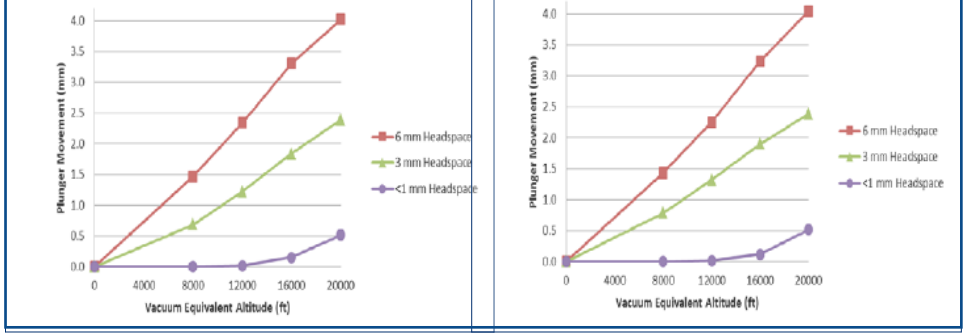
# Evaluation of Plunger Movement During Transit Conditions- Example

**West Plungers Evaluated: 1-3 ml FluroTec™ film laminated plunger and 1-3 mL NovaPure® plunger**

- Headspace Values
  - 6 mm (exaggerated vent-tube placement)
  - 3 mm (typical vent-tube placement)
  - <1 mm (typical vacuum placement)

| Altitude | Significance |
|---|---|
| 8,000 ft | Pressurized Jet |
| 12,000 ft | Mountain Passes |
| 16,000 ft | Unpressurized Jet |
| 20,000 ft | Highest Cargo Jet Altitude on Record |

**NovaPure® 1-3mL** | **1-3 ml FluroTec™ film laminated#2345**







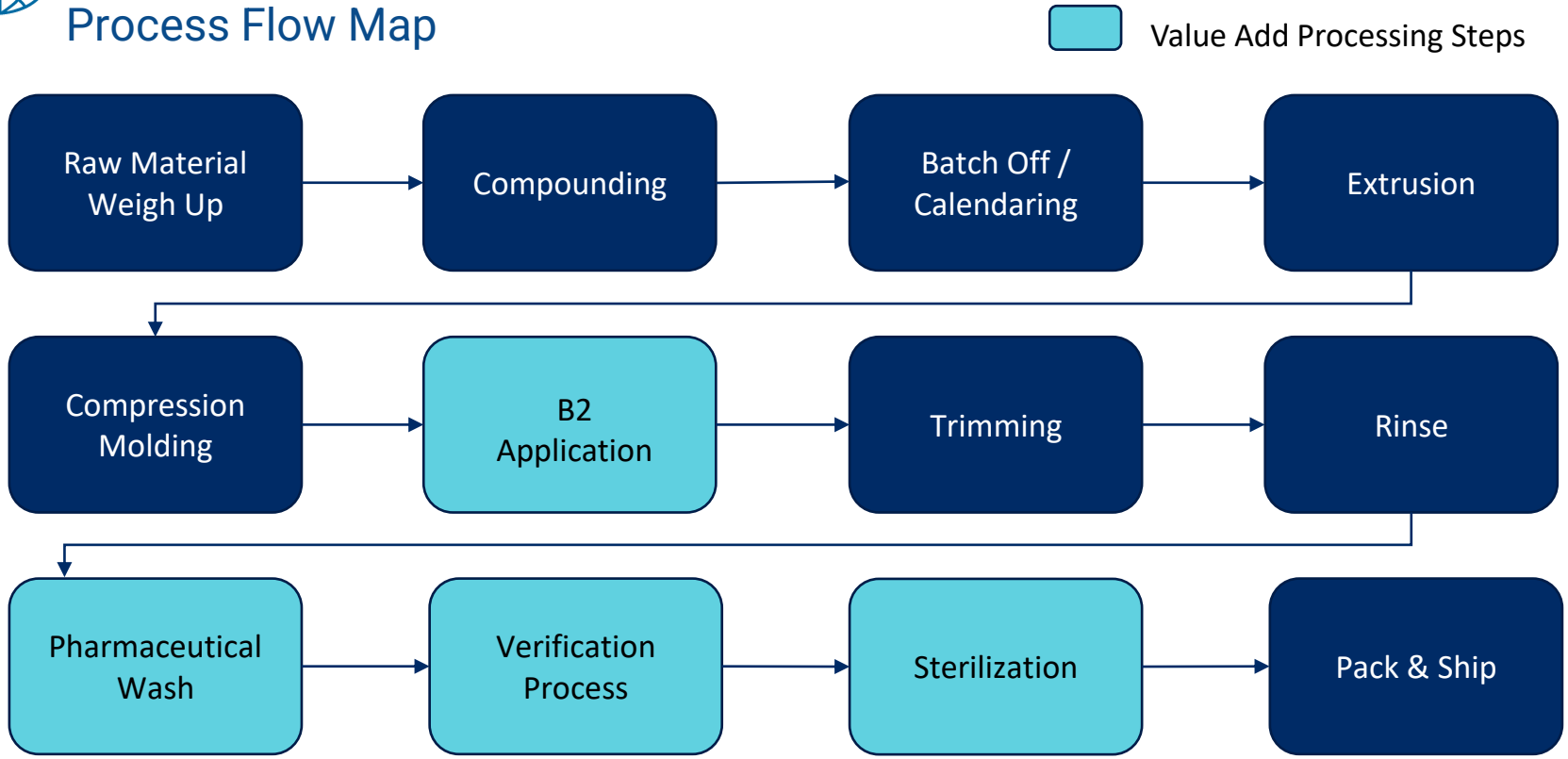
- Linear correlation between pressure and movement
- Higher headspace volume leads to stronger movement
- NovaPure® and legacy plunger performance is comparable




*Extract of Study – technical report available – TR 2016-172*

# Processing

# Process Flow Map



# Elastomer Manufacturing Process

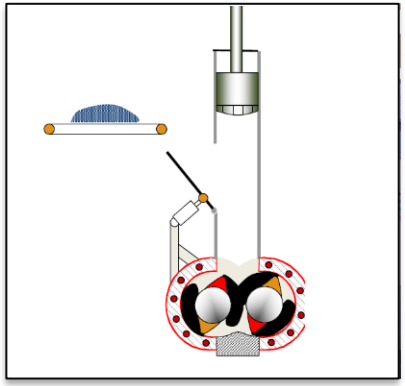
## Raw Material Weigh Up

- Formulation control – SAP
- Only approved raw materials
- Electronic weigh check against the ingredients list

## Compounding (Mixer/Open Mill)

- Distribute ingredients uniformly throughout the polymer matrix
- Use shear to reduce the molecular weight of the polymer and allow the ingredients to disperse

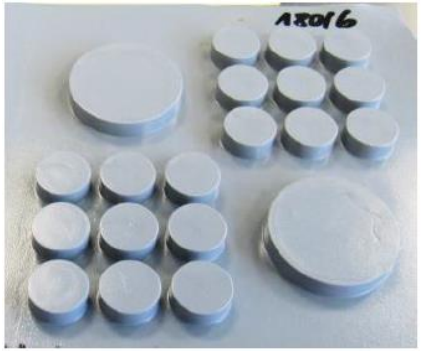
Internal Mixer



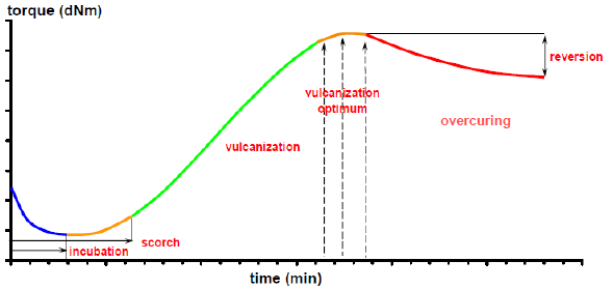
Open Mill

# Mixing Control (Mill Control)

| Curing of ISO – standard sample for testing purposes | |
|---|---|
| specific gravity | per batch |
| Shore A of vulcanized sample | per batch |
| dispersion of vulcanized sample | per batch |
| color of vulcanized sample | per batch |
| ash content | every 10th batch plus 1st and last |
| rheology of the compound | every 5th batch plus 1st and last |



Vulcanized Test buttons




Rheology Curve

# Elastomer Manufacturing Process

## Batch Off or Calendaring

- Intermediate step that allows the compounding facility to hold or distribute rubber stock prior to extrusion

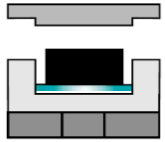
## Extrusion (Calendar/Dispersion Enhancement System)

- Aids in reducing undispersed materials
- Form the compounded rubber into panel shape, required for compression molding

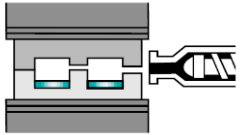
# Pharmaceutical Rubber Manufacturing

**Different 'shapes' need different molding technology:**

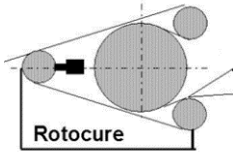
- Compression Molding (CM)
  e.g. Plungers, stoppers, disk
  .



- Precision Injection Molding (PIM)
  e.g Needle shields …



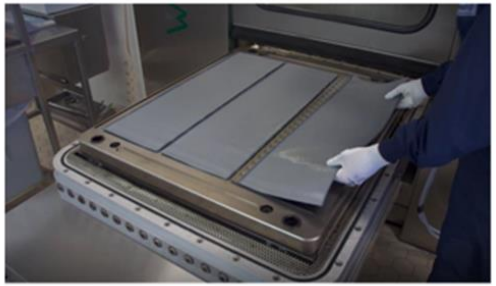
- Rotocure (Sheeting Material)
  e.g. Lined seals…

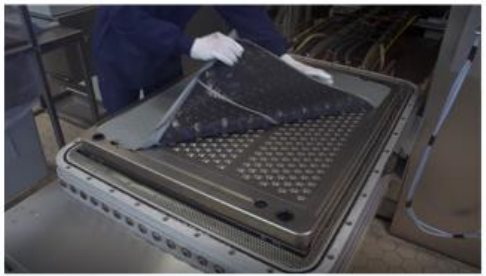



# Elastomer Manufacturing Process

## Compression Molding

- Mechanical force creates the shape
- Heat forms crosslinks and imparts final physical properties to the part

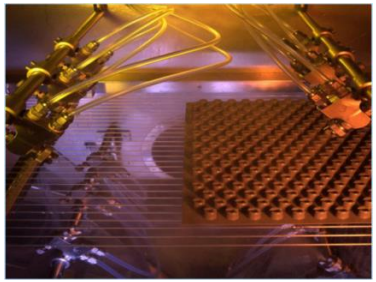




# Elastomer Manufacturing Process

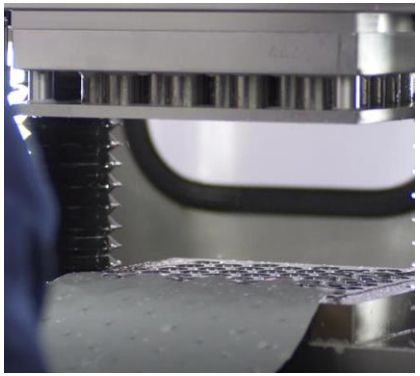
## B2-Coating Application

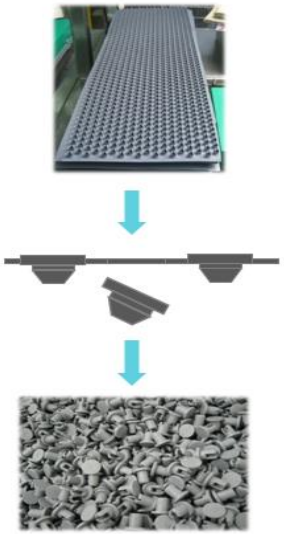
- Applied to the top and/or bottom of the molded panels



## Trimming

- Parts are trimmed from the molded panels





# Elastomer Manufacturing Process

## Rinse

- Removes Processing Aids
- Not a pharmaceutical wash

## Pharmaceutical Wash Process

- Pharmaceutical wash process for Ready-to-Sterilize (RS) product
- Application of silicone (if applicable)

# Pharmaceutical Wash Process

- Validated process according to GMP to demonstrate an endotoxin content reduction by at least 99.9% (3.0 $\log_{10}$).
- Components are unloaded from the washer in a Zone 5 clean room
- All associated process data is filed in Drug Master Files (DMF) with FDA and Health Canada.
- Particulate, bioburden and endotoxin are reported in the quality certificate provided with every batch

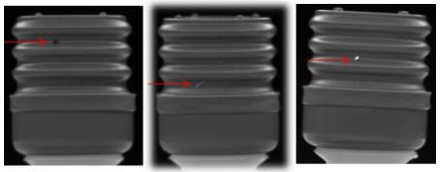
NOVAPURE
Westar SELECT

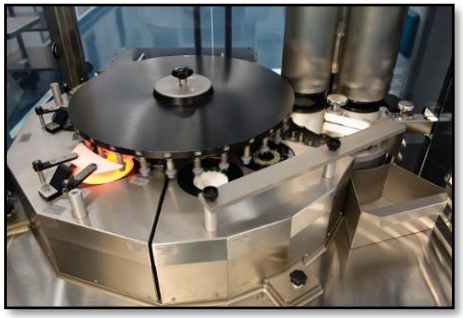
# Elastomer Manufacturing Process

## Verification Process

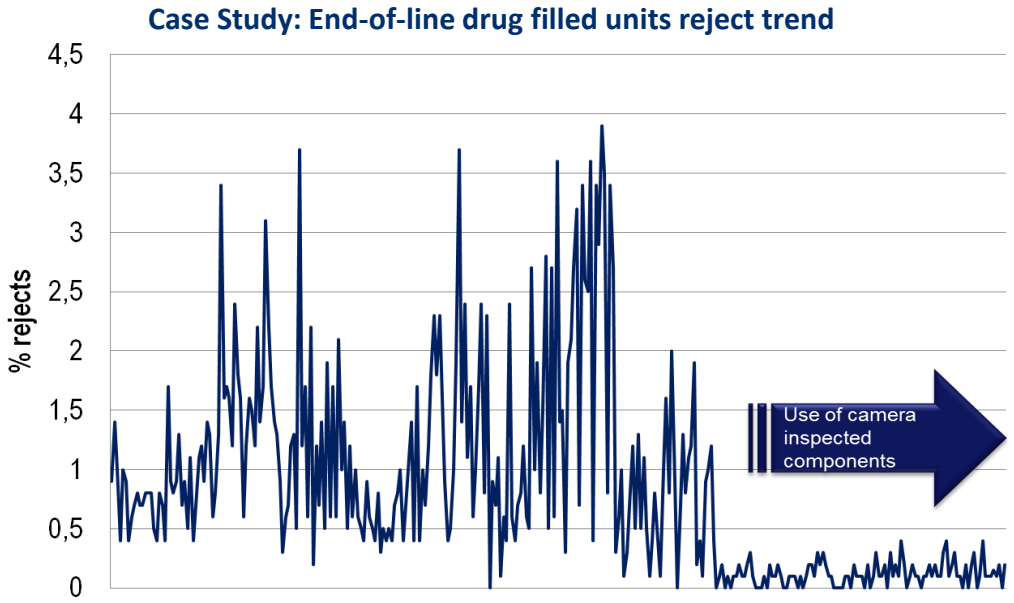
- 100% camera visual inspection for pre-defined defects

# End-of-Line Defect Reduction





100% Camera Inspection of rubber components



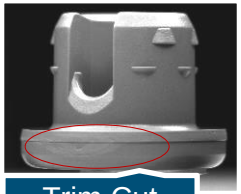




*technical report available – TR 2016-172*

# Automated vision inspection verification: defects examples

Flow Line

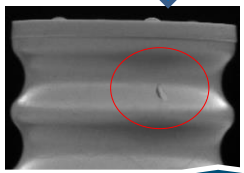


Trim Cut

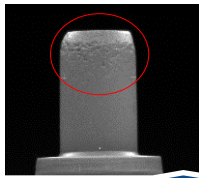
FluroTec™ film wrinkles and torn FT

Manufacturing Defects

Eccentric Trim

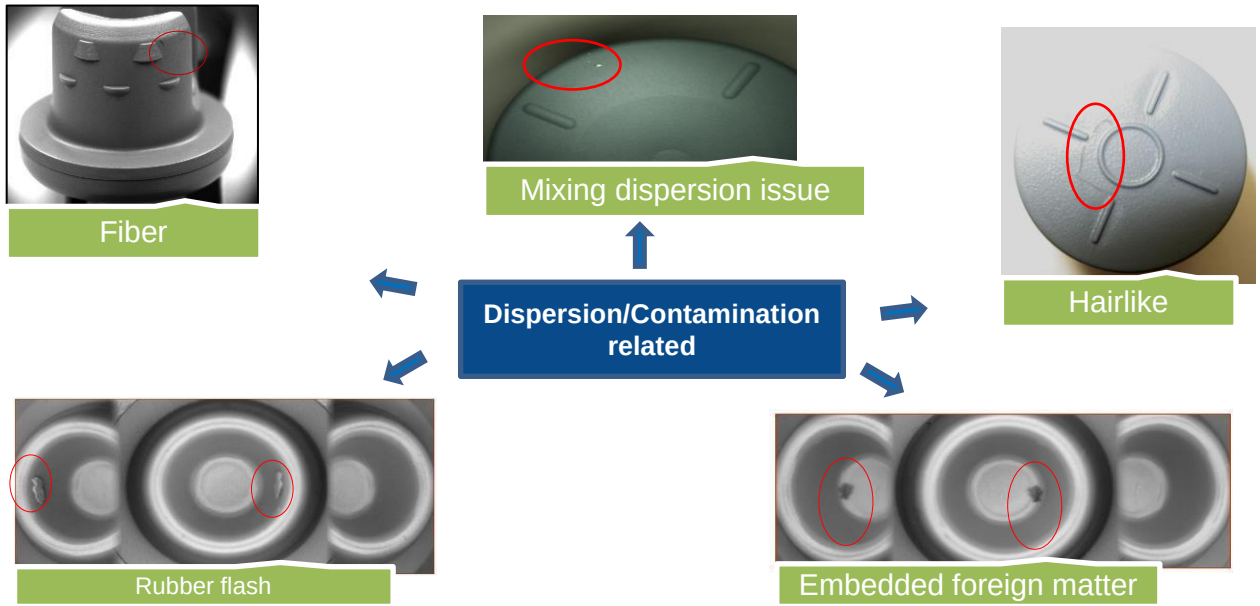


Damaged Cavity



Molding non-fills

# Automated vision inspection verification: defects examples



# Elastomer Manufacturing Process

## Steam sterilization

- Plungers, stoppers and lined seals
- The sterilization process is validated to assure a minimum SAL of $10^{-6}$ and in line with
  - ISO 17665-1 and 17665-2
- Steam processed elastomer formulations exhibit less degradation

## Gamma sterilization

- Plungers
- The sterilization process is validated to assure a minimum SAL of $10^{-6}$ and in line with
  - ISO 11137-1 and ISO 11137-2
- Gamma processing might impact degradation of the elastomeric formulation

**Sterility assurance is reported in the quality certificate coming with every batch**

# Elastomer Manufacturing Process

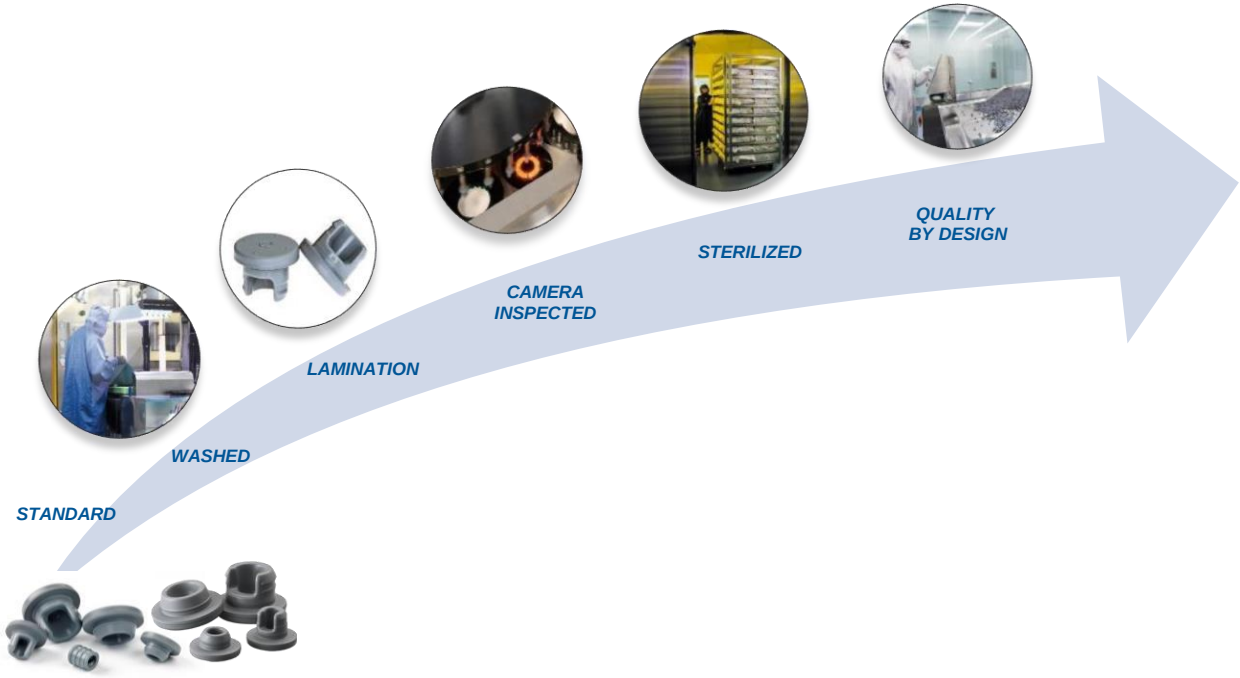
## Pack

- Product is packaged

## Ship

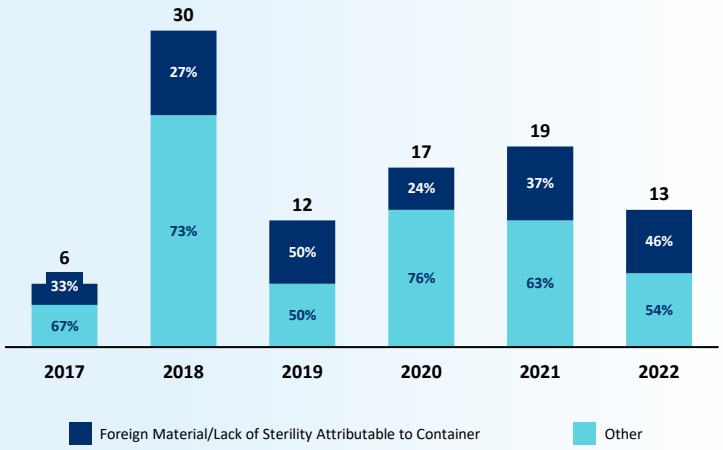
- Prepare for final shipment to the customer

# Differentiated Solutions: Increasing Quality & Inspection



# Particulates and Lack of Sterility Cause Most Product Recalls

## Reason For Injectable Product Recalls[1]




**34% of recalls are due to particulate or lack of sterility attributable to container closure.**

**Regulatory agencies driving for better product quality**

[1] https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls (Accessed September 1, 2022) and https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/recalls-biologics (Accessed October 17, 2022)

# Visible and Subvisible Particle Specification Example

| Attribute | NovaPure® 4023/50 Components | |
|---|---|---|
| Particulate > 5 µm < 10 µm | <100.0 particles / 10 $cm^2$ | |
| Particulate > 10 µm < 25 µm | <60.0 particles / 10 $cm^2$ | |
| Particulate > 25 µm < 50 µm | <8.0 particles / 10 $cm^2$ | |
| 0.9 Particulate > 50 µm < 100 µm | <1.0 particles / 10 $cm^2$ | |
| Particulate > 100 µm | <0.2 particles / 10 $cm^2$ | |
| Fibers > 10 mm | AQL - 0.010 | PPM ≤ 10 |
| Embedded Foreign Matter > 0.2 $mm^2$ | AQL - 0.015 | PPM ≤ 50 |
| Fibers ≥ 2 mm | AQL - 0.040 | PPM ≤ 250 |
| Defects potentially leading to non-sterility | | PPM ≤ 250 |
| Defects impairing processing | | PPM ≤ 250 |
| Fibers ≥ 0.5 mm, < 2.0 mm | AQL - 0.25 | PPM ≤ 2500 |

*Acceptable Quality Level (AQL) is a statistical measurement of the maximum acceptable number of defective goods in a particular sample size*

# Secondary Packaging

# Secondary Packaging - Flexibility for Filling Needs

- Filled bags are offered in ready-to-use (RU) quality by either steam or gamma validated processes
- The ported bag packaging system is qualified to maintain the package integrity and stability of the components throughout the recommended shelf-life period. Verification includes shipping distribution simulation studies.

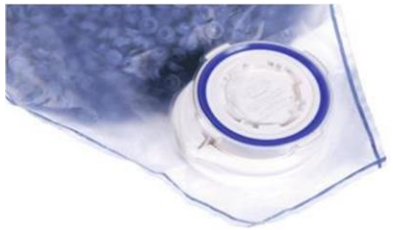
Image courtesy of Bausch+Stroebel. Used with permission

Image courtesy of Bausch+Stroebel. Used with permission



# High-quality packaging materials

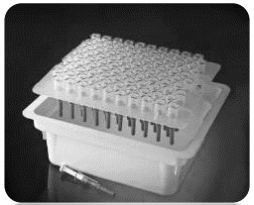
- Reduction of particle load of primary packaging → tighter specification
- Ease of use
- Pinhole resistant – physical – stress
- Plastic cartons & plastic pallets
- Qualified to maintain the package integrity and stability of the components throughout the recommended shelf-life period. Verification includes shipping distribution simulation studies



# Ready-to-Use Packaging Solutions

Bulk Packaging System (Gamma)

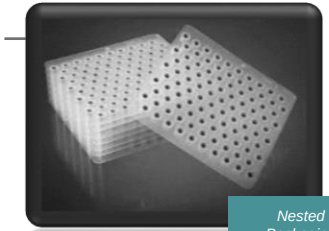
STERILIZABLEBAG™ Packaging System Small Pack or Commercial



Sartorius Stedim Biotech (SSB) 110mm BioSafe™ System (Steam and Gamma)

Getinge-La Calhene (GLC) 190mm DPTE-BetaBag® System (Steam and Gamma)

Not commercially available – Under Development Tub Nested Plungers

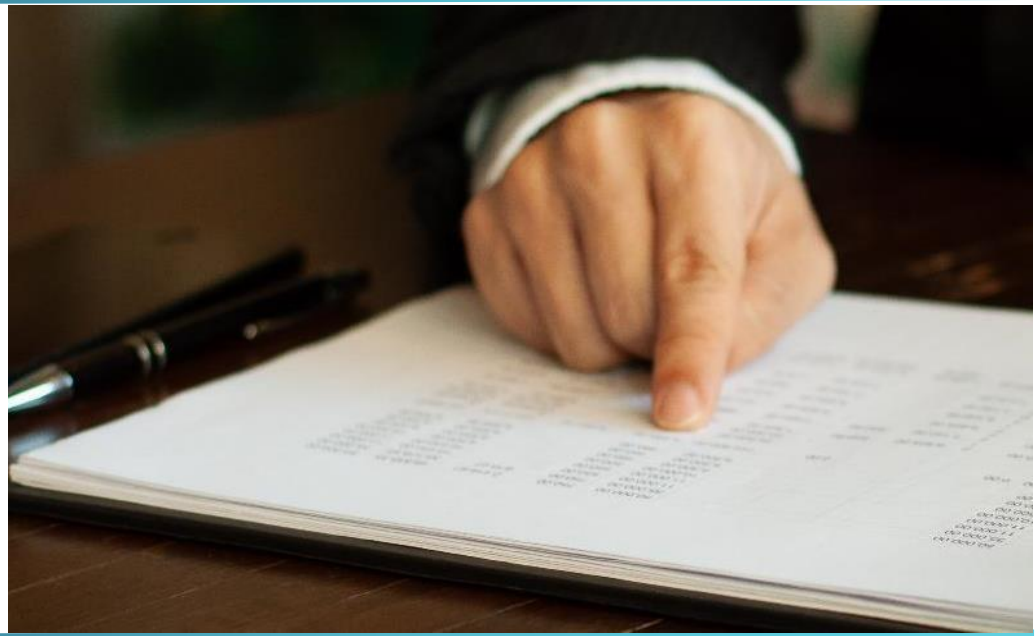


Nested Packaging System (Gamma)




*Please note, not all product offerings are available in these packaging formats*

# Relevant Compendial Chapters and Standards



# Global Comparison of Elastomer Chapters

| Purpose | Paragraph | USP <381> | Ph Eur 3.2.9 | JP 7.03 | YBB |
|---|---|---|---|---|---|
| Introduction | Definition of Elastomer Types | ✓ | ✓ | - | ✓ |
| Identification | e.g. IR, ash test | ✓ | ✓ | ✓ | ✓ |
| Physico-chemical Tests | Appearance of solution, absorbance, etc. .. | ✓ | ✓ | ✓ | ✓ |
| Potential Extractable | Ammonium, Volatile Sulfides | ✓ | ✓ | ✓ | ✓ |
| Functionality Tests* | Fragmentation, self-sealing, … | ✓ | ✓ | - | ✓ |

**functionality tests are moving to USP 382 starting from 2025*

# Introduction to USP <1382> and <382>

## <1382> Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems

- Assist in the functional suitability assessment of elastomeric components as part of packaging / delivery systems
- ISO references
- Sampling plan guidance

## <382> Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems

- Fitness for intended use functional suitability tests and requirements

Released December 2020 with 5-year implementation grace period

# Current <381> versus <382>

## From: USP <381>

**Elastomeric Closures for Injections**

- Functionality Tests
  - Penetrability
  - Fragmentation
  - Self-Sealing Capacity

**Container Closures for Vials and Bottles**

## To: USP <382>

**Elastomeric Component Functional Suitability in Parenteral Product Packaging and Delivery Systems**

- Package/Delivery System Integrity Tests
- Needle and Spike Access Functionality Tests
  - Fragmentation
  - Penetration Force
  - Needle Self-Sealing Capacity
  - Spike Retention and Sealability Capacity
- Plunger Functional Suitability Tests
  - Plunger Break Force and Plunger Glide Force
  - Plunger Seal Integrity
- Tip Cap and Needle Shield Functionality Tests

**System Closures for Vials, Bottles, Blow Fill Seal Containers, Plastics, Cartridges and Syringes**

# Medical Device Regulation

## Background

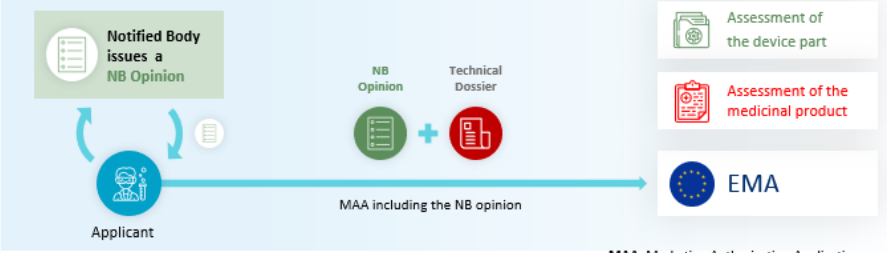
- Revision of Regulation 2017/745 on medical devices (MDR)
- Prefilled Syringe is a medical device
- MAA needs a Notified Body Opinion (NBOp)
- Need to fulfill Annex I General Safety and Performance Requirements (GSPRs)
- GSPRs have been expanded significantly
- Knowledge and Experience of the Container Closure System
- Primary Packaging components are also in scope

## What does this mean for you

- Need to obtain a NBOp
- Information from suppliers is part of this

New Process in EU

## EU filing Process under MDR




**MAA:** Marketing Authorization Application




GSPR: General Safety and Performance Requirements
NBOp: Notified Bodies Opinion
MAA: Marketing Authorization Applicant

# PFS Supportive Documentation

### PDA* Technical Report [TR73-2]

- application of Medical Device Regulations, Annex I Requirements (GSPR's) for Staked Needle
- creation of an Addendum TR73-**2** to facilitate

### Subject Matter Experts

- consists of a group of pharmaceutical companies, glass and rubber component suppliers, consultants (partially with NB background)

### TR 73-2 Content

- is following the structure of the submission file to the NB's

### Release Date & Access

- February 6th 2024
- PDA Technical Report Portal: TR 73-2

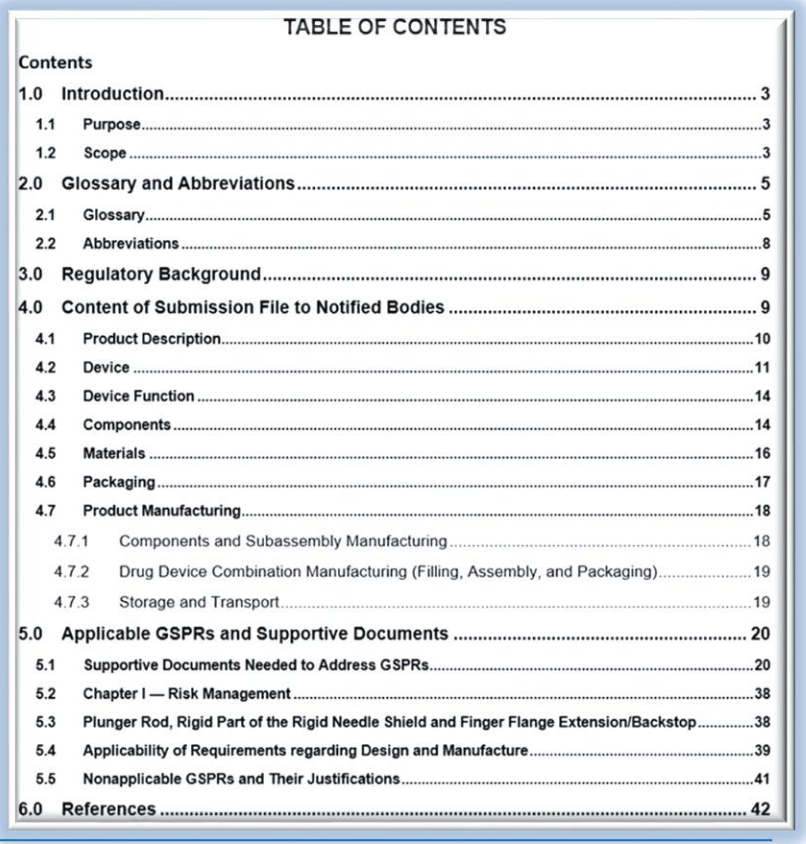


TABLE OF CONTENTS

Contents

# Technical Document Package – best practice


- Compliance Bulletins
- Packaging Configuration
- Biocompatibility
- Component Drawing
- Quality Statements
- West *Exclusive* Documents
- Characteristics
- Performance & Risk Control Strategy

Document includes component technical summaries, quality statements, bulletins and various exclusive documents generated by West in support of Annex I of the European MDR filing

# Thank you very much for your attention!

*Any Thoughts?*
*Any Questions?*

Christa.Jansen-Otten@westpharma.com