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Training and Research Institute

All about Pre-Filled Syringe Systems

From Initial Development to Final Fill Finish

Plungers, Needle Shields, Tip Caps

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Vienna, Austria

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Agenda –
DAY 1

Welcome and Introduction

Overview and Introduction into the Pre-filled Syringe Market

- Overview & trends
- Stakeholders
- User's perspective
- Syringe system overview

Pre-fillable Syringe

- Glass and COP/COC syringes
- Barrel forming and needle mounting
- Washing with WfI
- Siliconization
- Nest and tub, bags
- Sterilization
- Syringe specification: Example
- Regulatory guidelines and technical standards: EU/US/ISO/...

Plunger Stoppers, Needle Shields, Tip Caps

- Materials
- Physical and chemical properties
- Supporting documents
- Design and functionality
- Processing
- Regulatory guidelines and standards

Fill and Finish

- Bag opening
- Tub opening
- Filling
- Stoppering

Hands-on session

- 3 groups, 20 min pers station

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Customer Impact - Demands on Packaging Components are Increasing

Vial Components

PFS Components

Cartridge 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
- 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

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Considerations in Selection of Prefilled Syringe Components

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

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Rubber Material

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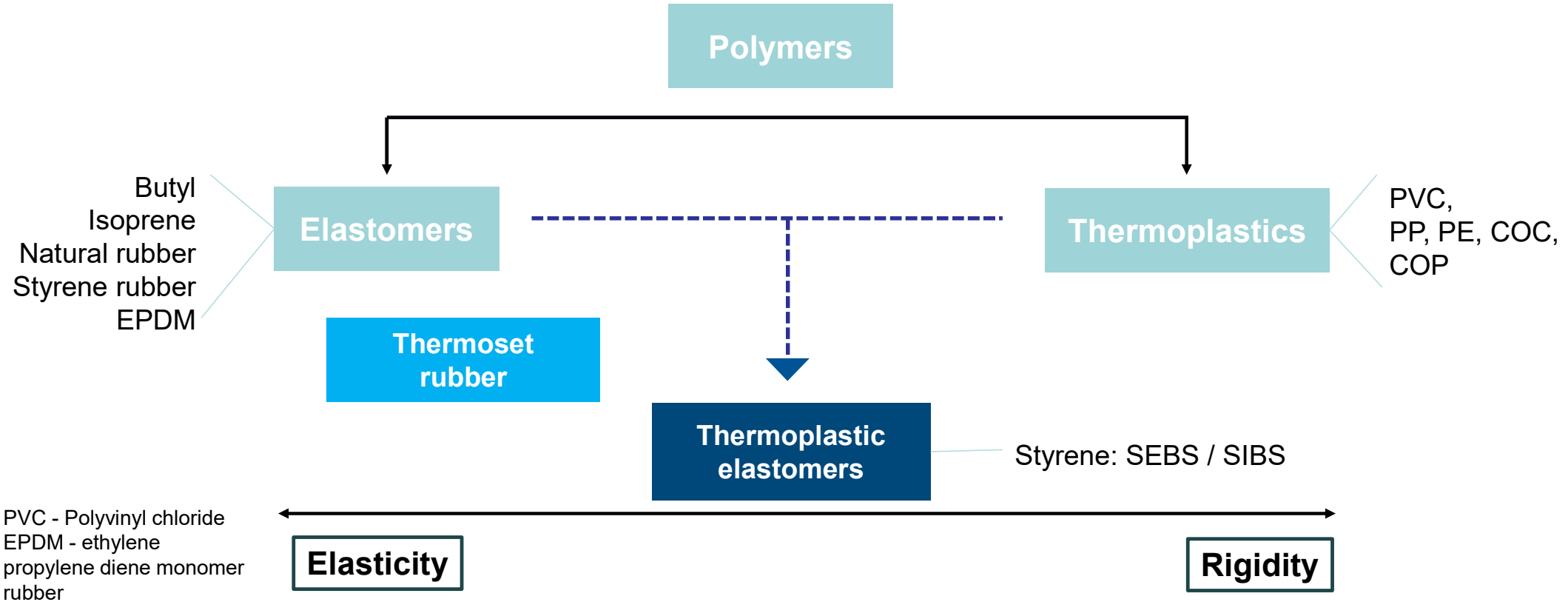
High-quality packaging materials

- 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

Polymers: Overview



PVC - Polyvinyl chloride
EPDM - ethylene propylene diene monomer rubber

Adapted from Deutsche Kautschuk Technologie, Educational Symposium, 2015
Leander Kenens ExxonMobil Chemical Europe Inc. Nürnberg

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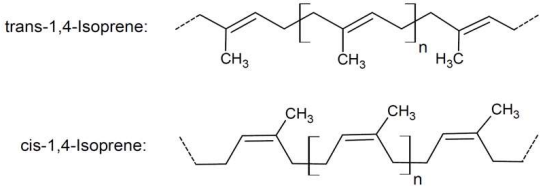
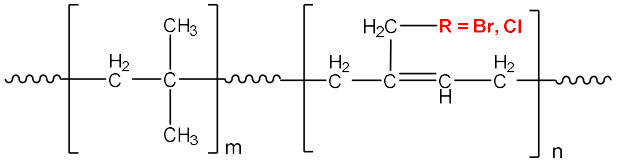
Main Elastomer Types Used for Parenteral Applications

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





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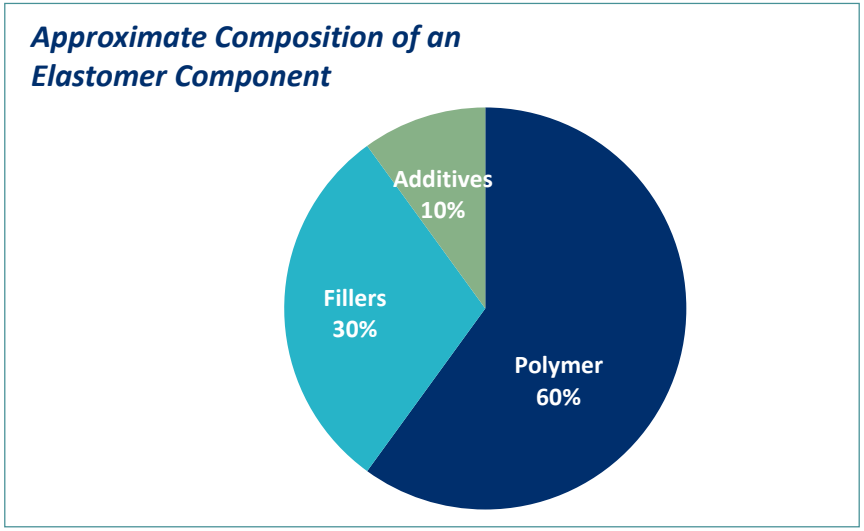
Elastomers Closures General Composition



Additives

can be antioxidants, colorants, plasticizers, acid scavengers, stabilizers, lubricants, crosslinking system agents e.g., activators, others

Fillers

are mainly defining the physical properties

→ **"Ask your supplier for theoretical extractable list"**

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Elastomeric Formulations for Pharmaceutical Use - Properties Butyl/Halobutyl

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

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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

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Potential Issues: Needle Shields and Tip Caps

Ozone Cracking

Accelerated test: Exposure to ozone at a level of 7g/m³, which is 14.000 times higher than the ozone level in the ISO test (500 µg/m3)

Sources: Technical Document: The Effects of Ozone and Various Steriliz. Techniques on Elastomeric Rubber NS & TC. TR 1999/048 Storage considerations for Polyisoprene Formulas; Article: The Effects of Ozone and Various Sterilization Techniques on Elastomeric Rubber Needle Shields and Tip Caps

Material related, visual phenomena's

- Frosting - rubber surface degradation:
  - Rubber component surface discoloration showing eventual cracking and fatigue

Example Frosting

- Blooming:
  - In rubber formulation, "blooming" refers to the phenomenon where certain additives or compounding ingredients, such as softeners, antioxidants, or accelerators, migrate to the surface of the rubber material over time.

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Supporting Documents

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Supporting Documents: Example

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

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Rigid Needle Shields and Tip Cap

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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)

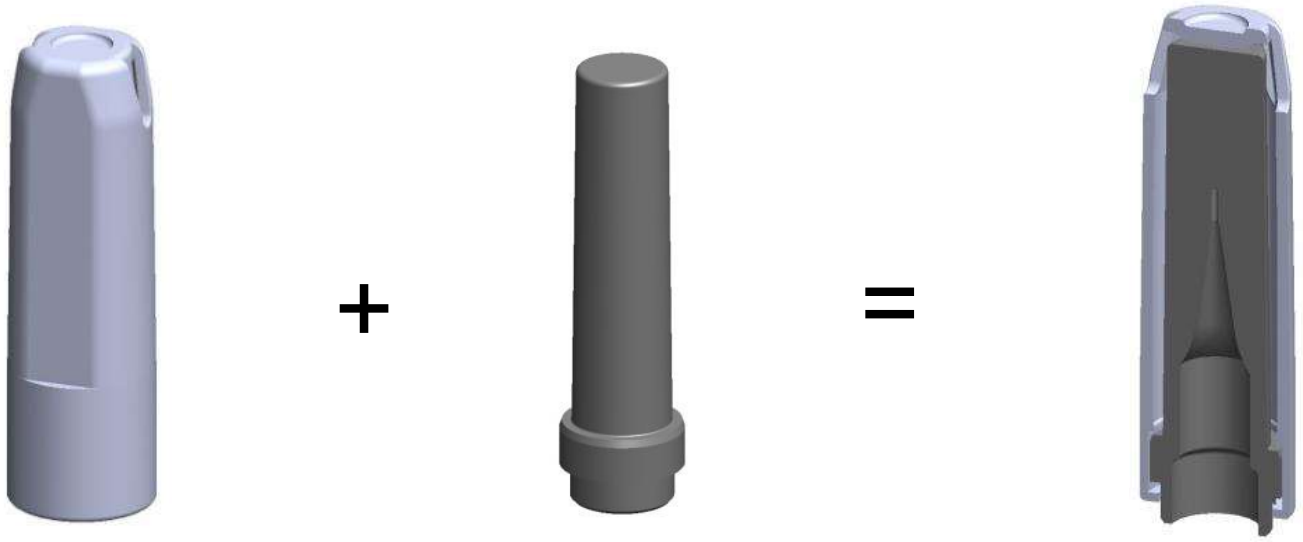
Head design of glass barrel with staked needle

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

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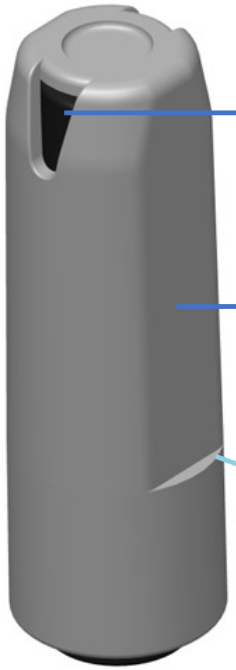
Design examples of Rigid Needle Shields

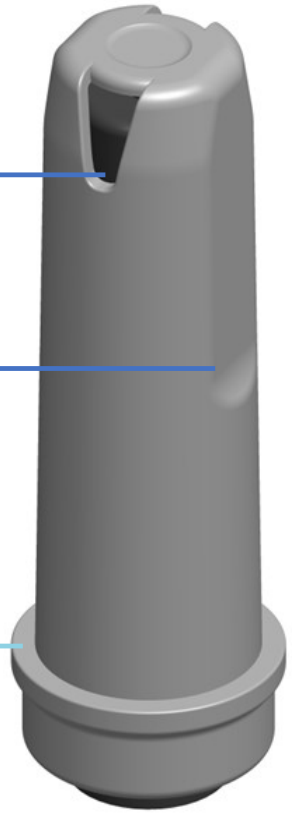


Needle length used for subcutaneous drug injection (into the tissue layer between the skin and the muscle)

Two sterilization windows for gas/vapor penetration

Flattened finger grip zones for good grip and easy shield removal

Shoulder for assembly machines with significant distance from center of gravity enabling high-speed assembly



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

Rigid Needle Shield 1/2” (13mm)

Rigid Needle Shield 5/8” (16mm)

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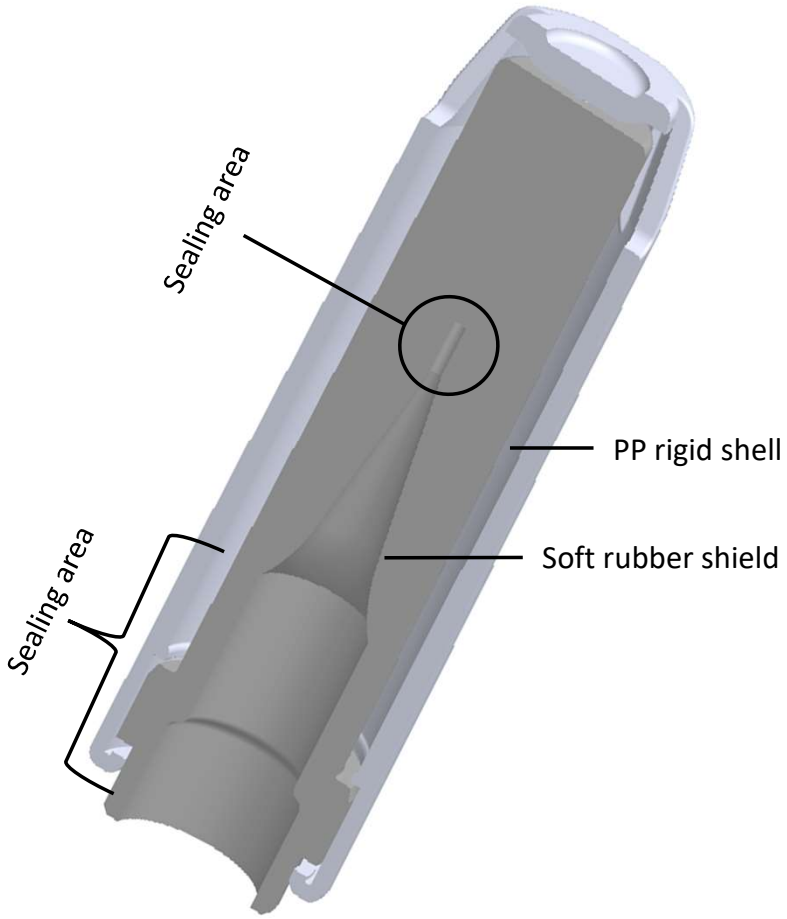
Rigid Needle Shields: Protection & Safety



- Rigid needle shields are recommended closures for prefilled syringes protecting the hypodermic needle tips through de-shielding via an optimized design.
- Combines the sealing properties of soft rubber shields with the rigidity of a polypropylene (PP) shell safeguarding against needle tip damage and deformation
- Manufactured from elastomers especially designed for prefilled syringe applications
- Helps assure container closure integrity through two sealing areas
- Designed to dimensionally fit ISO 11040-4 glass syringes with staked needles
- Designed for existing assembly machine and filling equipment.

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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

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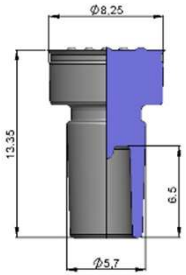
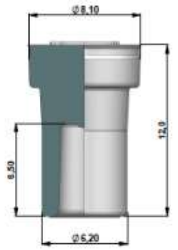
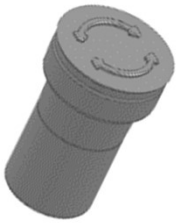
Example of various Tip Caps for Luer and Luer Lock Syringe



Tip Cap to be inserted a rigid plastic cap # 3155

Needs to be assembled to the rigid plastic part





Easy Turn Tip Cap # 3131

Multiple rubber formulation options (halobutyl and synthetic isoprene's)

Mushroom Tip Cap # 3379

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Barrier Film & Coatings

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Surface property enhancements and modifications

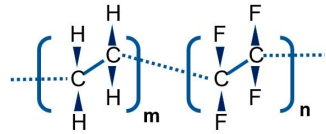
Surfaces of drug product packaging components or delivery systems are often modified to enhance their performance by:

- Reducing the interaction with the drug product
- Slowing down the migration of leachables into the drug product
- Facilitating the delivery (e.g. Easier plunger movement in a syringe)

Barrier film – sheet (e.g., PTFE, ETFE) which is laminated to the primary packaging rubber component during the compression molding process

– - Barrier function, e.g., FluroTec™ film

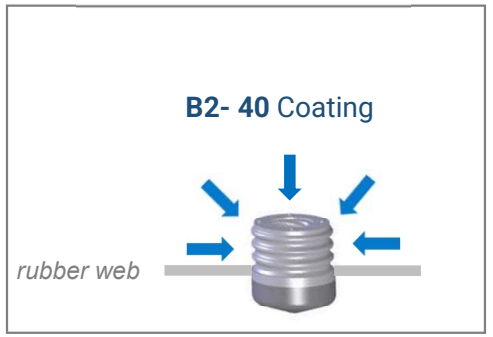
The blue color indicates FluroTec™ film



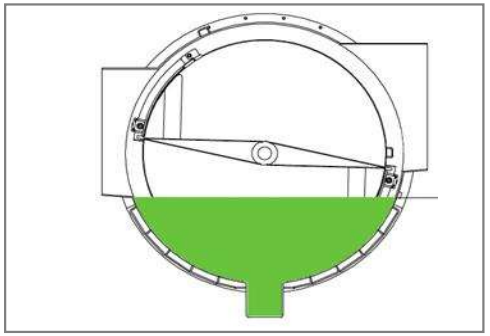
Structure of Poly(ethylene tetrafluoroethylene) (ETFE)

Coating – liquid or vapor that is sprayed, tumbled or vapor deposited onto a primary packaging rubber component, examples for coatings:

- Lubricity, e.g., B2-Coating spayed after molding and prior trimming on the rubber web
- Liquid silicone oil treatment in the final rinse cycle of pharmaceutical washing



Example West: B2 coating is sprayed onto rubber web and then crosslinked in a UV tunnel

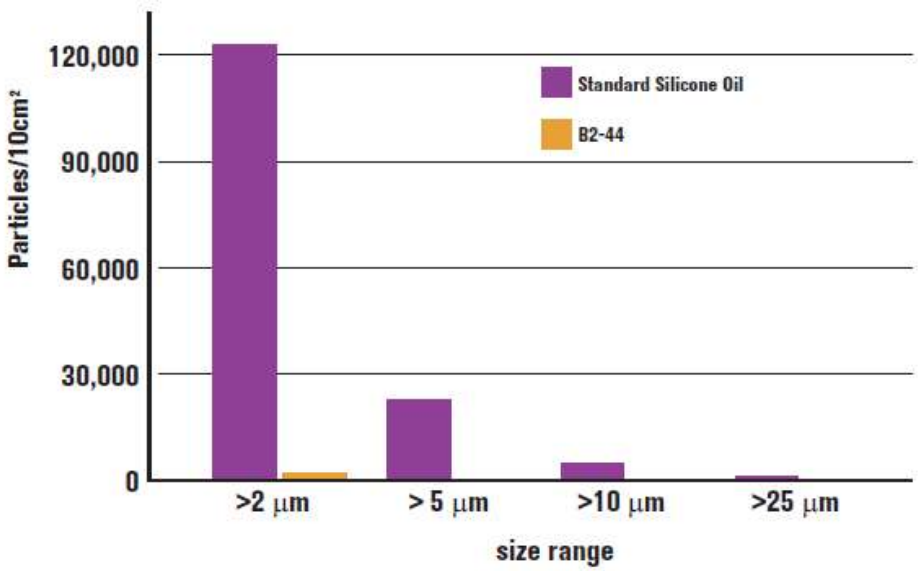


Siliconization : washing, emulsifying with silicone oil Polydimethylsiloxane DuPont™ Liveo™ 360 Medical Fluid]; rinsing, drying

Lubricity coating

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

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



FluroTec™ film:

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

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

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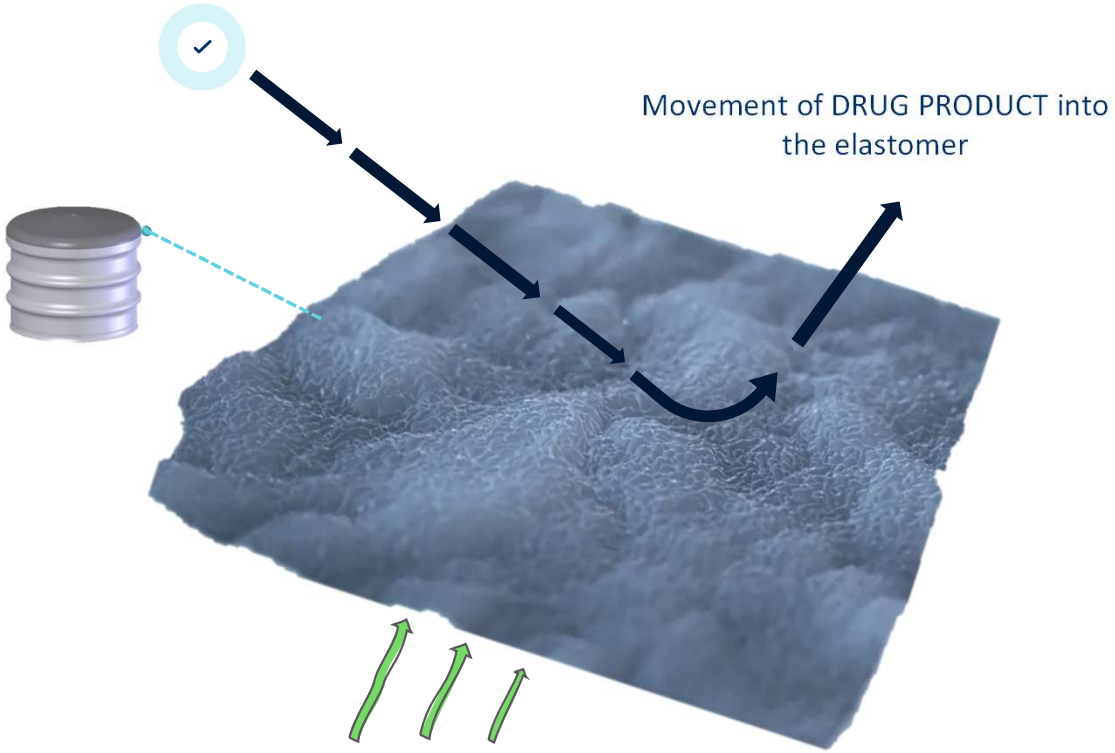
Film has Low Levels of Interactions

ETFE acting as a barrier reduces transport in two directions



FluroTec™ film:

1. is based on poly(ethylene) tetrafluoroethylene
2. is translucent, smooth & chemically inert
3. is adherent to brominated elastomer
4. is both steam & gamma sterilizable
5. is resistant to degradation
6. blocks chemical migrations
7. has no reactive functional groups

FluroTec™ film has very low levels of chemical interactions

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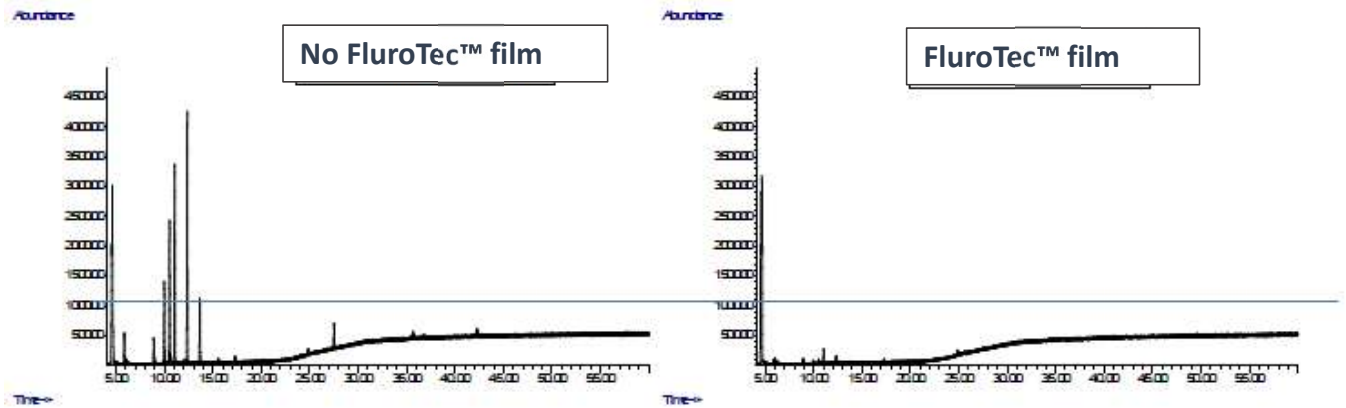
Fluoropolymer film coating Significantly Reduce Leachables



- 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)

West Technical Report 2019/210 FluroTec® Protecting Drug Product Quality Safety

Plungers

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Components are a critical consideration when transitioning from a vial to a prefilled syringe

Vials

NovaPure® vial Stopper

NovaPure® Syringe Plungers

Prefilled Syringes

The differences in components have direct implications for the drug product's Stability, Shelf life & Overall performance

Seamless Transition from Vial Stoppers to PFS Plunger format

The Same:

- ✓ Rubber Formulation
- ✓ B2-Coating
- ✓ Fluoropolymer Film lamination
- ✓ Manufacturing Technology
- ✓ Quality

Documentation to support multiple drug use case and applications are available.

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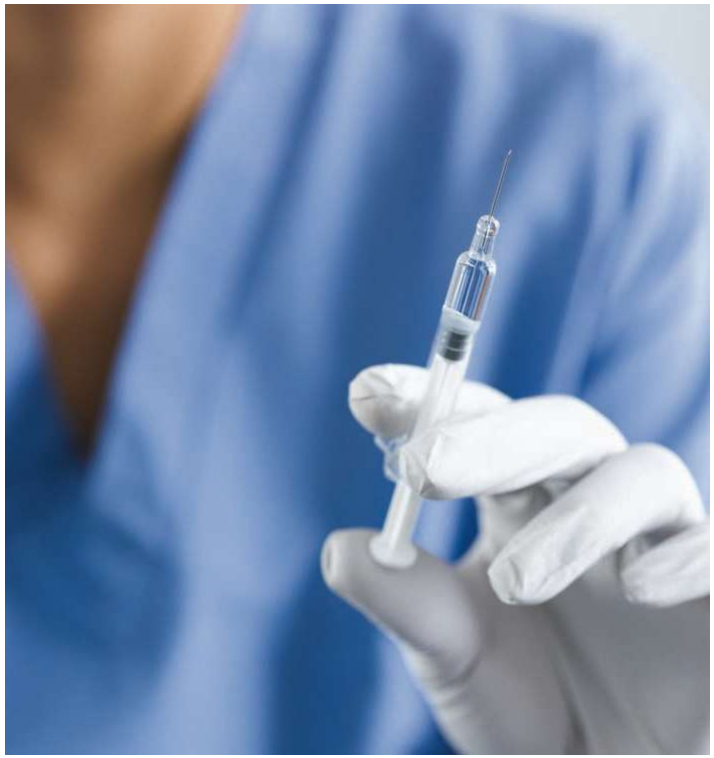
Main requirements for Prefillable Syringes Plungers

- Delivers a smooth injection profile [break loose & glide forces profile]
- Maintains Container Closure Integrity
- Well performance on fill-finish equipment
- Compatibility with the drug product
- Good compression set properties
- Fit for use with self-injection administration systems
- Compatible with gamma-irradiation and final steam sterilization treatment
- Compatible with glass and plastic (COC/COP) barrels
- Low Part-to-Part Variability



ISO 11040-5 for Plunger Stoppers

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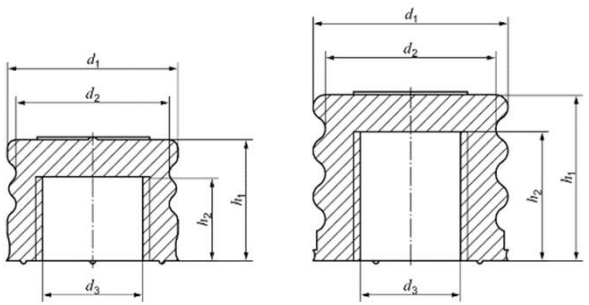

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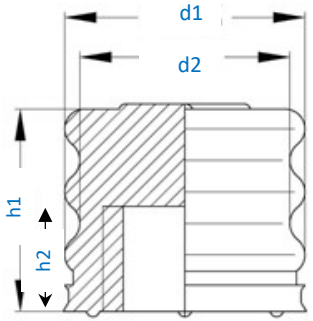
2012-01-15

b) Plunger stopper with thread (PST)

Prefilled syringes –
Part 5:
Plunger stoppers for injectables

Nominal ID	Nominal Volume	Type	d1		d2		h1		h2	
d2	ml		nom.	tol.	nom.	tol.	nom.	tol.	nom.	tol.
4,65±0,1	*0,5*	*PSL*	*5,2 to 5,3*		*4,1 to 4,2*		*6,85 to 7,0*		*5,3*	*±0,35*
6,35±0,1	*1 (long)*		*6,8 to 7*		*5,9 to 6*		*7,65 to 7,85*		*4,5*	
8,65±0,2	*1 to 3*		*9,05 to 9,25*	*±0,1*	*7,6 to 8*		*7,7 to 7,85*		*4,0*	
11,85±0,2	*5*	*PST*	*12,05 to 12,7*		*10,5 to 11,15*	*± 0,15*	*8,5*	*±0,4*	*6,0*	*±0,3*
10,14±0,2	*10*		*15 to 15,3*		*13,5 to 13,75*		*8,5 to 10*		*6 to 6,2*	
19,05±0,2	*20*		*19,9 to 20,1*	*±0,15*	*10,7*		*13,45 to 13,50*		*7*	



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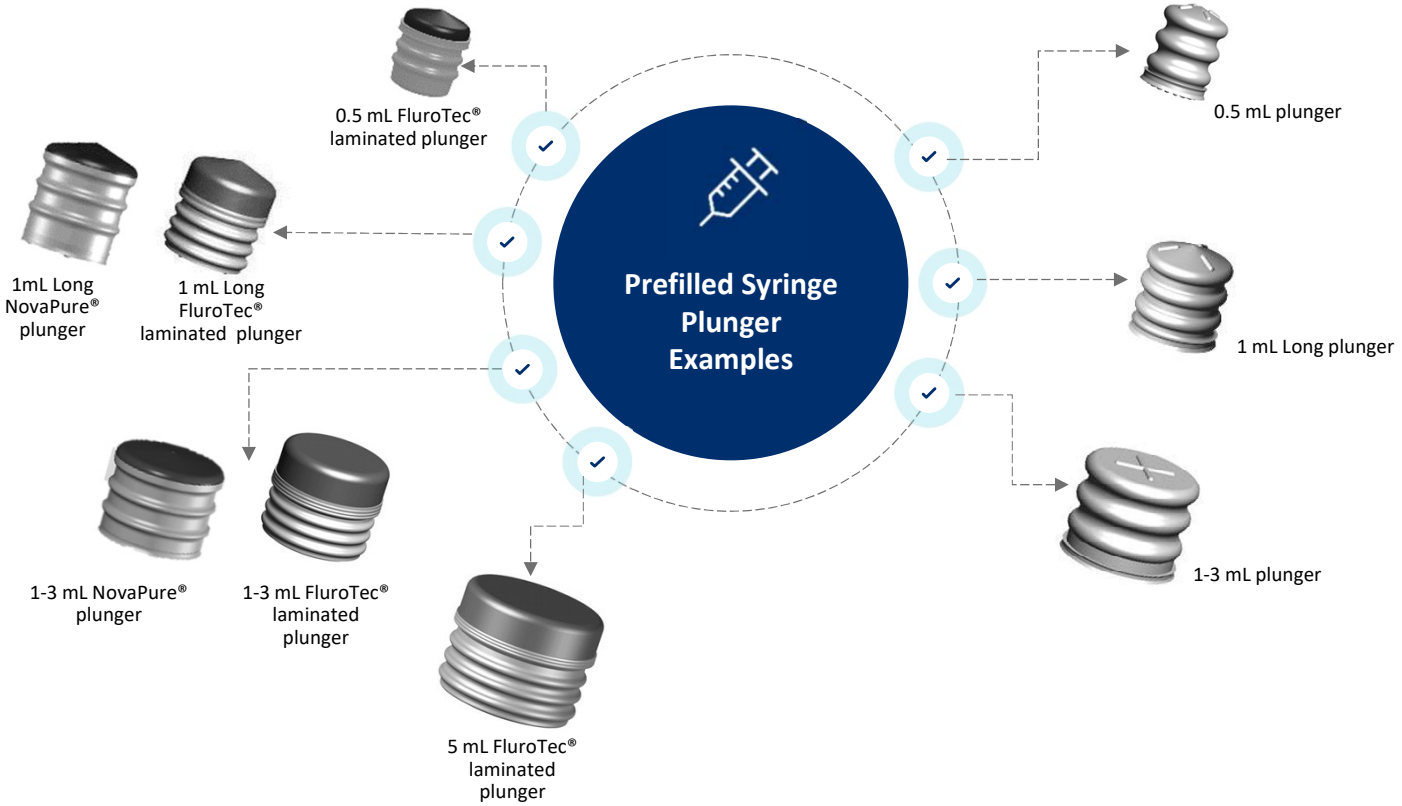
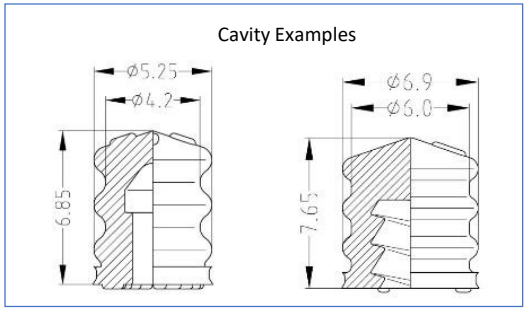
Example of Prefillable Syringe Plungers Portfolio at West

laminated plungers

none laminated plungers





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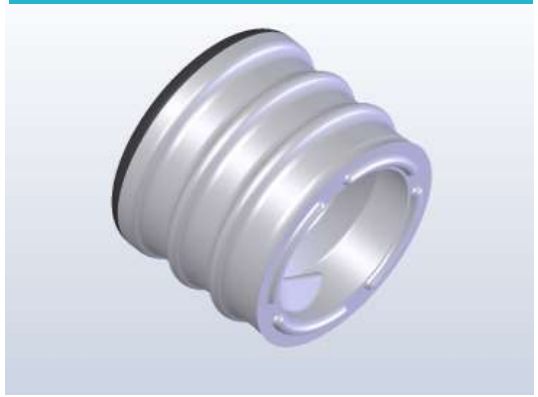
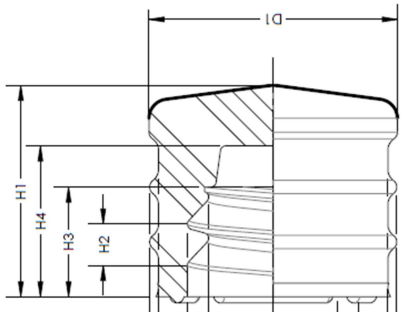
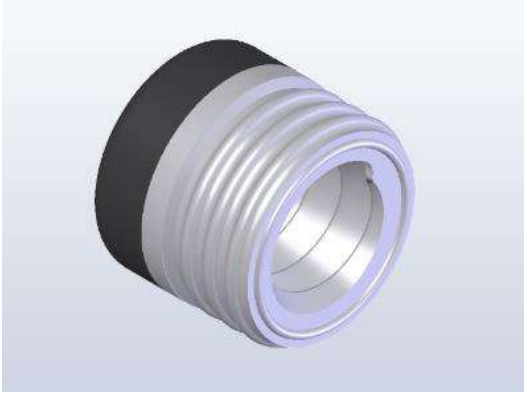
Examples of Prefilled Syringe plunger designs

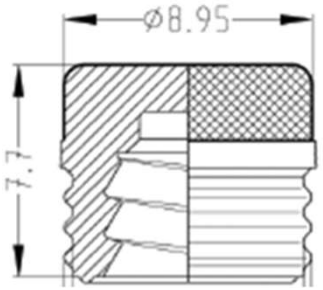
1-3 mL NovaPure® Plunger



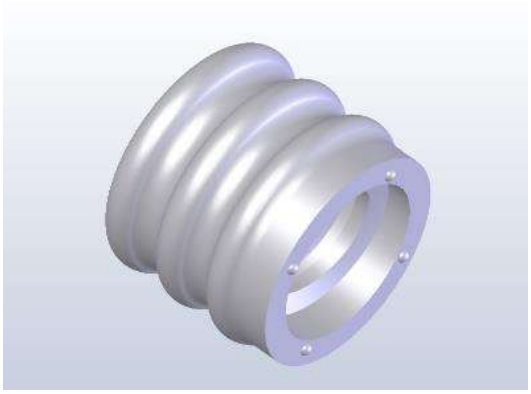


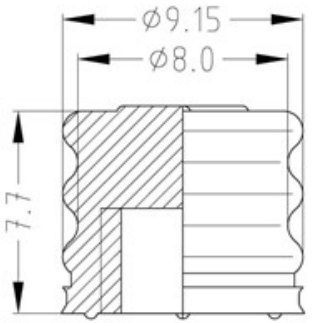
1-3 ml FluroTec® film laminated Plunger





1-3 ml Plunger

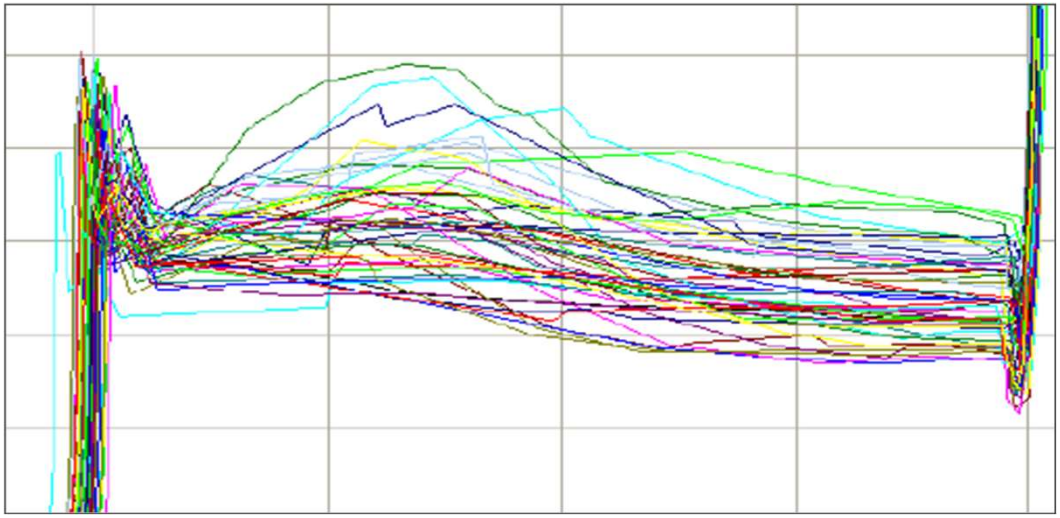




Manual PFS to Auto-injector Challenges

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

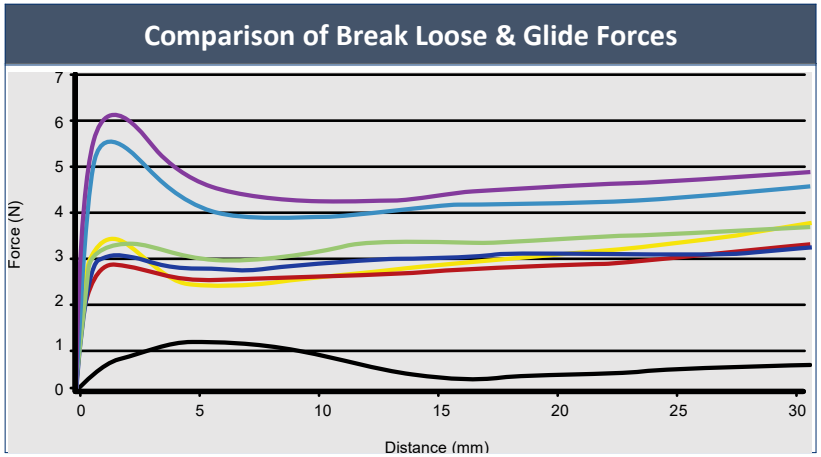
Auto-injector Reliability Risks

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

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

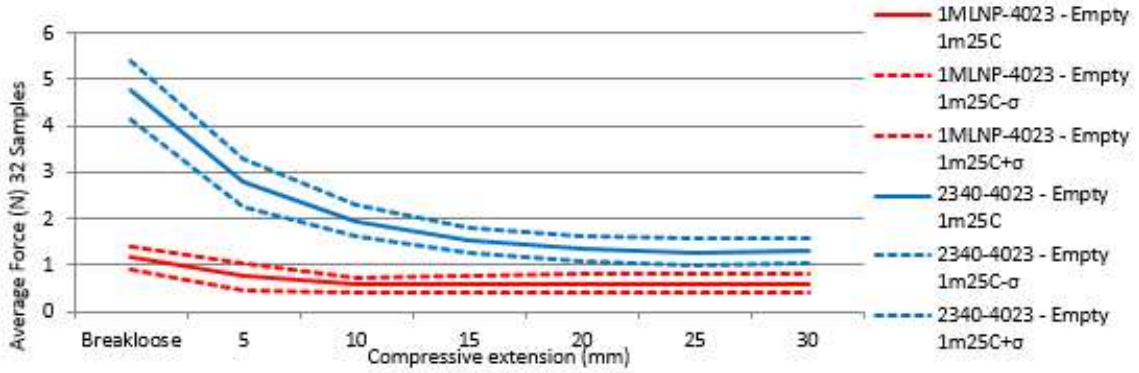
Critical design factors must be considered, especially functional compatibility

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

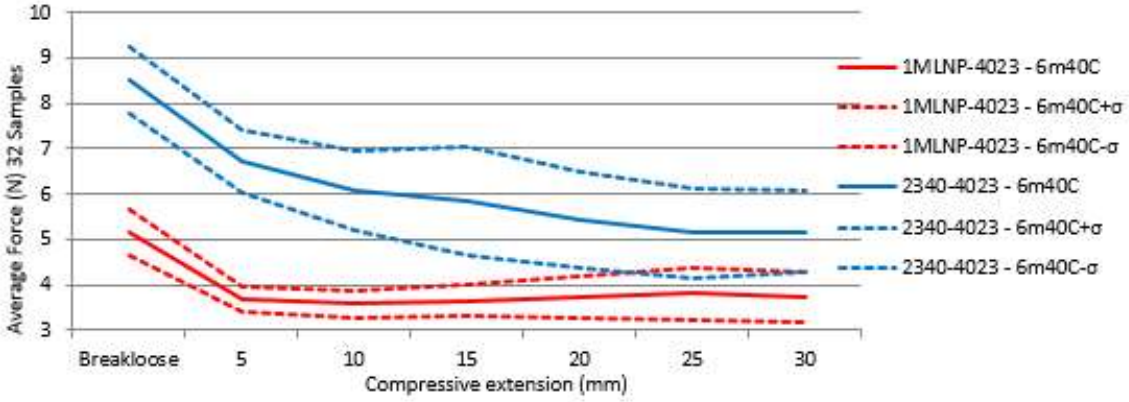


Performance: two different laminated 1 ml long Plungers

Empty



Water Filled



Source: West TR 2013/147

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Performance example with different 1-3 ml Plungers, syringes filled with different viscosities

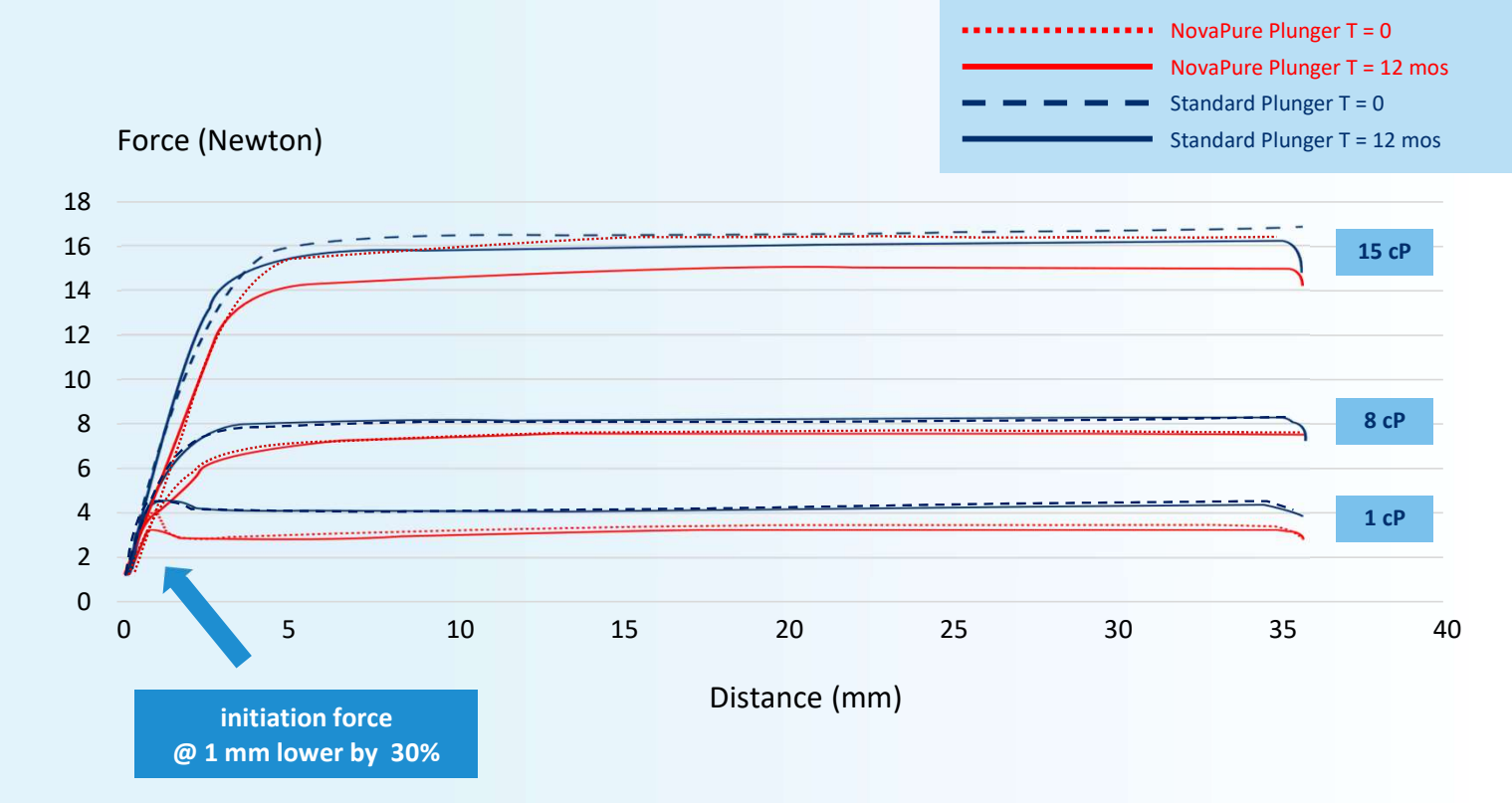
Curves represent averages of 30 plots

New generation 1-3ml Plungers (dotted red lines) demonstrated a **30% lower initiation force @ 1 mm**

New generation 1-3ml Plungers show consistently better Initiation / Sustaining Forces at all three viscosities

Overall, less variability over time with new generation plungers especially for high viscosities

Initiation / Sustaining Forces with new 1-3mL vs. Standard Plungers



Performance of NovaPure® Plungers for Syringes in Autoinjector Systems. A. Kim, L. Ho, T. Haarlander, P. McAndrew (2024)

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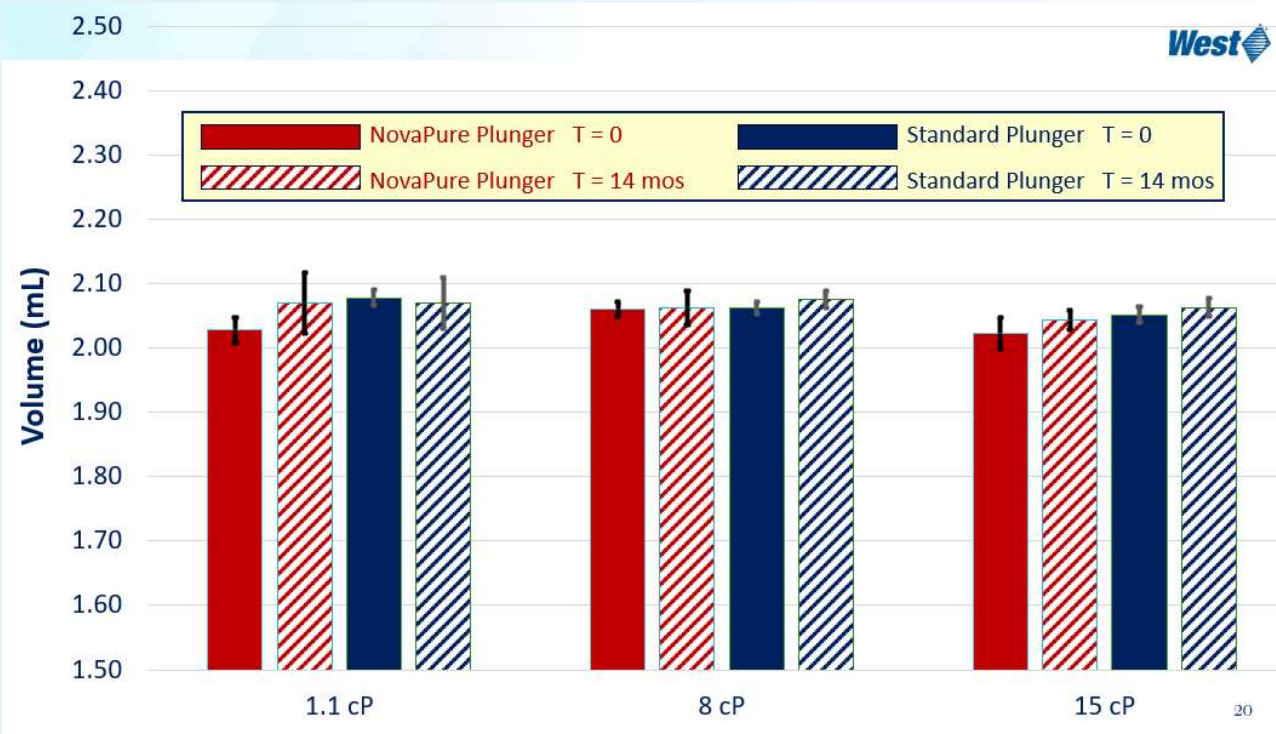
Accuracy of Volume Delivered & Precision

New generation Plungers demonstrated equivalent accuracy (in terms of volume delivered) and precision compared to standard plungers

Results of delivered volume and precision were consistent at all three viscosities

Accurate dosing volume and precision is key to patient safety

Volume Delivered & Precision : New generation 1-3mL vs. Standard Plungers



Performance of NovaPure® Plungers for Syringes in Autoinjector Systems. A. Kim, L. Ho, T. Haarlander, P. McAndrew (2024)

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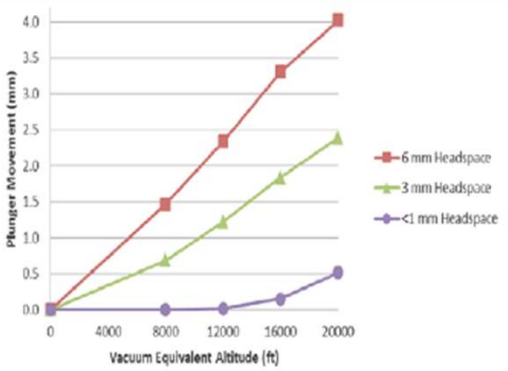
Evaluation of Plunger Movement During Transit Conditions-Example

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

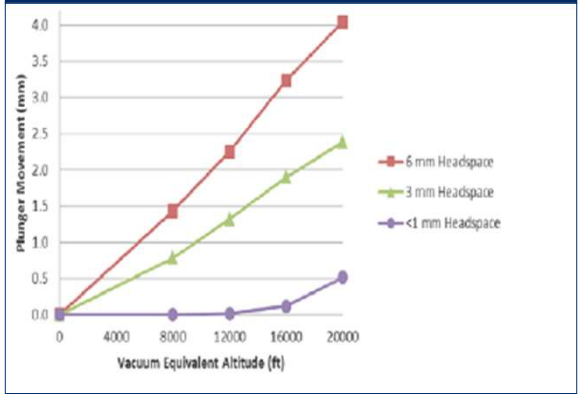
- Headspace Values
  - 6 mm (exaggerated vent-tube placement)
  - 3 mm (typical vent-tube placement)
  - <1 mm (typical vacuum placement)

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



- 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

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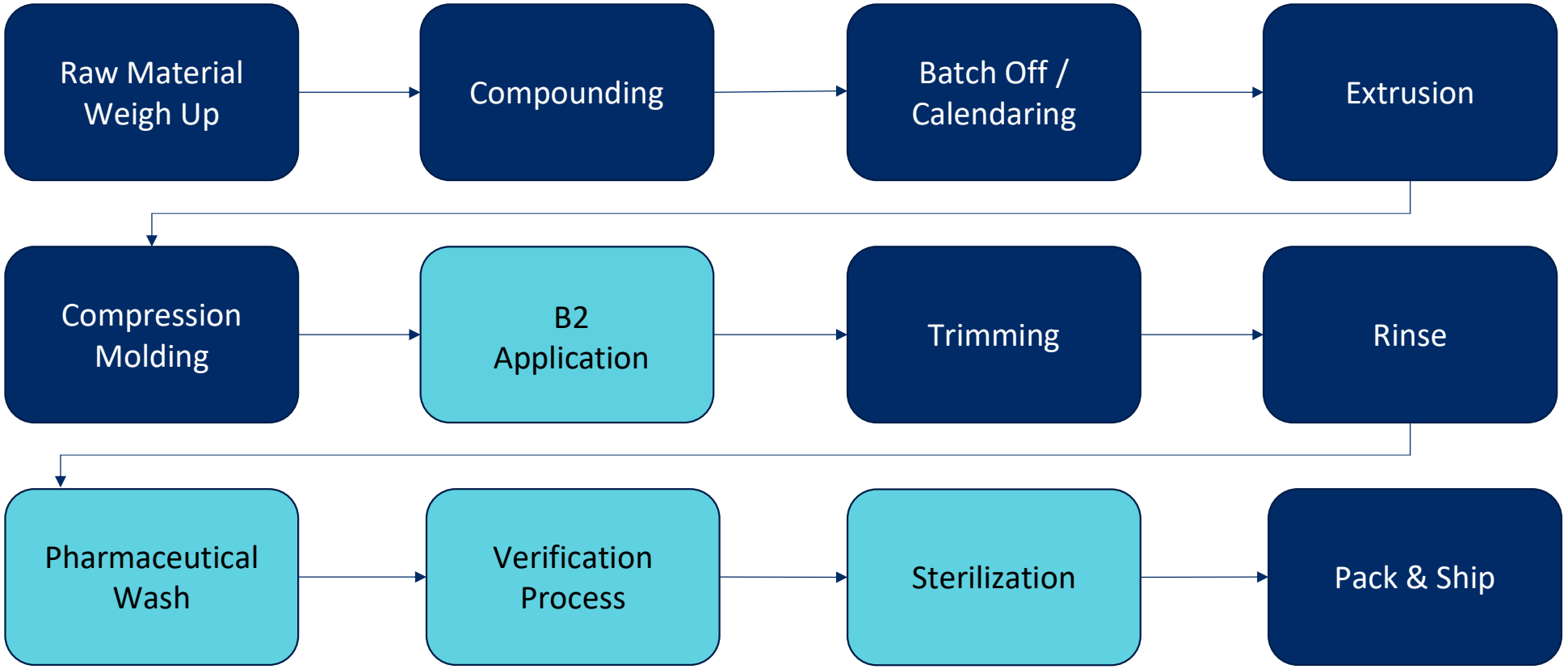
Process Flow Map: Example



Elastomer Manufacturing Process

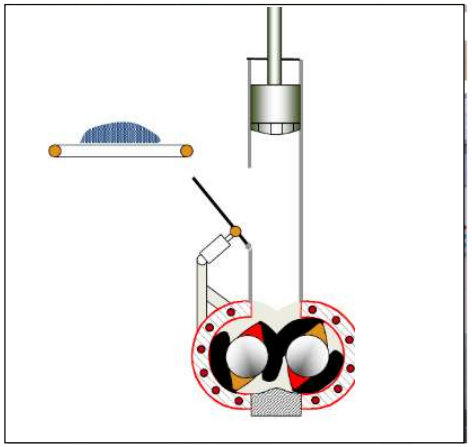
Raw Material Weigh Up

- 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

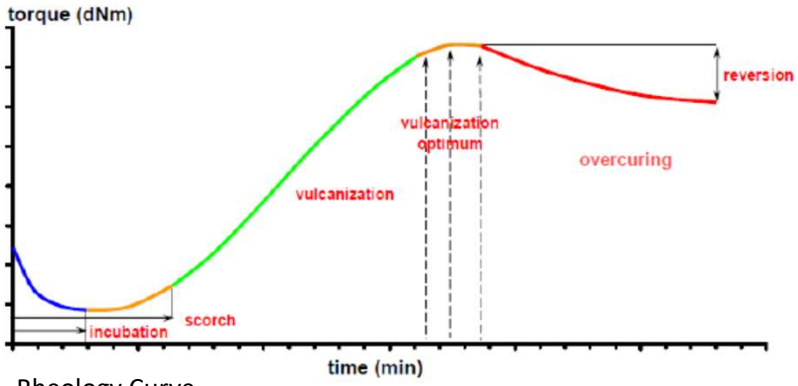


Open Mill

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
Calendaring & Extrusion

Batch Off or Calendaring

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

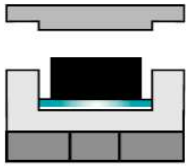
Extrusion (Calendar/Dispersion Enhancement System)

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

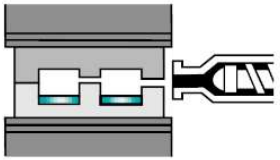
Elastomer Manufacturing Technologies

Different 'shapes' need different molding technology:

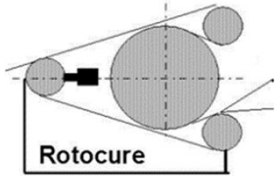
- Compression Molding (CM)
  e.g. Plungers, stoppers, disk
  .



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

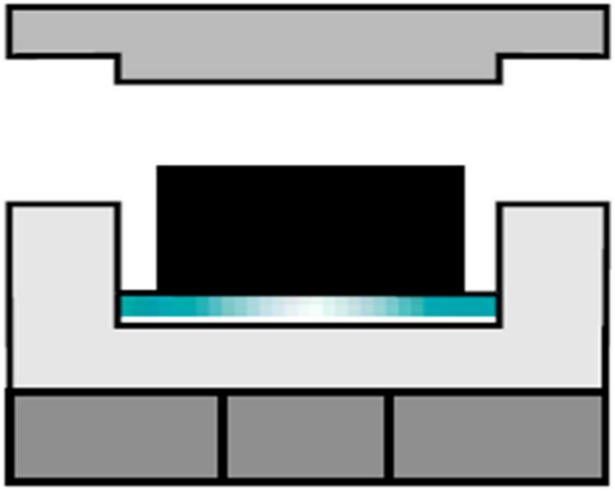


- Rotocure (Sheeting Material)
  e.g. Lined seals…



Compression Molding

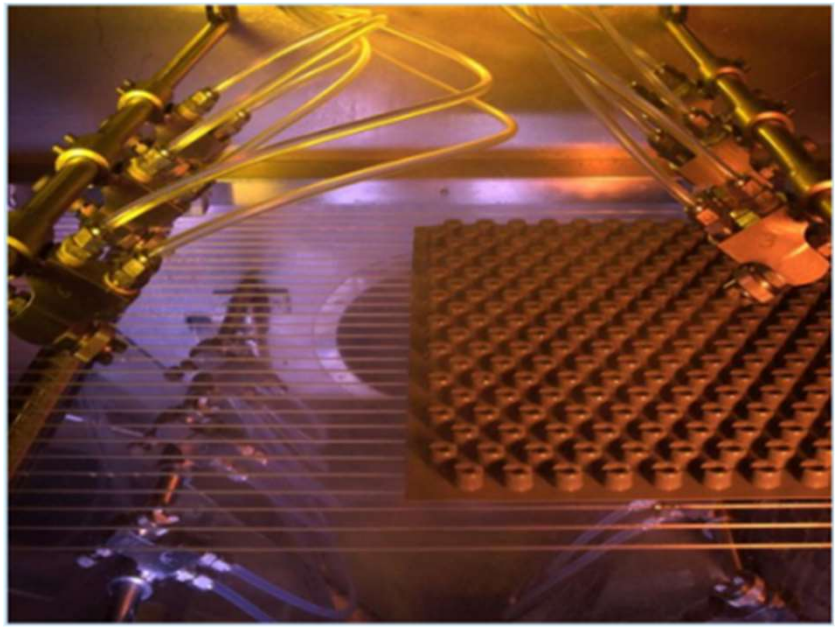
- Mechanical force creates the shape
- Heat forms crosslinks and imparts final physical properties to the part



Elastomer Manufacturing Process Coating and Trimming

B2-Coating Application

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



Trimming

- Parts are trimmed from the molded panels

Elastomer Manufacturing Proce
Rising and Washing

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

Elastomer Manufacturing Process
Automated vision inspection verification

- Verification Process
- 100% camera visual inspection for pre-defined defects

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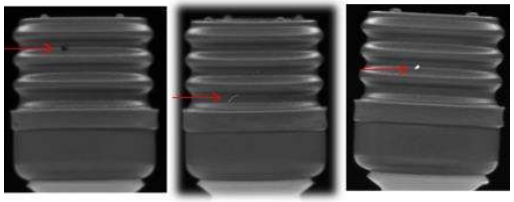
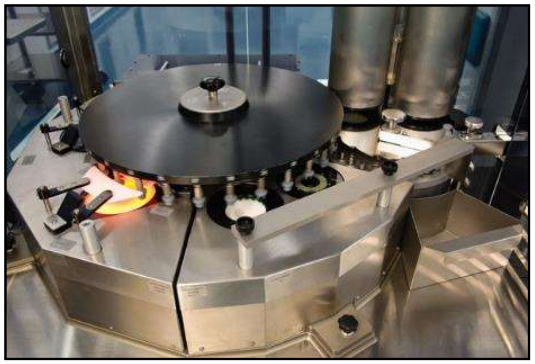
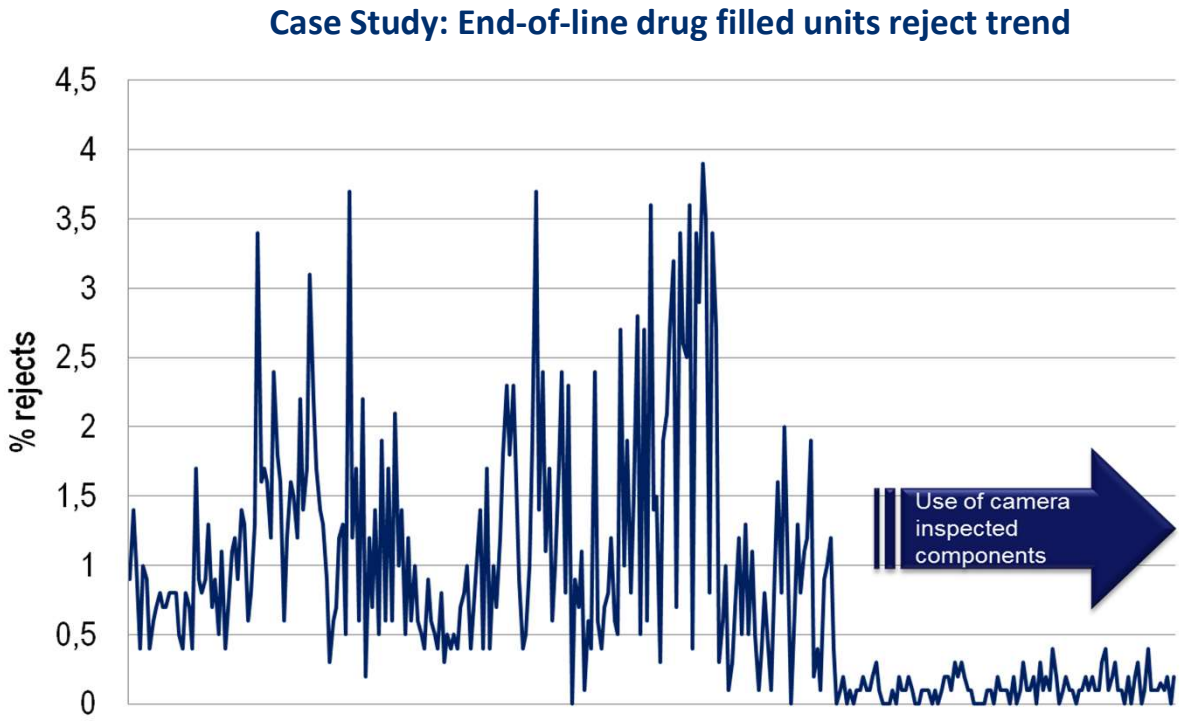
Elastomer Manufacturing Process Verification
Automated vision inspection verification





100% Camera Inspection of rubber components



technical report available – TR 2016-172

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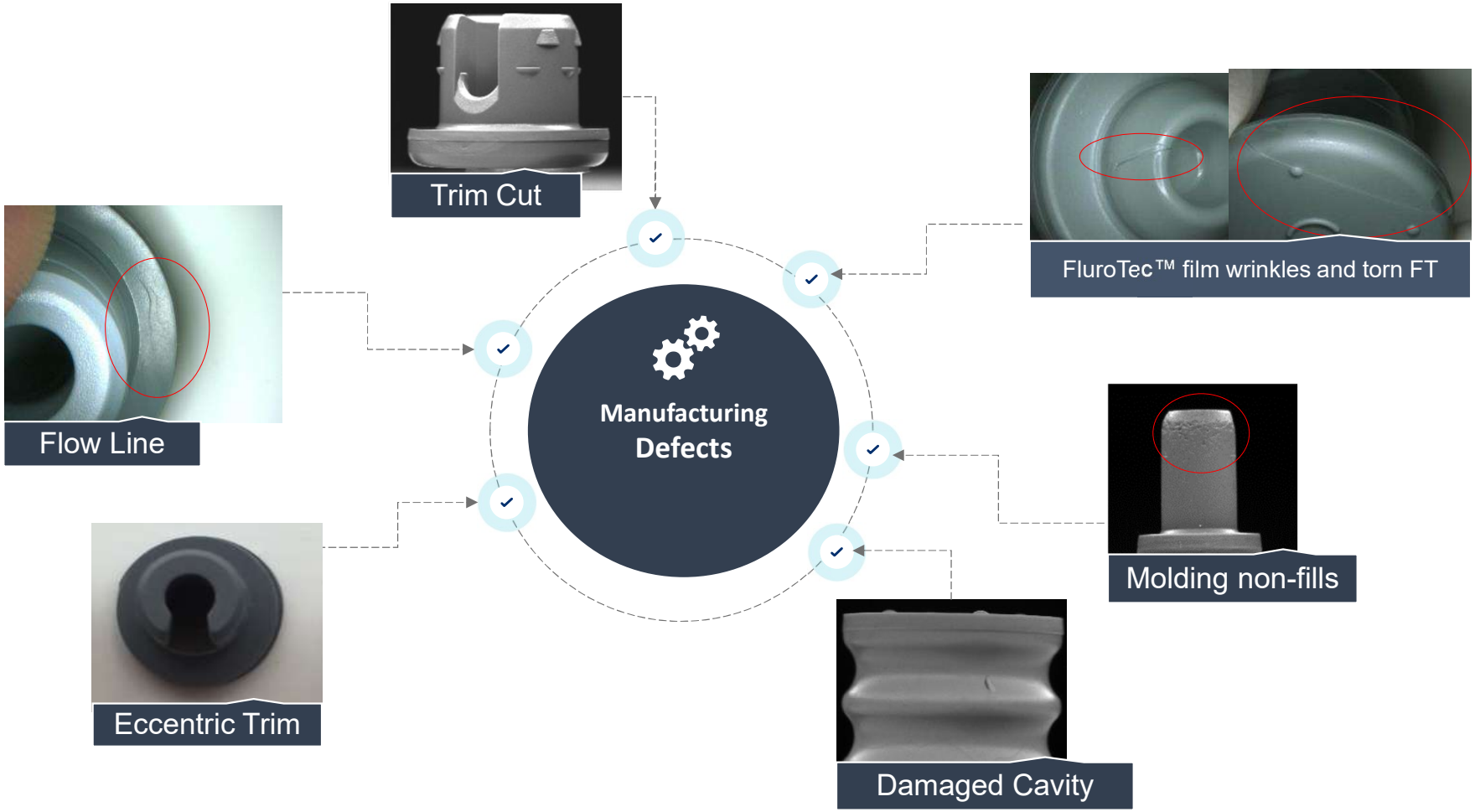
Automated vision inspection verification: defects examples



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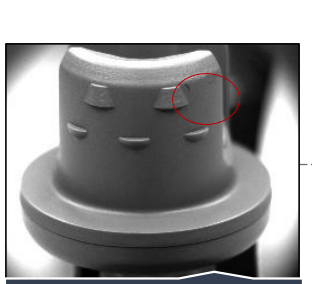
Automated vision inspection verification: defects examples



Fiber

Mixing dispersion issue

Manufacturing Defects

Rubber flash

Hairlike

Embedded foreign matter

Elastomer Manufacturing Process Sterilization

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

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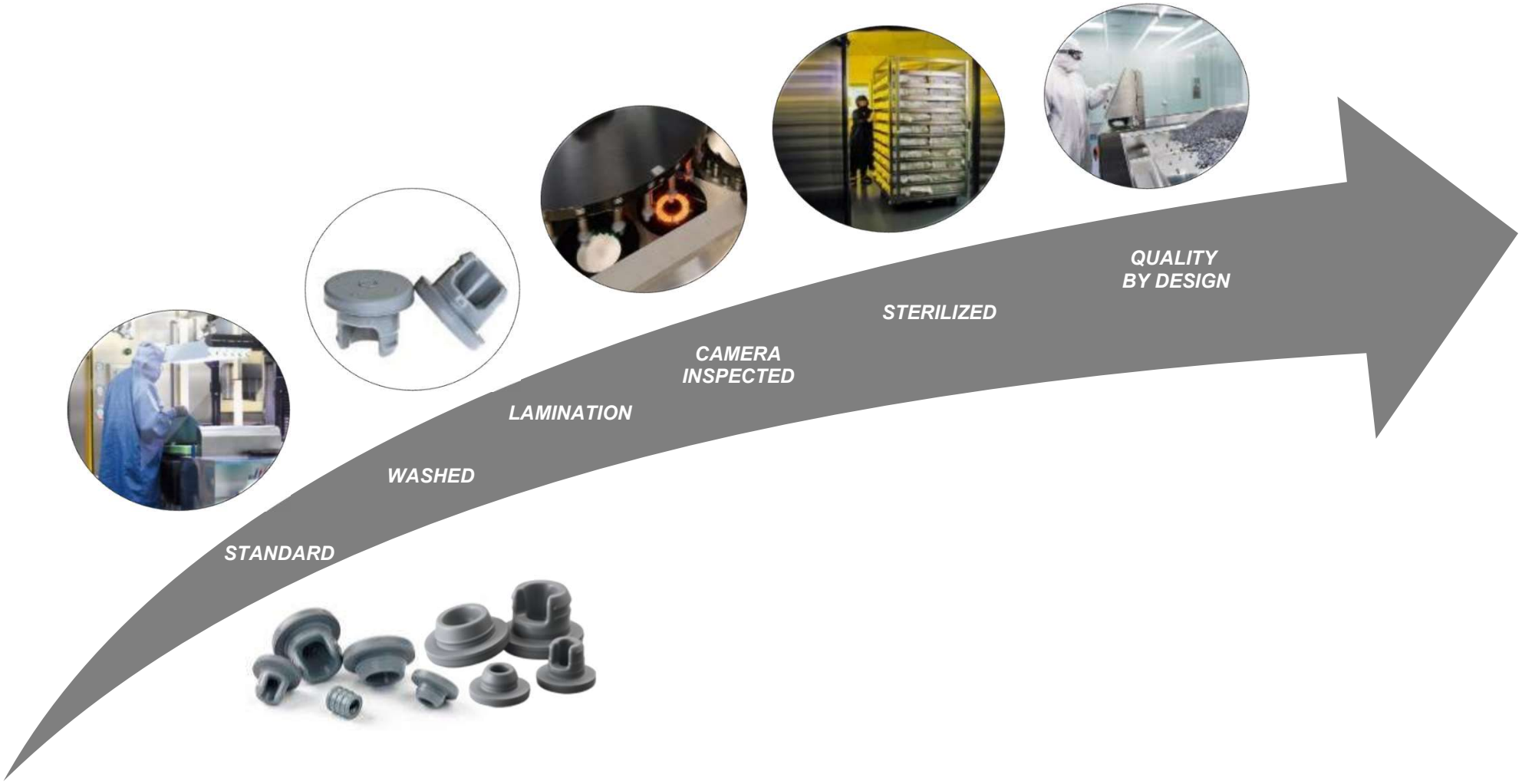
Differentiated Solutions: Increasing Quality & Inspection



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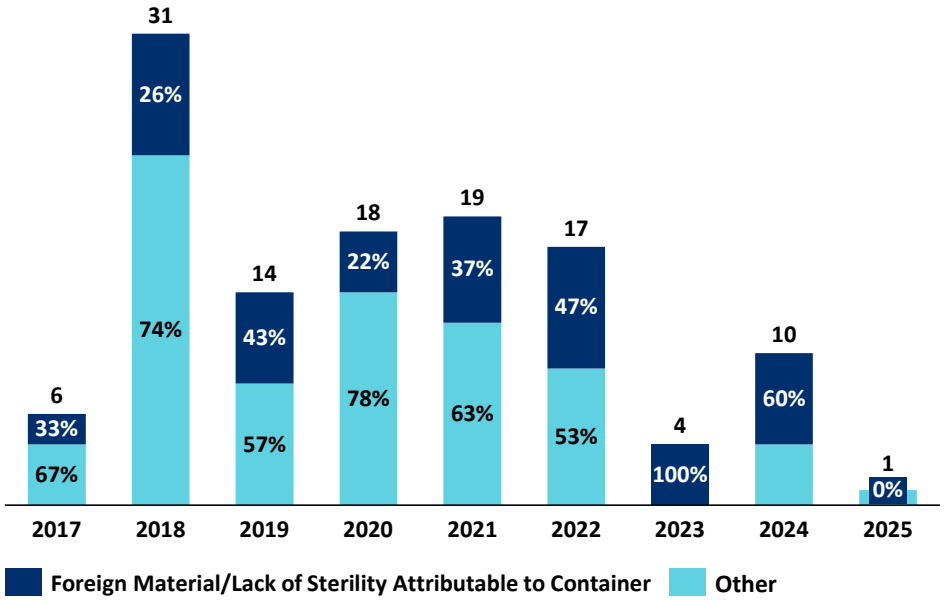
Particulates and Lack of Sterility Lead to Product Recalls

Reason For Injectable Product Recalls[1]



38%
of US FDA injectable drug recalls are due to particulate or lack of sterility attributable to container closure.

United States Pharmacopeia	"Every lot of all parenteral preparations is essentially free from visible particulates"
Japanese Pharmacopoeia	*Injections … must be free from readily detectable foreign insoluble matters"* **Source :** *JP 17, Chapter 6.06*
European Pharmacopoeia	*Solutions for injection…are clear and practically free from particles"* **Source :** *EP 10.0, Section 7*
Chinese Pharmacopoeia	*"Injections, Ophthalmic Solutions and sterile APIs should be free of visible foreign matter* **Source :** *ChP 2020, Chapter 0904*
United States FDA	*Manufacturers should control such [intrinsic] particulates before the actual manufacturing process through careful selection and quality control of components, containers and closures, packaging materials* *"container closure screening during development is critical to reduce the formation of product-related intrinsic particulates"* **Source :** *FDA Guidance for Industry: Inspection of Injectable Products for Visible Particulates*

Regulatory agencies driving for better product quality

[1] https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls and https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/recalls-biologics (Accessed February 14, 2025)

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Manufacturing Process Video

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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

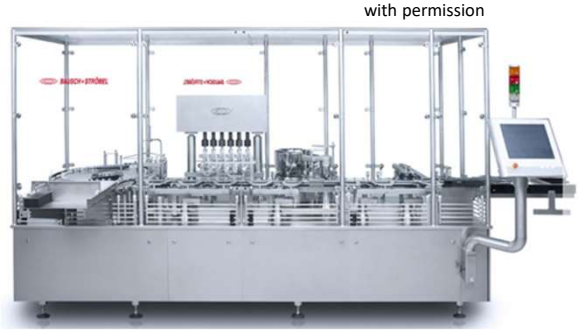

Image courtesy of Bausch+Stroebel. Used with permission

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

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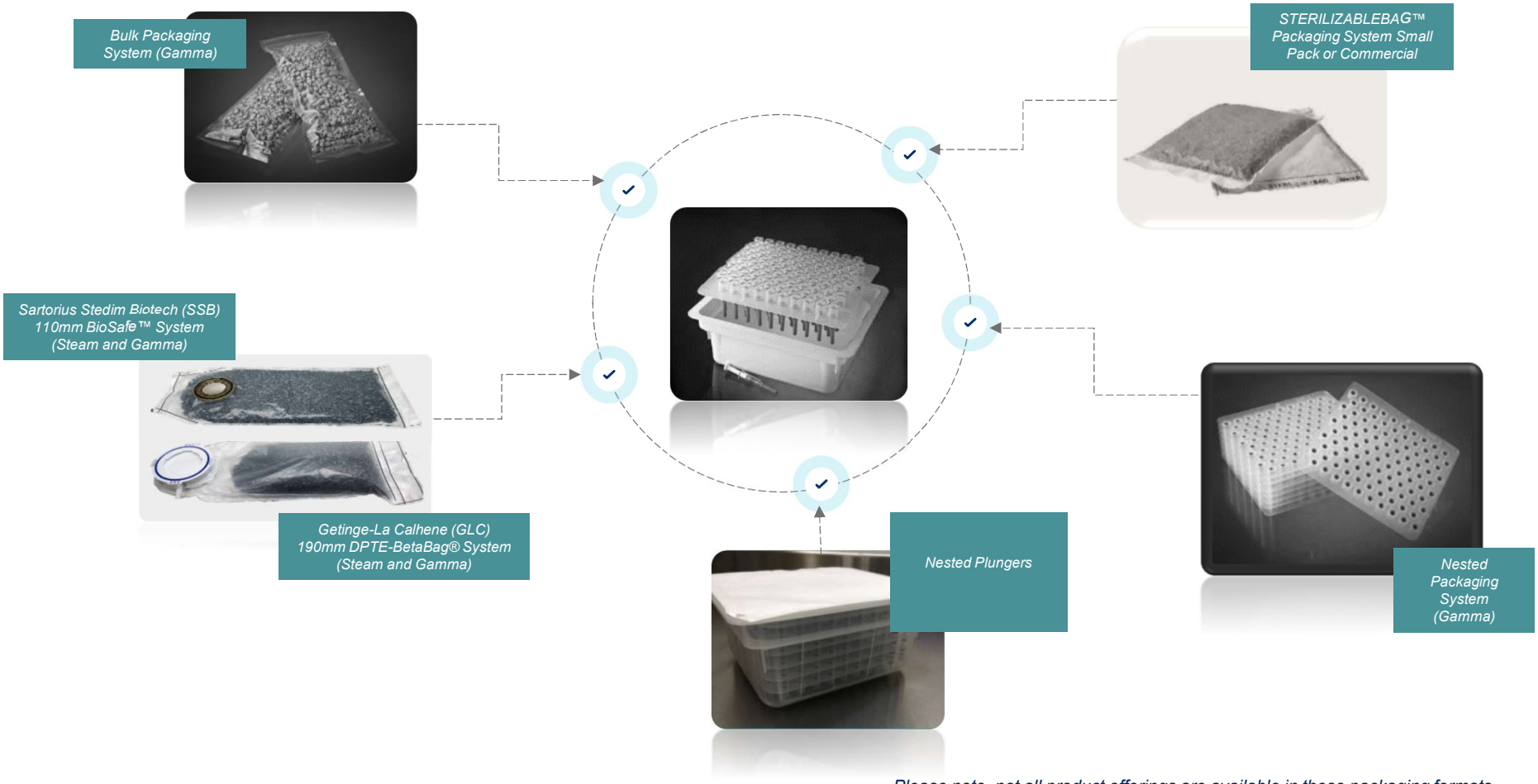
Ready-to-Use Packaging Solutions



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

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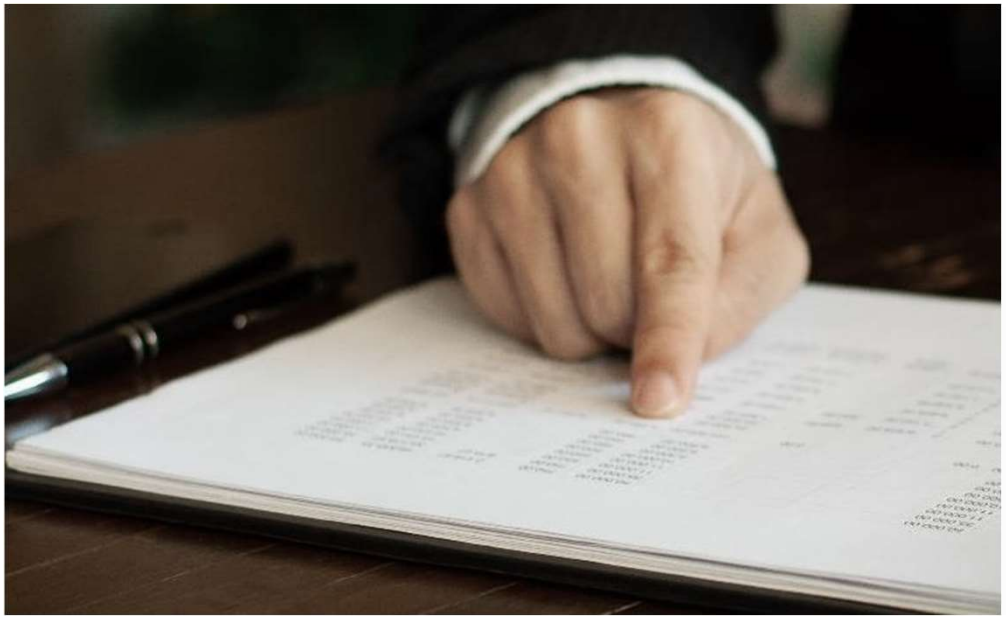
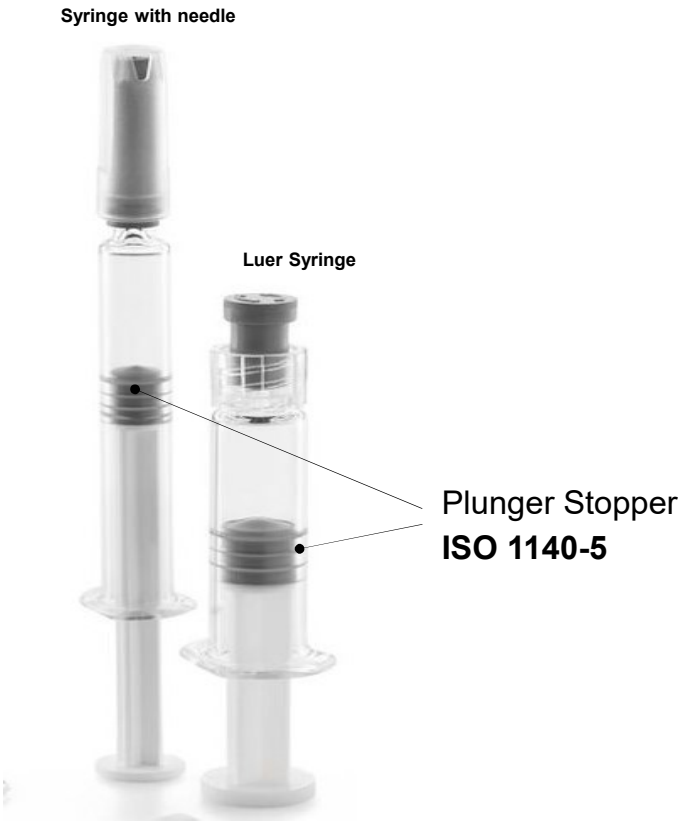


Relevant Compendial Chapters and Standards

ISO for Plunger Stoppers



ISO TC76/WG4: 11040-5 Plunger PFS Proposed Update

INTERNATIONAL STANDARD **ISO 11040-5**

Third edition
2012-01-15

Prefilled syringes –
Part 5:
Plunger stoppers for injectables

The review started , update of shapes, dimensions, general updates [expected to be released in 2026]

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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…..	✓	✓	✓	✓
Potential Extractable	Ammonium, Volatile Sulfides	✓	✓	✓	✓
Functionality Tests*	Fragmentation, self-sealing, penetrability (only vial)	✓	✓	-	✓

**functionality tests are moving to USP 382 starting from December 2025, only fragmentation will remain in 381 until an agreement of test method*

Overview of Relevant USP Chapters

- **Glass Containers**
  - 660
  - 1660
- **Elastomer Components**
  - 381
  - 1381
  - 382**
  - 1382**
- **Plastics Materials & Packaging**
  - 661.1
  - 661.2
  - 1661
- **Polymer Manufacturing Components**
  - 665
  - 1665
- **Extractable& Leachable**
  - 232*
  - 233
  - 1663
  - 1664
- **Particles**
  - 787
  - 1787
  - 788
  - 1788
  - 789
  - 790
  - 1790
- **Biological Reactivity**
  - **87** *in vitro*
  - **88** *in vivo*

Currently under revision, 1st December 2026 will be official

- *Chapters > 1000 informational*
- *Chapters < 1000 mandatory if required by monograph*
- *** will be official 01 December 2025*

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Overview of USP Elastomer Initiatives: Changes and Implementation

Current

<381> Required

- Biological Reactivity
- Physiochemical Tests
- Functional Tests

<1381> Informational

- Assessment of Elastomeric Component Used in Injectable Pharmaceutical Product Packaging/Delivery Systems

Effective: 01-Dec-2025

<381> Required

- Biological Reactivity
- Physiochemical Tests
- Fragmentation Tests

<382> Required

- All other functional tests

<1381> Informational

- Assessment of Elastomeric Component Used in Injectable Pharmaceutical Product Packaging/Delivery Systems

<1382> Informational

- Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems

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Current <381> versus <382>: Functional

From: USP <381>
Elastomeric Closures for Injections

Functionality Tests

- Penetrability
- Fragmentation
- Self-Sealing Capacity

Functionality: **Containe**r 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*

- 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

**Fragmentation removed from USP <382> in April 25th revision bulletin*

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Impact of <382> on Pharma customers

What does it mean for the Pharmaceutical Companies?

Pharmaceutical companies' compliance responsibilities need to demonstrate **system compliance** with USP <382> for:

Vial systems:
Vial + stopper + crimped cap + drug/placebo

Prefilled Syringe System:
Syringe + Plunger + Rod + Tip/Needle Shield + drug/placebo [+ Autoinjector]

Cartridge systems:
Cartridge + Plunger + Seal + drug/placebo [+ Pen Injector]

Marketed products:
Needs to be addressed, somehow e.g. testing, bracketing approach, scientific rational, justifying an equivalent standard e.g. ISO

Change on existing products:
Assessment according to USP <382> must be included

New products:
Compliance to USP <382> is required

EU GMP Annex I Revision Requires Drug Manufacturers to Implement Contamination Control Strategy

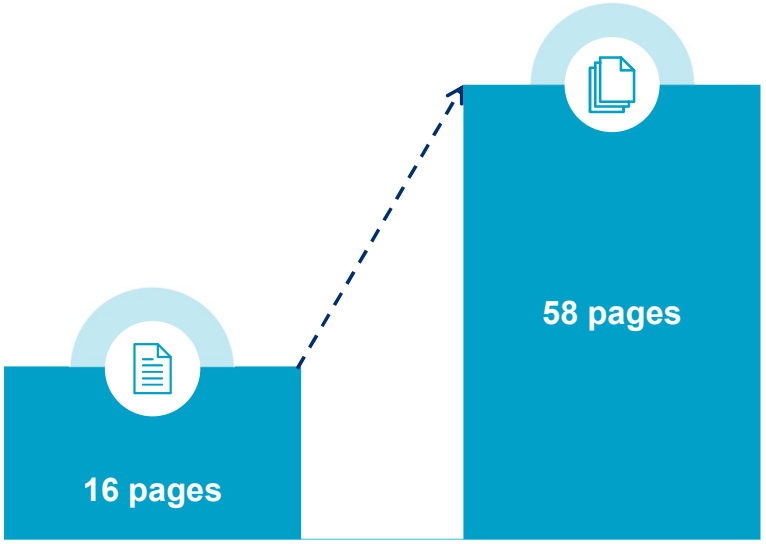
Primary Packaging Components are in Scope

Revision of Annex 1 *Manufacture of Sterile Medicinal Products of the EU Guidelines for good manufacturing practices for medicinal products*

- Endorsed globally
- Focus on CCS*
- Strongly recommends RABS** & isolators
- Focus on assurance of Container Closure Integrity (CCI)
- Knowledge and experience of the Container Closure System
- Identify & remediate contamination opportunities

What this means for the pharmaceutical manufacturer

- **Proof of Compliance:** End to End
- **Holistic CCS:**
  Document may require supplier support



*CCS = Contamination Control Strategy **RABS = Restricted Access Barrier System

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EU Medical Device Regulation (MDR) Changes the Approval Process for Combination Products

Background

Revision of Regulation 2017/745 on medical devices (MDR)

- Prefilled Syringe is a medical device
- Marketing Authorization Applicant (MAA) needs a Notified Body Opinion (NBOp)
- Need to fulfill EU GMP Annex I General Safety and Performance Requirements (GSPRs)
- GSPRs have been expanded significantly

EMA
(European Medicine Agency)
&
Notified Bodies

What does this mean for the Pharmaceutical Company?

- Need to obtain a NBOp
- Technical information from suppliers is required for conformity assessment

Opinion on GSPRs

The prefilled syringe is categorized as an integral drug device combination

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

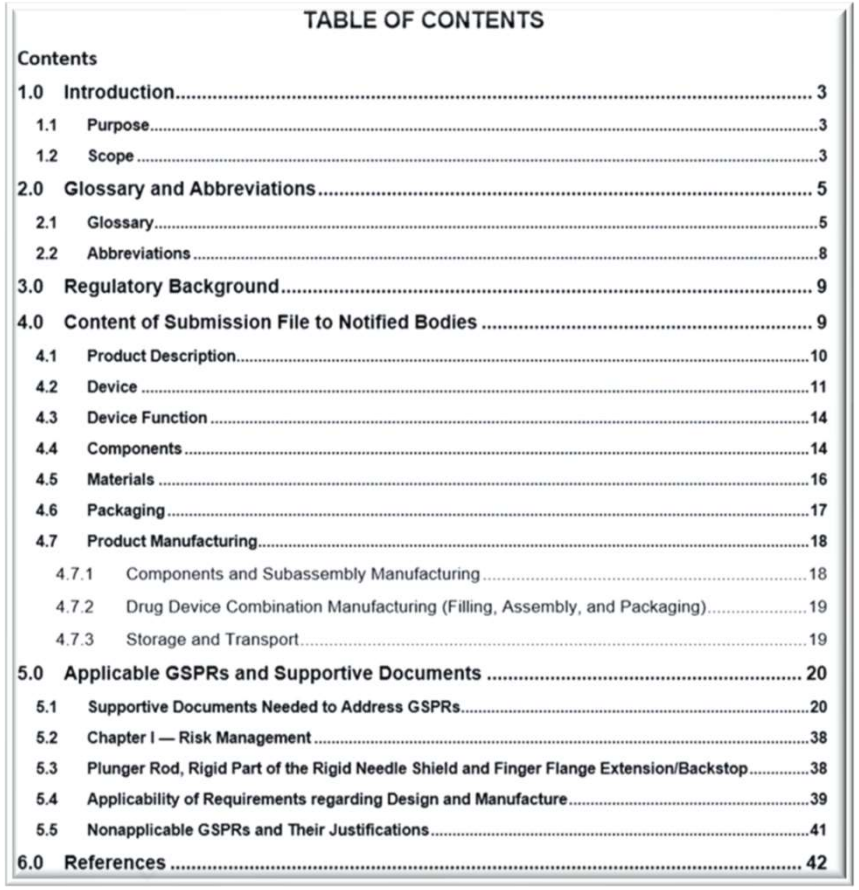

TABLE OF CONTENTS

Contents

PDA Parenteral Drug Association Training and Research Institute

Customized Technical Data Plunger Package for MDR Filing

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

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

PDA Parenteral Drug Association Training and Research Institute

West By your side for a healthier world™

Thank you very much for your attention!

Christa.Jansen-Otten@westpharma.com