

All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

Christa Jansen-Otten

Basel, June 31st and Mai 1st 2022



Agenda – DAY 2

The “Ready-to Fill” Syringe

Material • Shape • Properties • Siliconization • Impact of different drug • Nest and Tub • Needles and LL • backstops • Rods • Regulatory Guidelines

Plunger Stoppers, Needle Shields, Tip Caps

Materials • Properties • Functionality • Production • Extractables • Regulatory

Manufacturing Aspects in Fill & Finish and Assembly

Bulk versus Nested • Nest Sizes • Rod insertion • Handling of Syringes, Labeling • Glass to Glass Contact

Assembly of Syringes and Administration Devices

Pen Injectors • Safety systems • Autoinjectors • Manual vs Automated

Design Independent Assembly

Hands-on Session 2, Mind map, Lottery

Syringe Components



Considerations in Selection of PFS Components



COMPATIBILITY WITH DRUG

- Type of drug
- pH
- Viscosity
- Excipients

APPLICATION – MANUAL OR AUTO SYSTEM

- Break loose & glide force requirements
- Accuracy of delivery volume

CONTAINER CLOSURE INTEGRITY (CCI)

- Interference fit of plunger with barrel
- Sealing ribs and their function
- Preservation of drug potency and sterility

QUALITY SPECIFICATIONS

- Particulate level – visible & sub-visible
- Dimensional control
- Endotoxin level
- Bioburden level
- Visual defects

FINISHING

- Mode of sterilization
- Lubricity
- Consistency

Customer Impact - Demands on Packaging Components are Increasing



- ➔ **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
- ➔ **New manufacturing approach**
 - Flexibility
 - Time to market
 - Total cost of ownership (TCO) focused
- ➔ **Brand differentiation critical**

Rubber material



Why Use a Rubber Material?



Sealing properties that maintain container – closure seal integrity over time

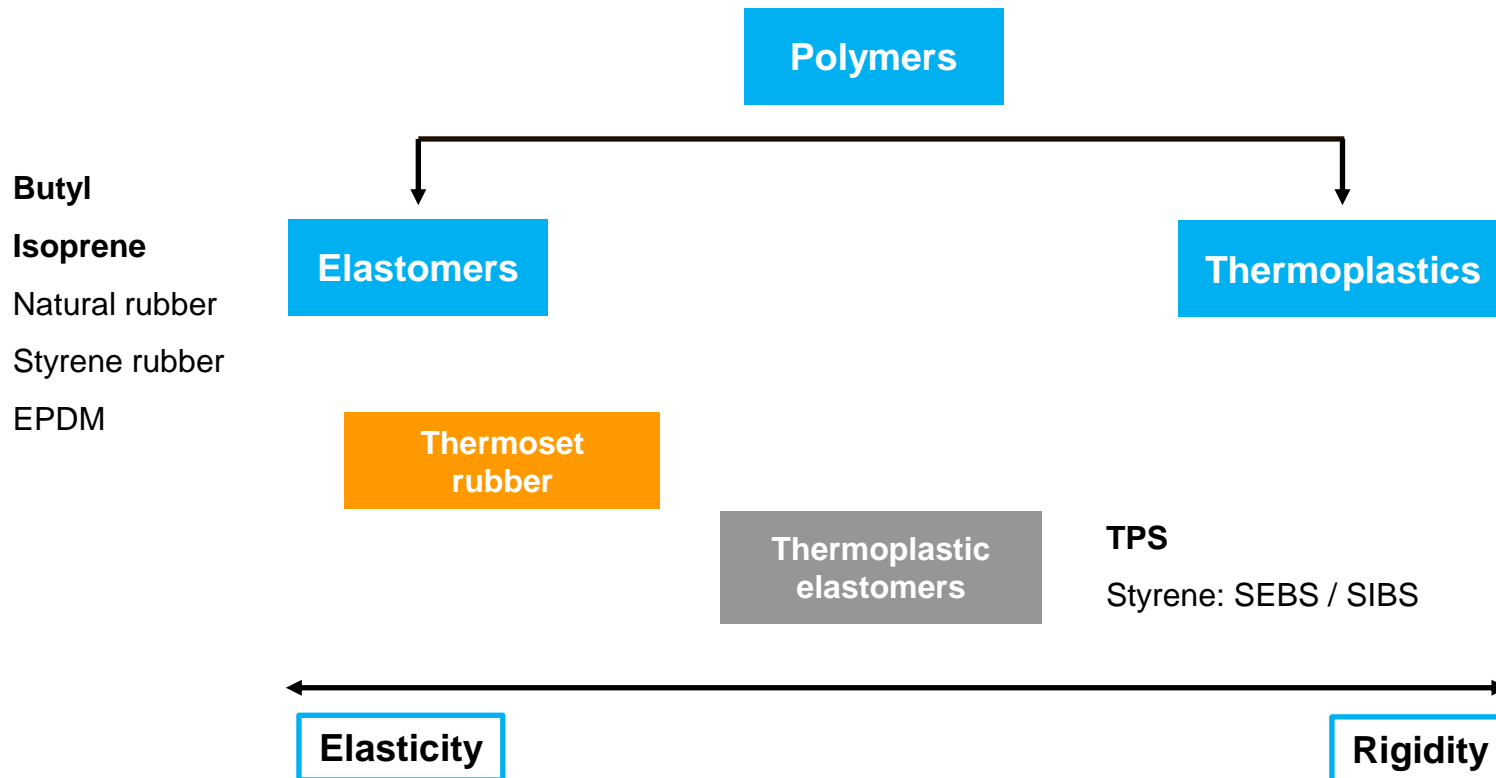
Physically and chemically compatible with different sterilization methods

Different range of material permeability

Compatible in long-term contact with drugs

Wide range of product designs

Polymers: thermosets and thermoplastics



Polymers

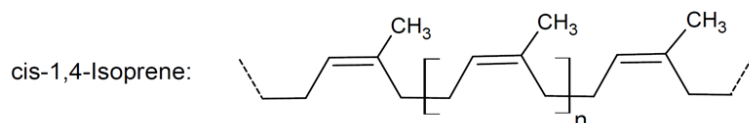
- Halobutyls:
 - Chlorobutyl
 - Bromobutyl
- Butyl
- Synthetic Polyisoprene
- Dry Natural Rubber [DNR]: Not recommended for new applications



If you need an elastomer for special applications such as oily solutions, please refer to your supplier for special formulation offerings

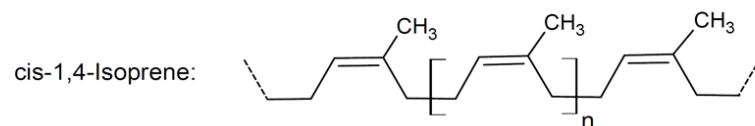
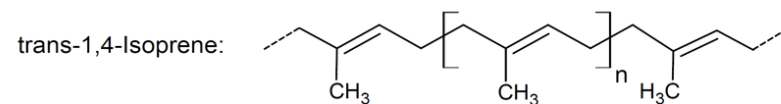
Polymers

Natural rubber (NR)



- Based on latex of *Hevea Brasiliensis*
- High Mw & broad Mw distribution
- >99.5 % cis-1,4 content
- Excellent mechanical properties e.g. fatigue, elasticity, abrasion
- High permeability
- Latex Allergy Concerns / cytotoxicity

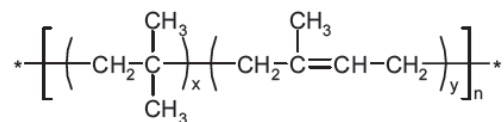
Synthetic polyisoprene (IR)



- Blend of cis-1,4, trans-1,4 and 3,4 vinyl polymer
- Lower elasticity and tear resistance than NR
- High permeability
- Poor resistance to ozone and many organic solvents

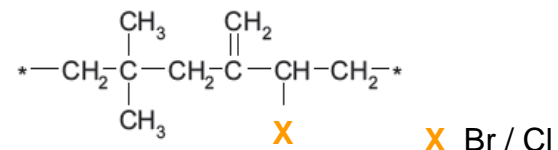
Polymers

Butyl (IIR)



- Low permeability
- Good heat resistance
- Good ozone resistance
- Resistance to acids, bases and other chemicals
- A low level of impurities
- Limited radiation resistance (< 25kGy gamma)
- Slow crosslinking because of its low unsaturation

Halobutyl (BIIR / CIIR)



- Greater crosslinking activity
- BIIR has greater cure activity than CIIR (C-Br bond weaker than C-Cl)
- BIIR has higher cure versatility than CIIR
- BIIR less sensitive to compounding variables e.g. water
- BIIR stabilizers ESBO (Epoxidized Soy Bean Oil) & calcium stearate, CIIR calcium stearate

Potential Sources of Extractable from Elastomeric Closures

- Elastomer
 - Oligomers, Calcium Stearate, Antioxidant (BHT etc.), Epoxidized Soybean Oil, Halide ions
- Filler & Pigments
 - Metallic Ions
- Cross-linking system
 - Sulphur, Phenolic resins, Metallic Ions i.e., Zn, Peroxides
- Plasticizer (Silicone oil, Wax, Oils)
- Reaction-by products
- Processing aids (Rubber closure, Raw materials)



→ Ask your supplier for potential extractable lists

Elastomeric Formulations for Pharmaceutical Use

Properties Polyisoprene

- Good permeability rates towards moisture and gases (ETO)
- Cleanliness, drug compatibility
- Low fragmentation / coring
- High elasticity
- Optimal penetrability
- Good resealing properties
- Sterilization: ETO, steam, gamma
- Ozone resistance (low cracking)*
- No blooming, no frosting*
- DNR, MBT, Nitrosamine free*



Properties Butyls/Halobutyls

- Low permeation rates towards moisture and gases
- Cleanliness, drug compatibility
- Low fragmentation / coring
- High elasticity
- Optimal penetrability
- Good resealing properties
- Sterilization: steam, gamma



*only valid for Polyisoprene

Potential Issues: Needle Shields and Tip Caps

Ozone Cracking



Frosting (Bloom)



Tip Caps, Needle Shields & Rigid Needle Shields Synthetic Isoprene Elastomer Formulations

Typical modern rubber formulations

- 7028/55 Gray
 - no ozone cracking observed
- 7025/65 Gray



Not made with natural rubber

Elastomer Physical Properties



What we Measure	Why it Matters
Hardness (Durometer)	Can affect physical attributes of the elastomer (coring, break loose and glide force, compression and CCI)
Crosslink Density (% Swelling)	Can predict gross compatibility issues (coring, break loose and glide force, compression and CCI)
Barrier Properties (O ₂ and Moisture)	Can predict the amount of gas transfer in a given thickness.
Compendia (USP, EP and JP)	Compliance
Identity Tests (Ash, Specific Gravity and IR)	Ash and specific gravity tell you that you have the right ingredients in the right ratios. Surface IR can identify surface treatments

Supporting Documents



Example of Supporting Documents

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

Confidential - West proprietary information



West
Elastomer Formulation
Biocompatibility
4023/50 Gray



FORMULATION CHARACTERISTICS
WEST FORMULATION 4023/50 GRAY




West By your side for a healthier world™
Material Characterization for Elastomeric Formulation 4023/50 Gray
Executive Summary



VeriSure

Confidential Technical Package
West Pharmaceutical Services 4023/50 Gray Formulation Extractables Analysis

Formulation Documents



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 LvoTec™ coatings.

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
Residual Solvent Content:	0.00%



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.

Formulation Documents

West  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

1	INTRODUCTION	2
2	ANIMAL DERIVED MATERIALS	2
3	HEAVY METALS	2
4	NATURAL RUBBER LATEX/DRY NATURAL RUBBER CONTENT	3
5	ADDITIVES OF CONCERN	3
6	ROHS	4
7	FOOD REGULATIONS	5
8	PROPOSITION 65	5
9	ELEMENTAL IMPURITIES	5
10	HALAL	6
11	KOSHER	6



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.

Examples of Uncontrolled Drawings

NOTES:
1. A MAX. OF 15 [0.05"] RADIUS ALLOWABLE ON ALL SHARP CORNERS.
2. VALUES DENOTED BY [XXX] ARE IN INCHES.

THICK LINE INDICATES FLUOROTE[®]FILM COVERAGE

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SECTION A-A

ACTUAL SIZE

REV.	DATE	DESCRIPTION	DR.	APP.
5	21 JUN 2018	PR# 49414	ARD	HG
4	DEC 15	ECN #11579, ADD DIM H4 TO TABLE & DWG.	DB	HG
3	SEPT 2012	ECN# 11404	HG	RB
2	MAY 2012	ECN# 11370	CPC	JML
1	MAR 2012	ECN# 11361	CPC	RB

TOLERANCES UNLESS NOTED		APPROVALS	DATE
DECIMAL	METRIC	DRAWN	
XXX ± .01	XX ± .3	C.P.Ching	21 FEB 12
XXX ± .05	XX ± .15	D. Melton	21 FEB 12
XXXX ± .1	XXX ± .3	J. Brinkhaus	22 FEB 12
FRACTIONAL INCH: ± .004		CHECKED	
ANGULAR: ± 1'		J. Gilleland	22 FEB 12
SURFACE FINISH: ✓		J. Laubach	21 FEB 12
THE INFORMATION ON THIS DRAWING IS PROPRIETARY. THIS INFORMATION SHALL NOT BE DISCLOSED, REPRODUCED IN ANY FORM OR USED FOR ANY PURPOSE, WITHOUT PRIOR WRITTEN CONSENT OF WEST PHARMACEUTICAL SERVICES.			
SCALE: AS SHOWN		DATE	
SCALE: 6:1		DATE	

West

1ML LONG PLUNGER NOVAPURE[®]4023/50G

WP-451 Rev 5

SCALE: 6:1 WEIGHT: LB. SHEET 1 OF 1

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Notification of changes will not be provided unless requested

A-A (4:1)

B-B (4:1)

1:1

West

CAD System: Solid Works Projection: Units:mm

Sheet 1 of 1

INDEX	Address:	Name:	Date:	Checked:

Made ohne Toleranzangabe DIN 19901, TAB2 Tot.Gr.150
Dimensionen sind in Millimetern nach DIN 10901, TAB2 Tot.Gr.150
Unlimited dimensions DIN 19901, TAB2 Tot.Gr.150

Zeichn.Nr.: 4144-00
Drawing No.: 4144-00

Erstellt durch: 15 Nov 2012
Replaces part: DZ
Replaced by: 15 Nov 2012

Scale: 4:1
Drawing: DZ
Checked:

Rigid Needle Shield 1/2"

Art. No.: 4144
Art. No.: 4144

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Ce document est notre propriété. Il ne peut être reproduit ou communiqué à des tiers sans notre autorisation écrite. Il doit être restitué immédiatement sur simple demande de notre part. This drawing is our property. It is not allowed to make copies or to communicate with third without written permission. It must be returned immediately on our demand.

Rigid Needle Shields and Tip Cap



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



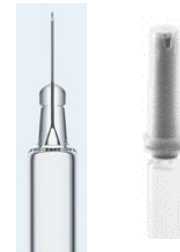
Head design of glass barrel with
a 6% Luer cone



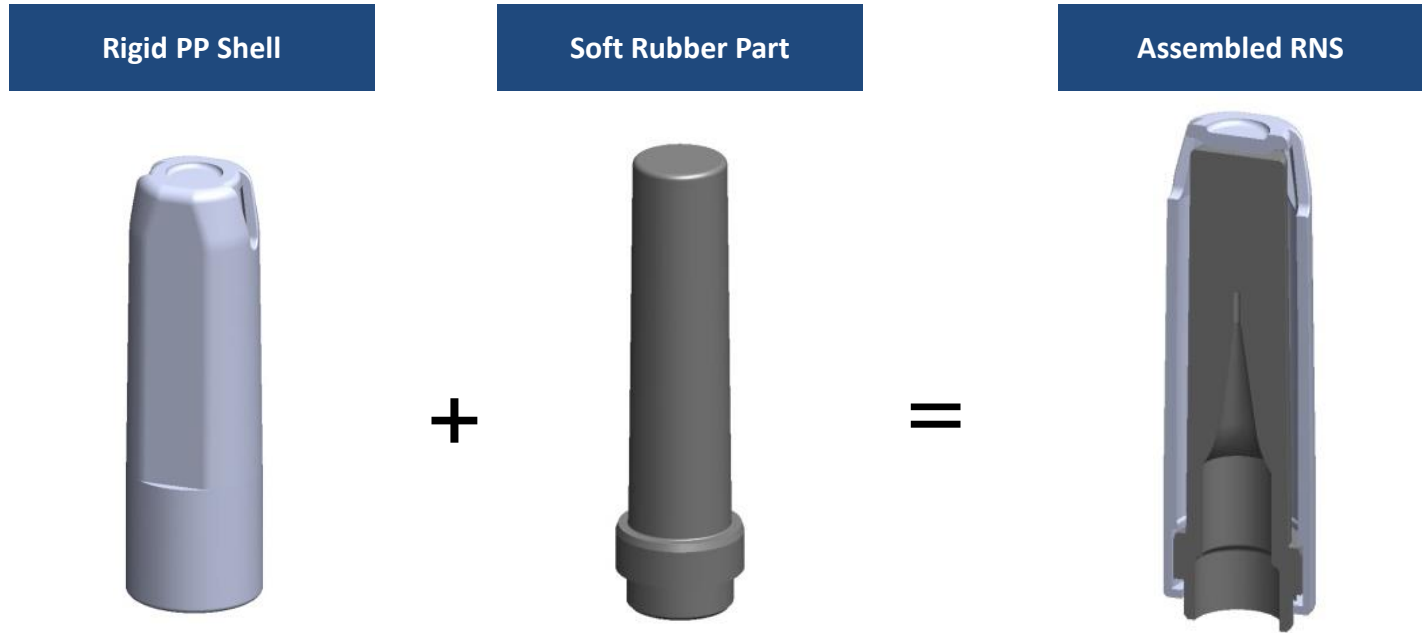
Head design of glass barrel
with a 6% Luer cone for Luer
Lock (LL)



Head design of glass barrel
with staked needle



West Rigid Needle Shields



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

Design Examples of Rigid Needle Shields

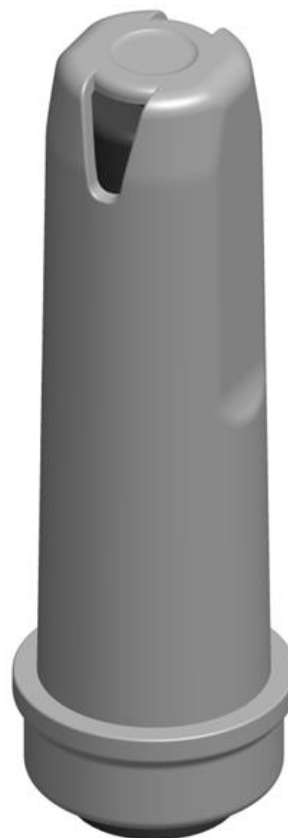
RNS ½" [13 mm]

*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)*

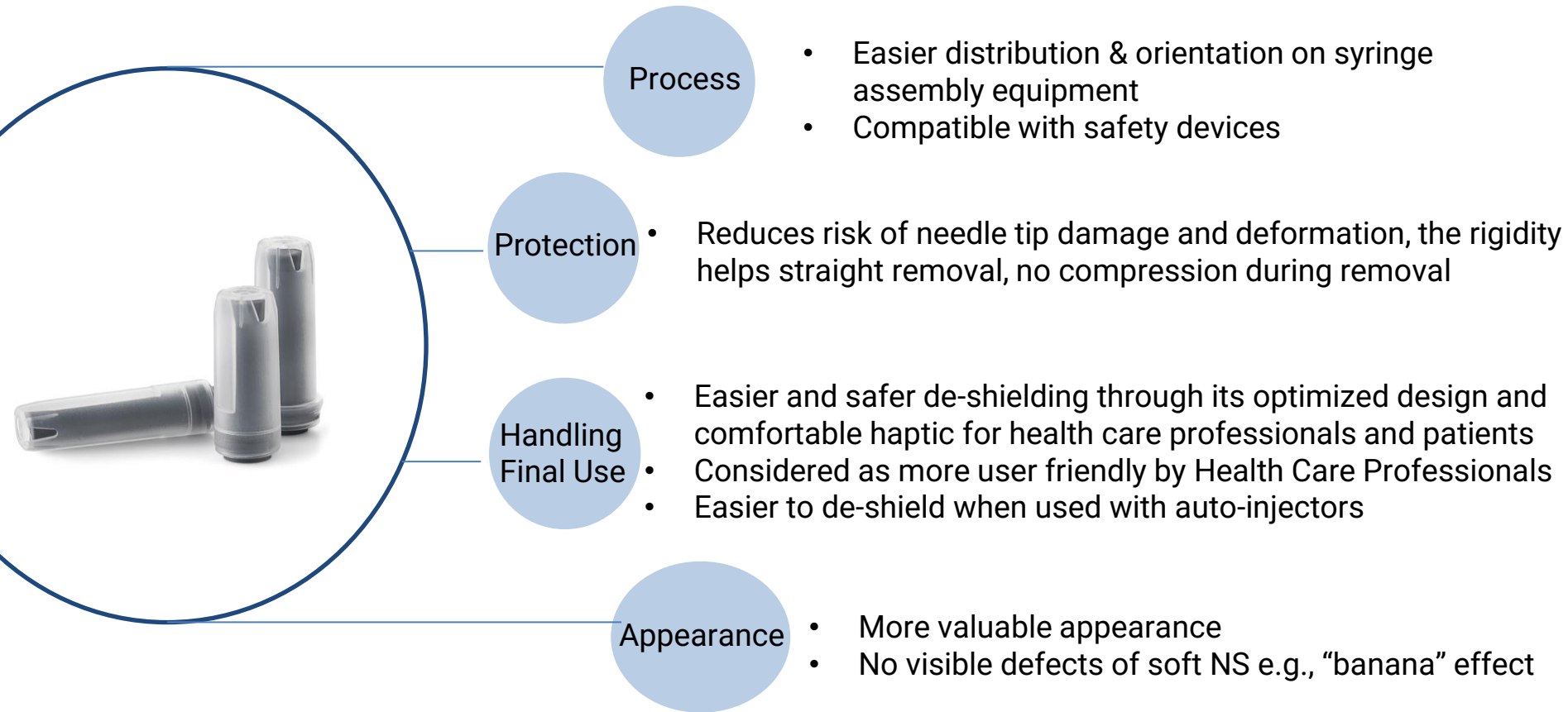


Solution

- 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 EtO or steam

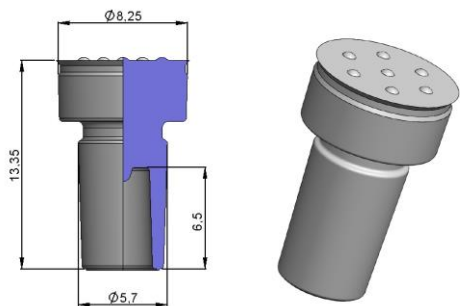


Advantages of Rigid Needle Shields vs Soft Needle Shields

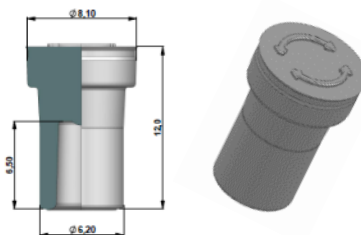


Rigid Needle Shields are the preferred closure for staked needle syringes

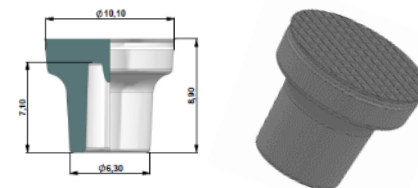
Example of various Tip Caps for Luer and Luer Lock Syringe



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

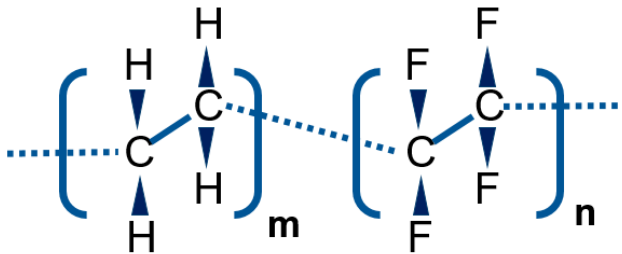
Coating – liquid or vapor that is sprayed, tumbled or vapor deposited onto the elastomeric component

- 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)

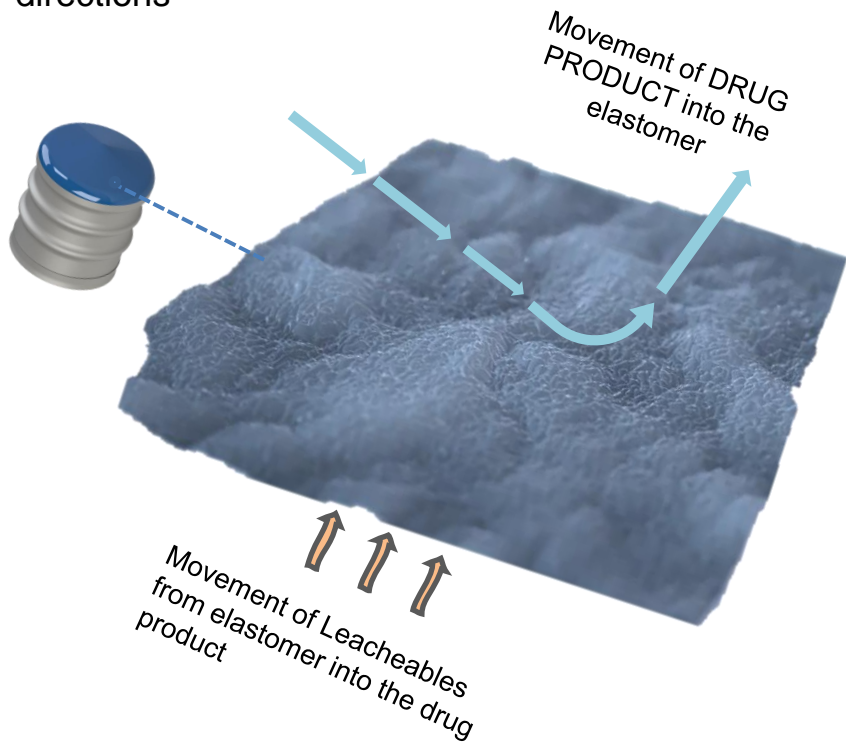
- ➔ translucent

- ➔ compatible with sterilization by either:
 - autoclave
 - gamma irradiation

- ➔ Applied during the compression molding process

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



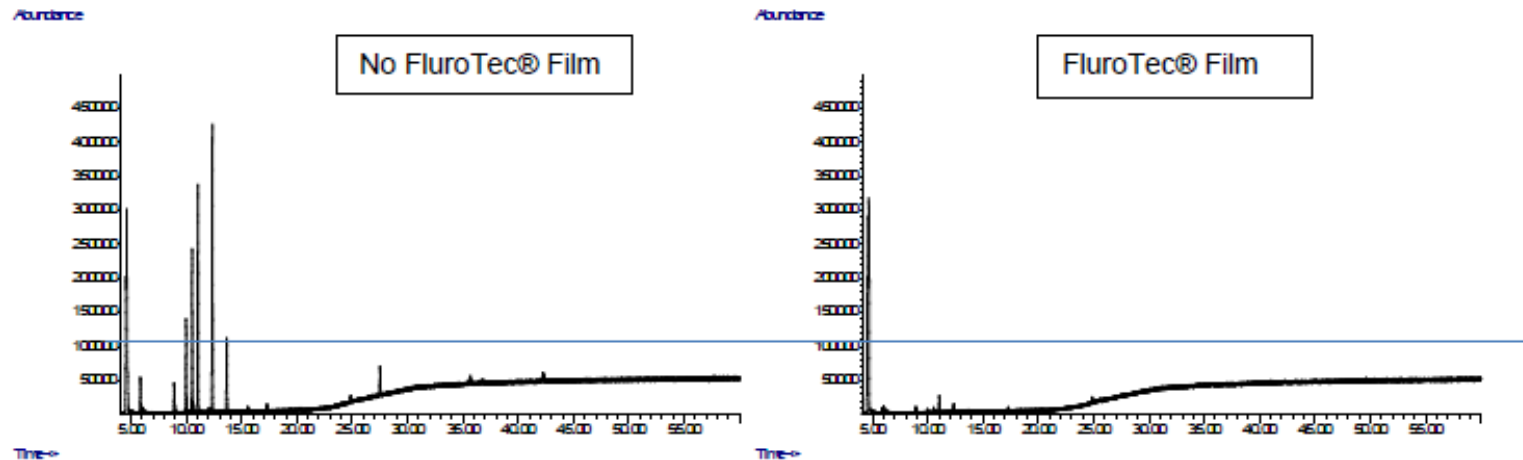
resistant to degradation



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

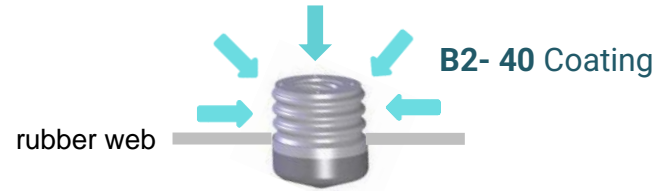
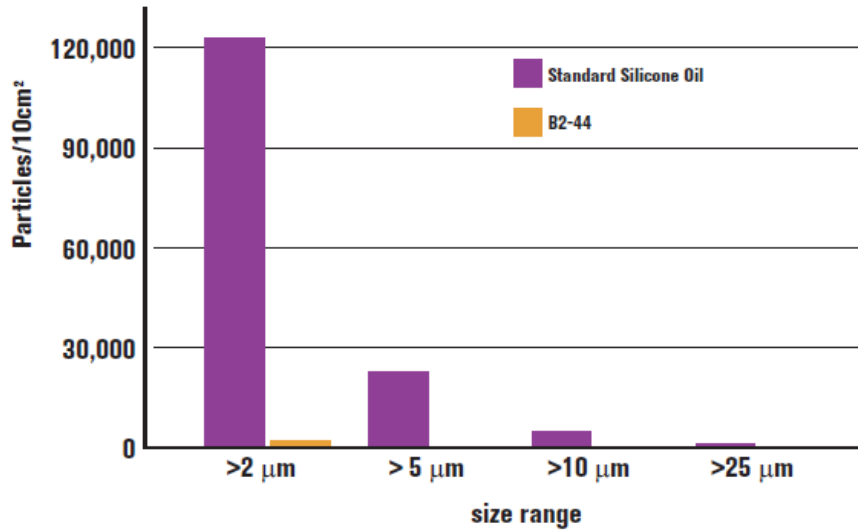


Elastomers with FluroTec® film did not show any peaks > 0.5 µg/unit [blue line]

Most marketed biopharmaceuticals use fluoropolymer-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

Lubricity Coating: Classical Silicone Oil

Polydimethylsiloxane (DC 360 Medical Fluid) added during washing operation into the washing drum:

- 350 centistokes → USA
- 1000 centistokes → Europe

ADVANTAGES

- Commonly used
- Applied during wash cycle
- Low cost

DISADVANTAGES

- Particles/droplets may be found in drug product
- Silicone level may be inconsistent if process is not validated

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**

Pre-filled Syringes Plungers

Main requirements for PFS Plungers

- Good break loose and glide forces
- 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

Fluoropolymer Lamination
on Drug Contact side



Plunger ISO 11040-5



Example of Prefilled Syringe - Plunger Portfolio at West

Plungers suitable for DIN/ISO 11040-4 Syringes

Size	Article	Recommended Rubber Formulation (Halobutyl) in combination with FluroTec® Film
0.5 mL	2342	4023/50 grey B2
1 mL Long	2340	4023/50 grey B2 and 4432/50 grey B2
1 mL Long NovaPure® Plunger		4023/50 grey B2
1 mL std.	2345	4023/50 grey B2 and 4432/50 grey B2
1-3 mL NovaPure® Plunger		4023/50 grey B2
5 mL	2346	4023/50 grey B2
10 mL	Y-2667	4023/50 grey B2

Size	Article	Available Rubber Formulation (Halobutyl)
0.5 mL	2211 and 2247	4023/50 grey and PH 701/50/C black
1 mL Long	2212	4023/50 grey and 4432/50 grey and PH 701/50/C black
1 mL std.	2116	4023/50 grey and 4432/50 grey and PH 701/50 C black

Majority of designs are customized



Fluoropolymer film

Plungers with film lamination and B2-Coating



Plungers without coating (with silicone)

Manual PFS to Auto-injector Challenges



Challenges



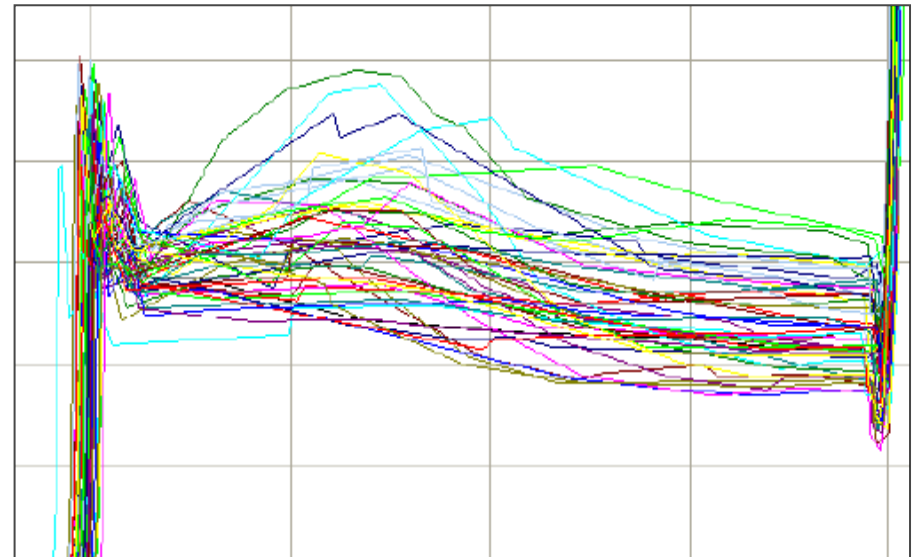
Complex container closure



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



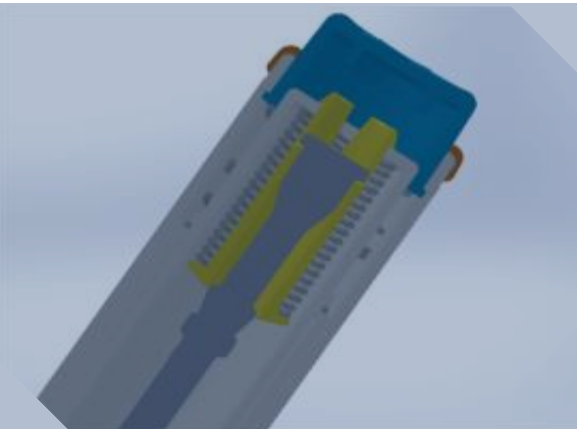
If injection times vary between doses with an auto-injector:

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

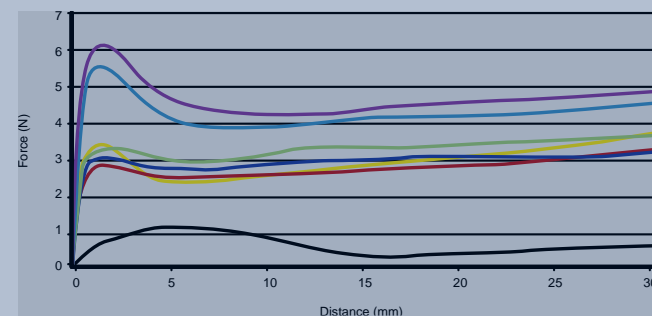


Critical design factors must be considered, especially functional compatibility

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



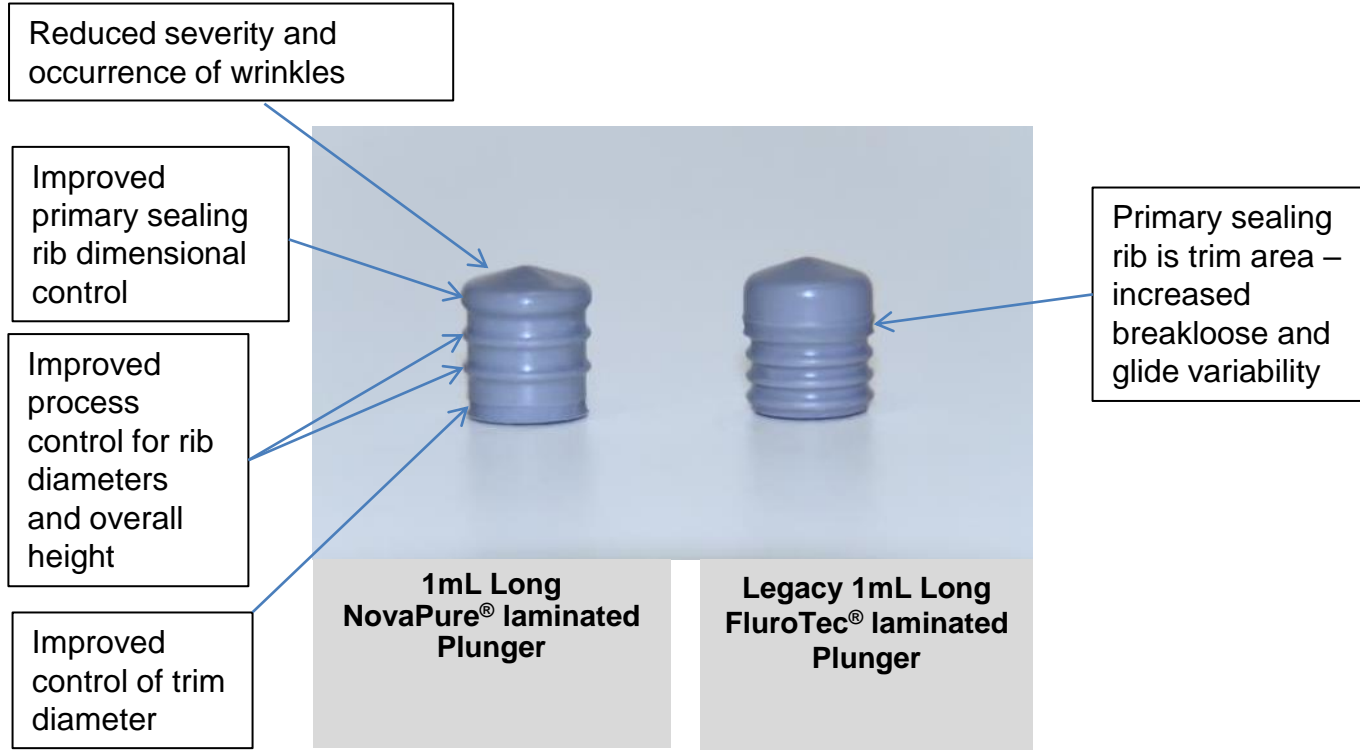
Comparison of Break Loose & Glide Forces



Market Requirements for plungers

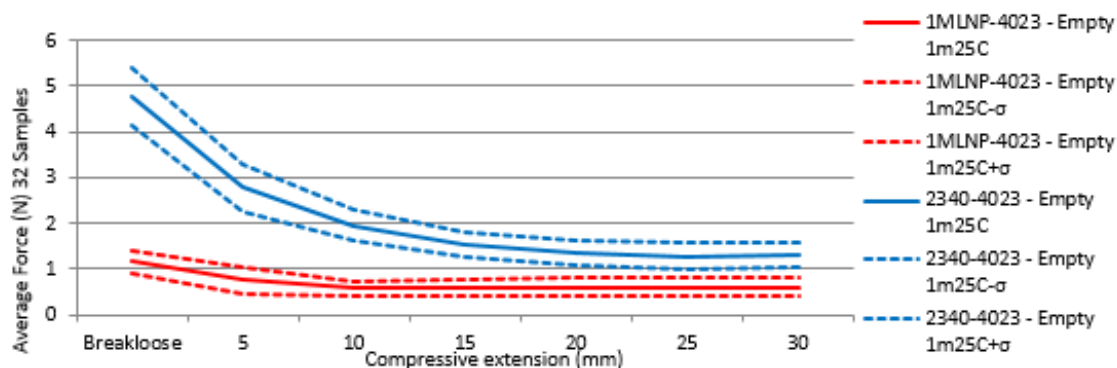


Design example: laminated Plungers

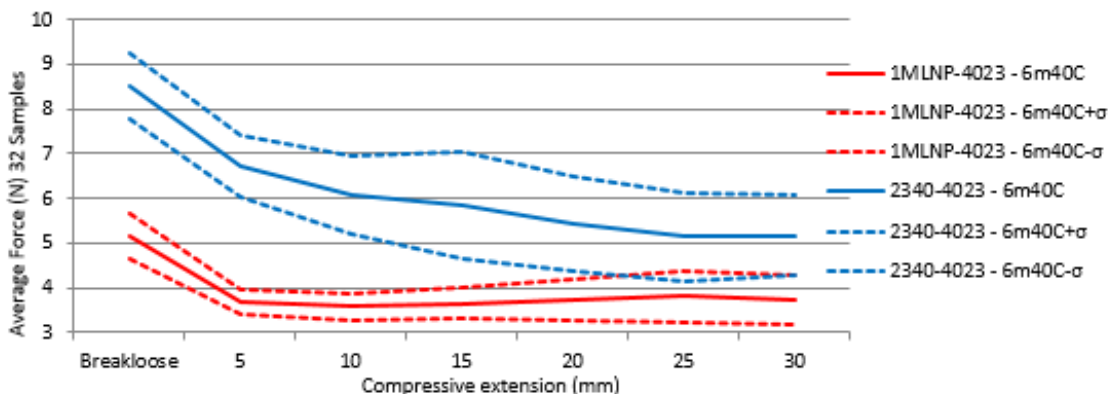


Performance: two different laminated 1 ml long Plungers

Empty



Water Filled

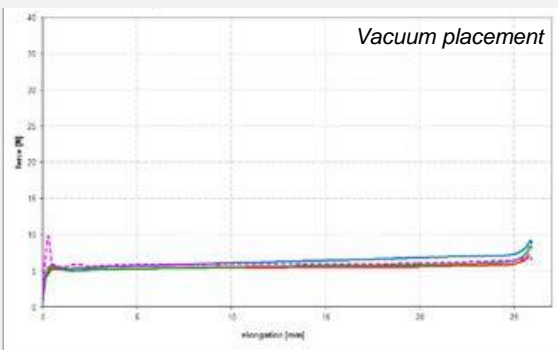
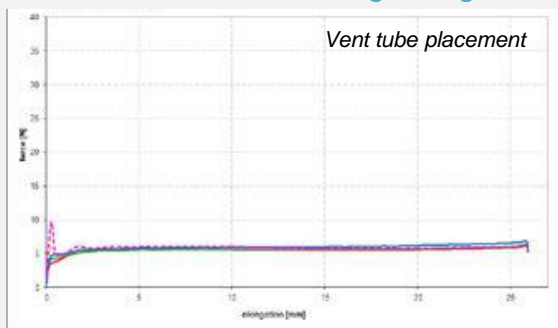


*Extract of Study –
technical report available*

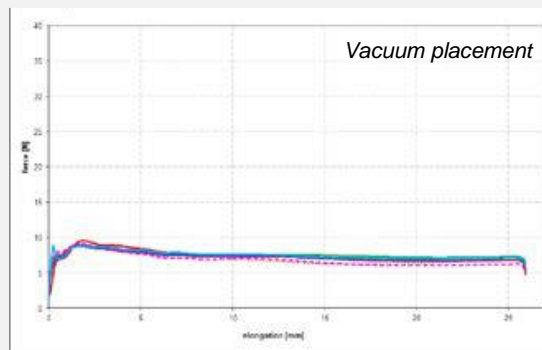
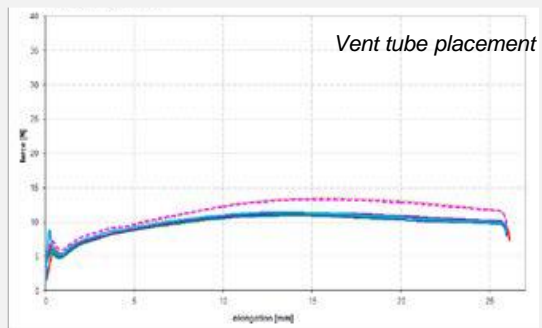
Ref.: TR 2013/147

Functionality 2340 vs. NovaPure® 1ml long Plunger

NovaPure® 1ml long Plunger



2340



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.

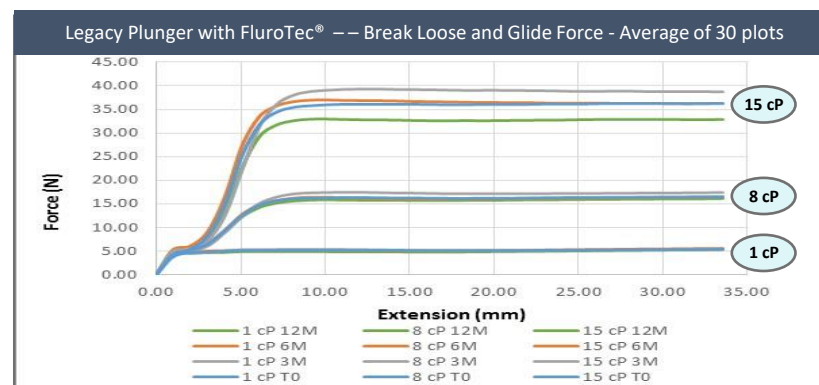
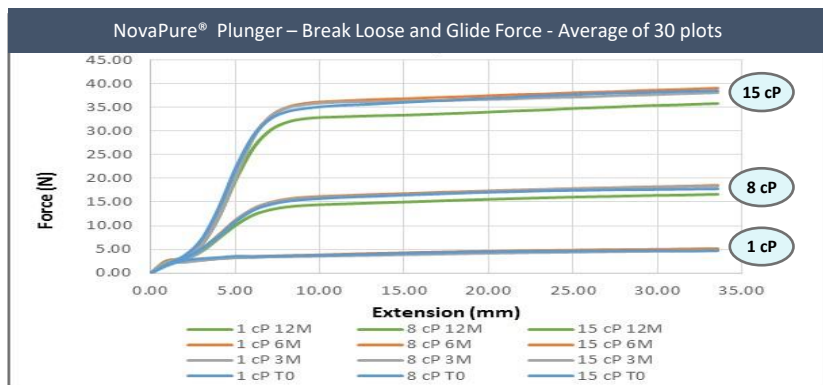
NovaPure® plunger showed low break loose and glide forces with very consistent, smooth profiles and

Neither plunger placement method nor storage conditions have a determinable influence on the optimized break loose and gliding forces profile of 1ml long NovaPure® plunger

Meeting functionality requirement for use with auto-injectors and other medical delivery devices.

Break-loose and Glide Force - 1 ml Long Plungers

Curves represent averages of 30 plots.



Time	Fluid Viscosity	NP Plunger Force [N]	Legacy Plunger Force [N]	% lower (with NP)
T0	1cP	1.63	3.68	55.8%
	8cP	1.77	4.23	58.2%
	15cP	1.89	4.00	52.7%
3M	1cP	2.16	4.55	52.5%
	8cP	2.31	4.64	50.3%
	15cP	2.35	4.89	52.0%
6M	1cP	2.05	4.45	54.1%
	8cP	2.55	4.34	41.2%
	15cP	2.20	5.21	57.8%
12M	1cP	2.63	4.71	44.3%
	8cP	2.53	4.43	43.1%
	15cP	2.39	4.55	47.6%

- 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

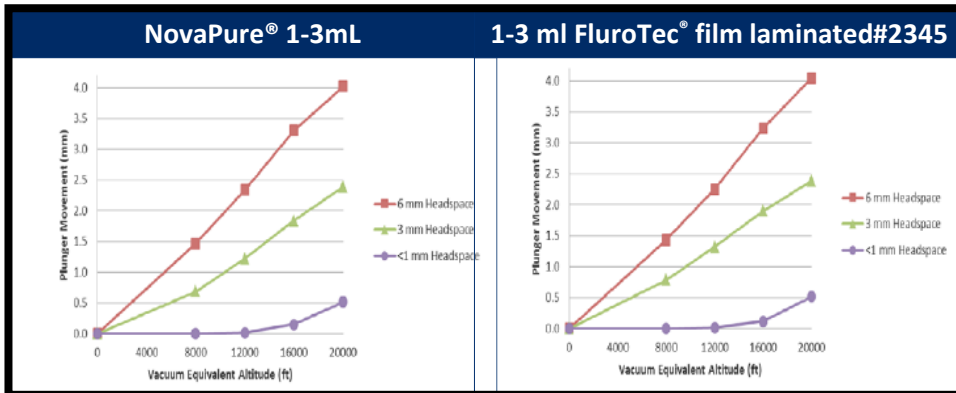
Break Loose Forces at 1 mm extension

Evaluation of Plunger Movement During Transit Conditions

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



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

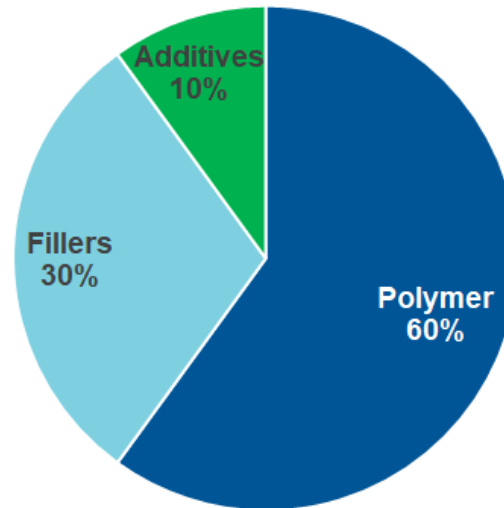
Extract of Study – technical report available – TR 2016-172

Processing



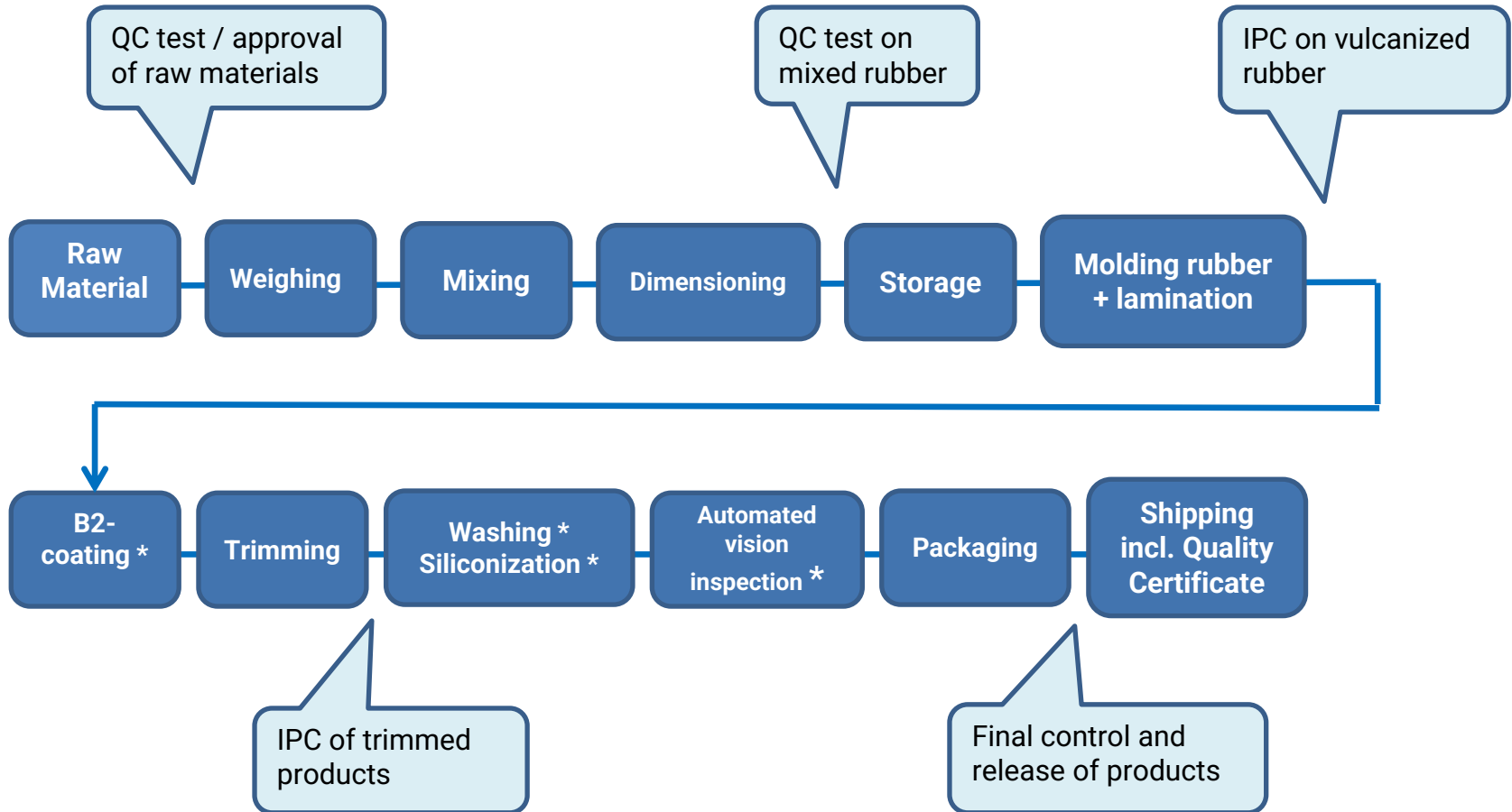
Elastomers: General Composition

Approximate Composition of an Elastomer Component



- Fillers are mainly defining the physical properties
- Additives can be curing agents, antioxidants, accelerators, activators, protective agents, colorants, plasticizers, acid scavengers, light and heat stabilizers, lubricants, anti-static agents, etc.

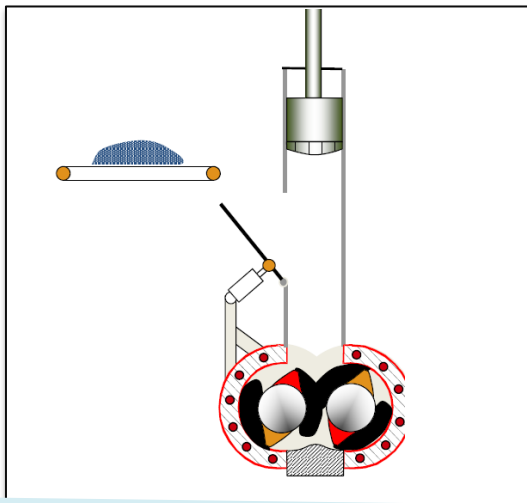
Production Overview [Plungers]



* optional upon request

Manufacturing Process

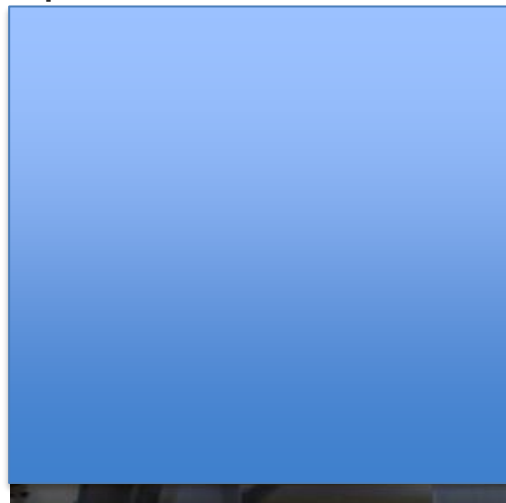
Internal Mixer



Mixer all components are mixed by turning rotors

- Shearing the elastomer, squeezing out air, Incorporating all material
- Critical parameters are specific for the individual formulations: rotor speed, temperature, time, filling volume, etc.
- Caution not to start vulcanization

Open Mill



Mill additional homogenization of the mixture by compactors

- Squeezing out air, cooling down
- Caution not to start vulcanization
- Elastomer mixture is collected in "puppets"

Mixing Control (Mill Control)

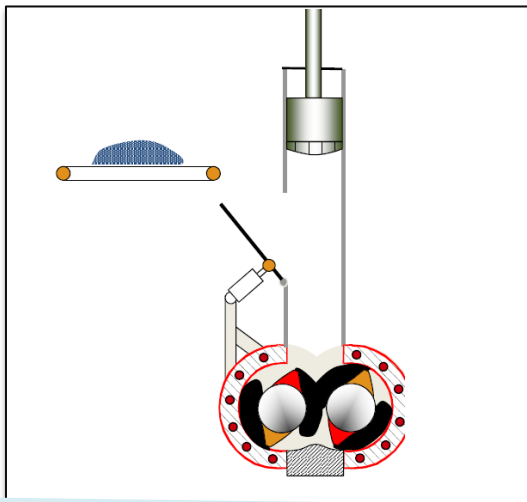


Curing of ISO – standard sample for testing purposes

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 10 th batch plus 1 st and last
rheology of the compound	every 5 th batch plus 1 st and last

Manufacturing Process

Internal Mixer



Mixer all components are mixed by turning rotors

- Shearing the elastomer, squeezing out air, Incorporating all material
- Critical parameters are specific for the individual formulations: rotor speed, temperature, time, filling volume, etc.
- Caution not to start vulcanization

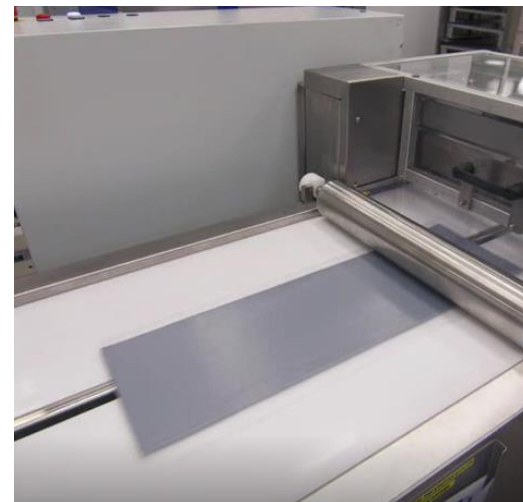
Open Mill



Mill additional homogenization of the mixture by compactors

- Squeezing out air, cooling down
- Caution not to start vulcanization
- Elastomer mixture is collected in "puppets"

Calandering & Dimensioning

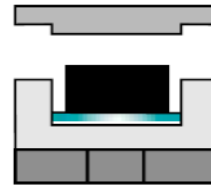


- "Puppets" are finally cooled down in rollers
- Cooling & Cutting
- Coated into webs with defined thickness and width
- Webs are led to relax for some time

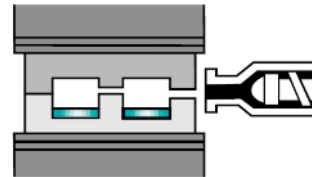
Pharmaceutical Rubber Manufacturing

Different 'shapes' need different molding technology:

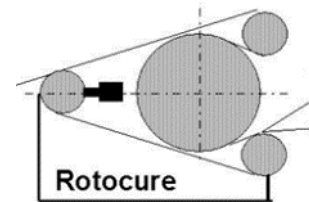
- Compression Molding (CM)
Plungers, stoppers, disks...



- Precision Injection Molding (PIM)
Needle shields ...

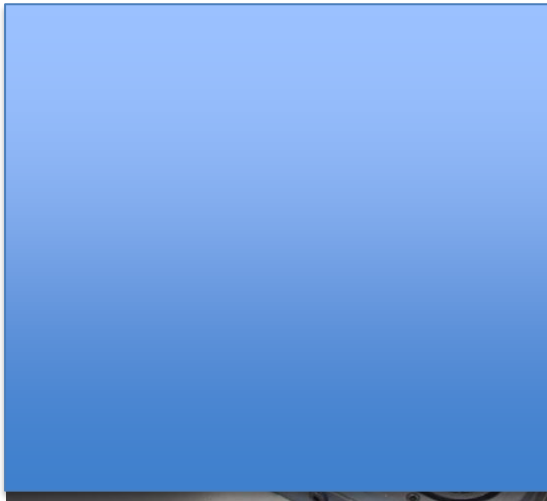


- Rotocure (Sheeting Material)
Lined seals...



Manufacturing Process

Compression Molding



- Compression and Precision Injection Molding
- Vulcanization takes place
- Critical parameters are specific for the individual formulations: press speed, temperature, time, vacuum, etc.

Trimming

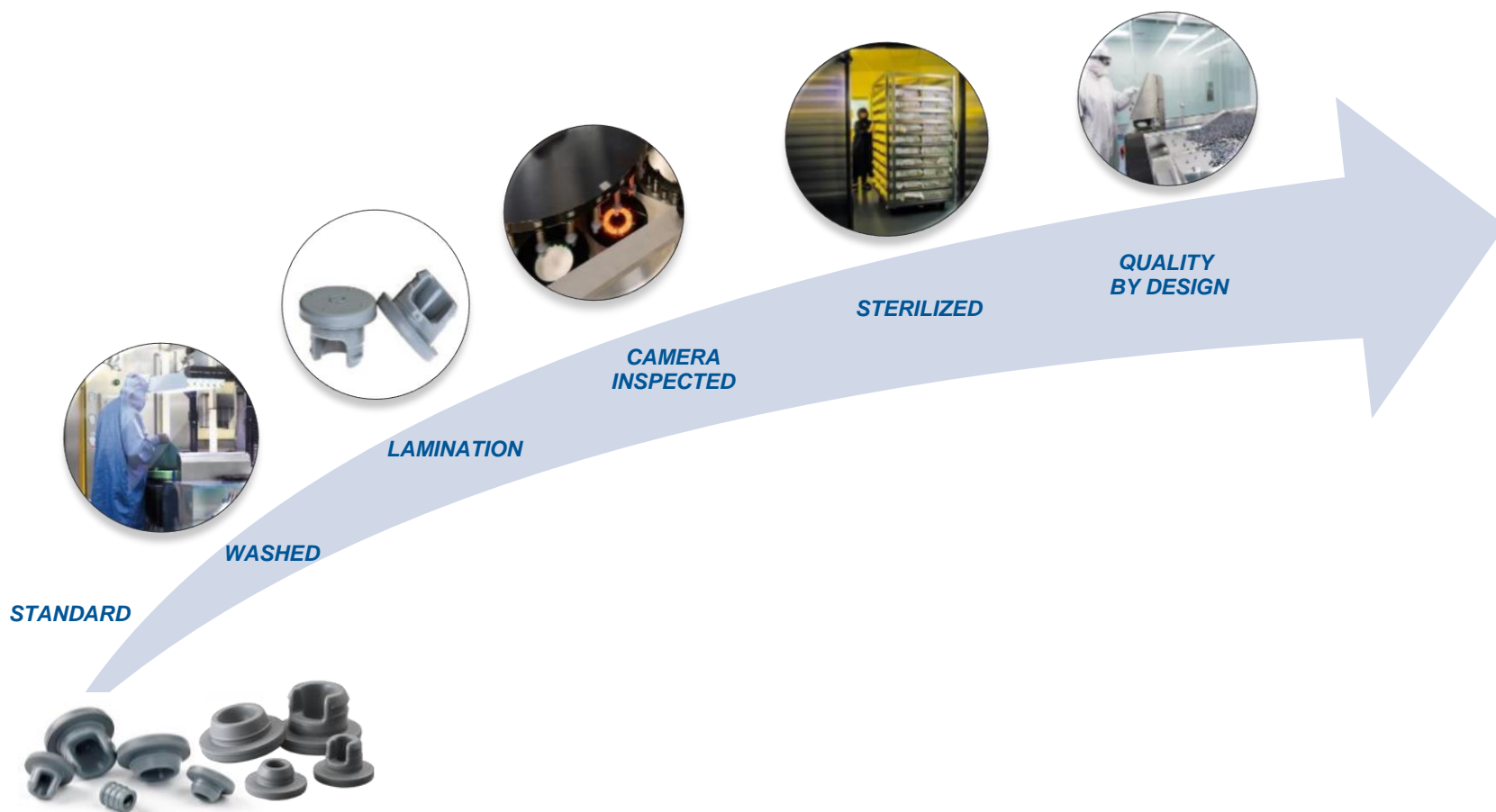


- Trim presses designed for cleanroom manufacturing
- Enhanced trim dies to lower particle contamination
- Automated control of web positioning
- Automated web spraying for lubrication



- Single parts transferred to Washing operations

Differentiated Solutions: Increasing Quality & Inspection



Finishing: Washing and Siliconization



- **Westar**[®] wash process is a validated pharmaceutical washing process with defined levels of silicone, bioburden and particles, which is certified in a CoA coming with every batch
- Available in a DMF, Type V
- Loading in ISO 8
- Unloading and packing in ISO 5
- Quality Certificate for each Batch
- Ready-to-Sterilize or Ready-to-Use

Final Inspection: Sampling, Packing and Release Testing



- Evaluation of sample size according to ISO [2859](#)
- Visual check according to the defect evaluation list for rubber parts
- Defect / individual characteristics
- Dimensional Inspection



- AQL Samples
- Customer Samples
- Retain Samples
- Test Samples

Envision™ Verification Process



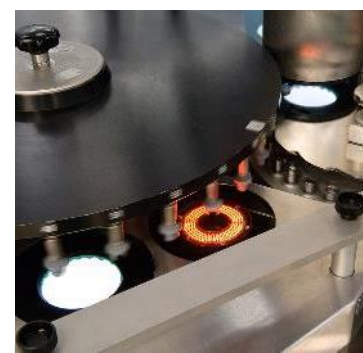
- Product transfer into the automated vision room
- Product scanned into facility traceability system



- Product placed into vibratory hopper
- Product is oriented and fed into the vision machine



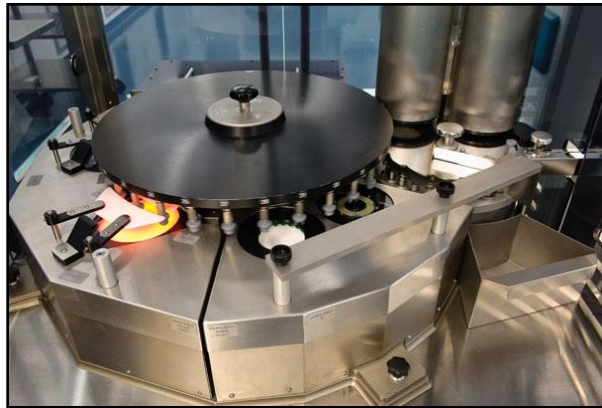
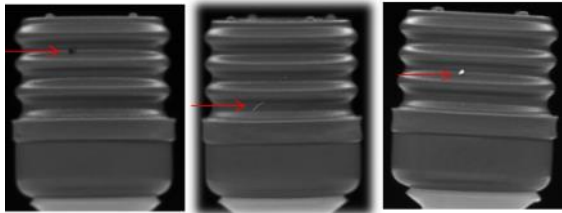
- Machine started with appropriate configuration verified during setup



- Multiple camera arrangements
- Envision verification is performed through optimized camera station design and set-ups

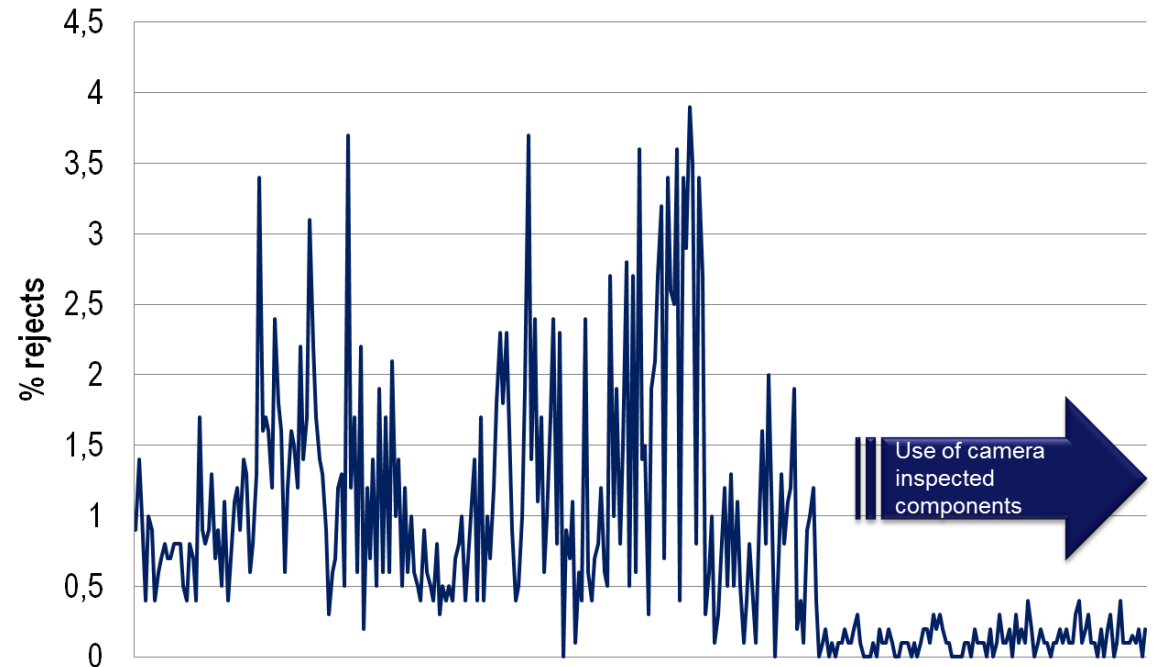
ISO 5 [Class 100]

End-of-Line Defect Reduction



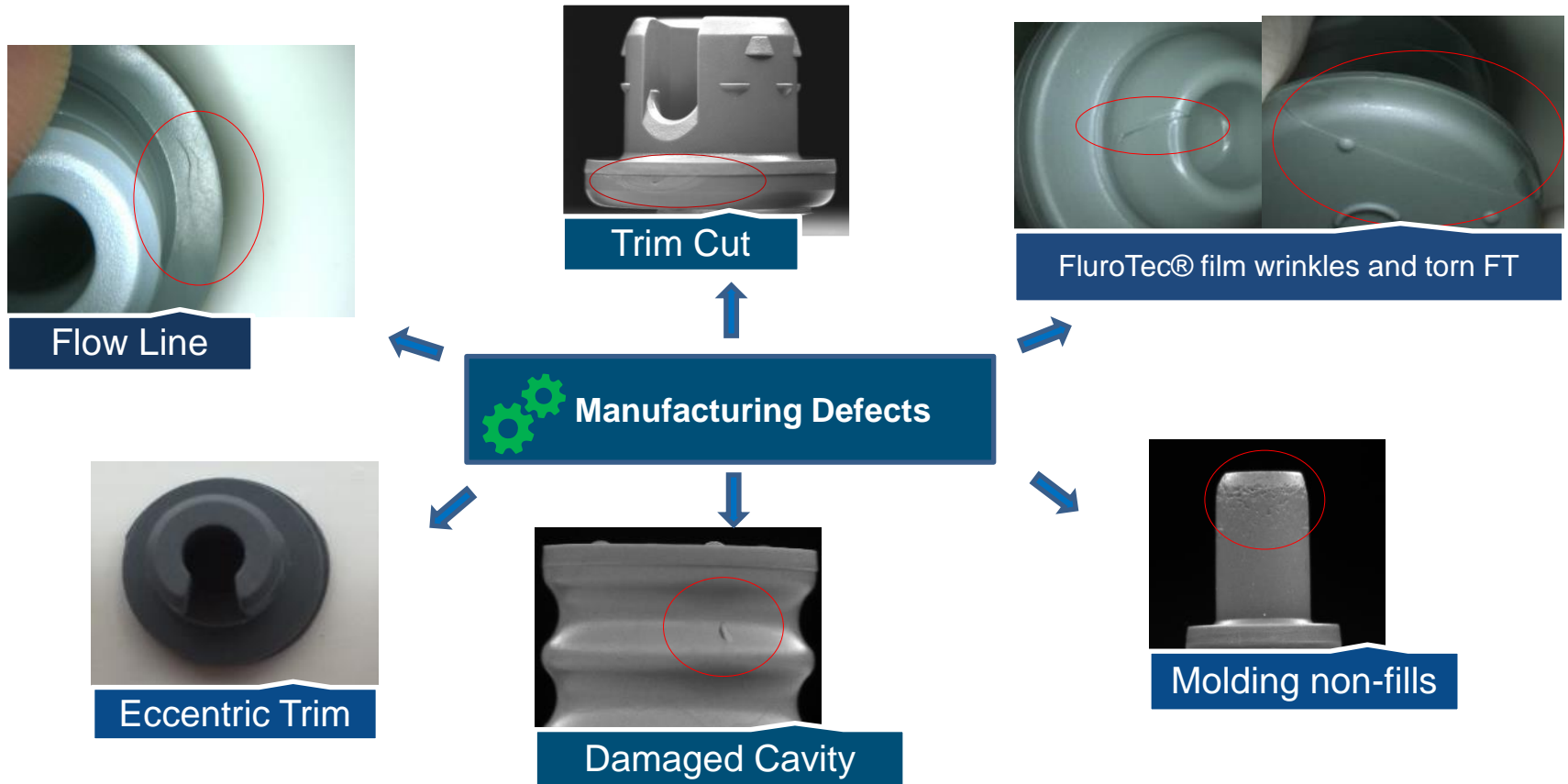
100% Camera Inspection of rubber components

Case Study: *End-of-line drug filled units reject trend*

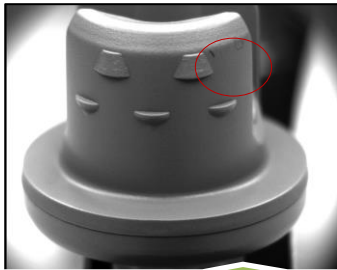


Use of camera inspected components

Envision™ Verification: Defects Examples



Envision™ Verification: Defects Examples



Fiber



Mixing dispersion issue



Hairlike

Dispersion/Contamination related



Rubber flash



Embedded foreign matter



Manufacturing Process

Typical Sterilization Treatments for Elastomeric Components

Ready-to-Use Elastomeric Closure

Steam
sterilization
stoppers and
plungers

Low Gamma
sterilization
mainly plungers

High Gamma
sterilization
mainly plungers

ETO
Sterilization TC,
NS, RNS

Steribag

Portbag

Bag/portbag

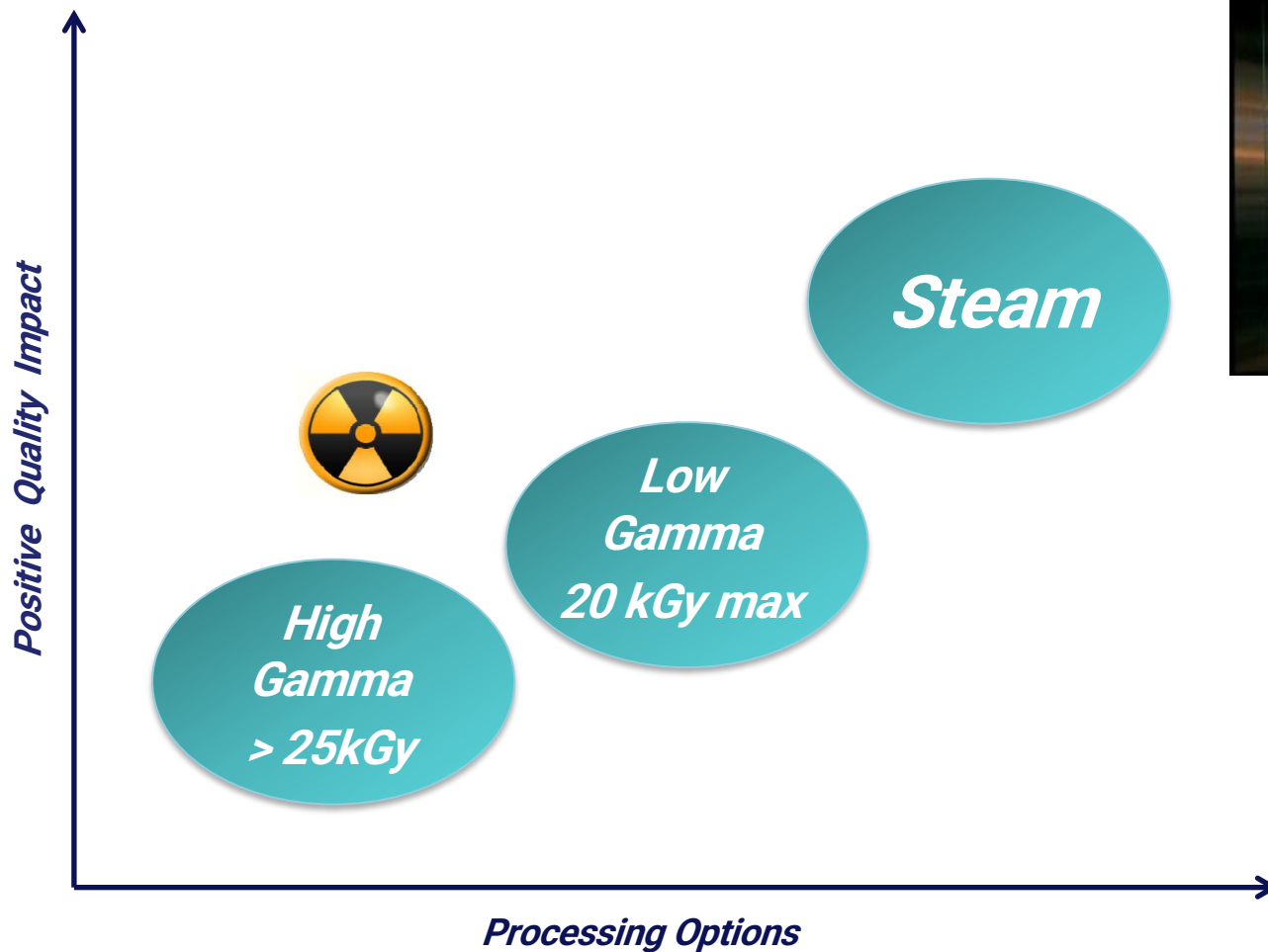
Nest

Bag/Portbag

Nest

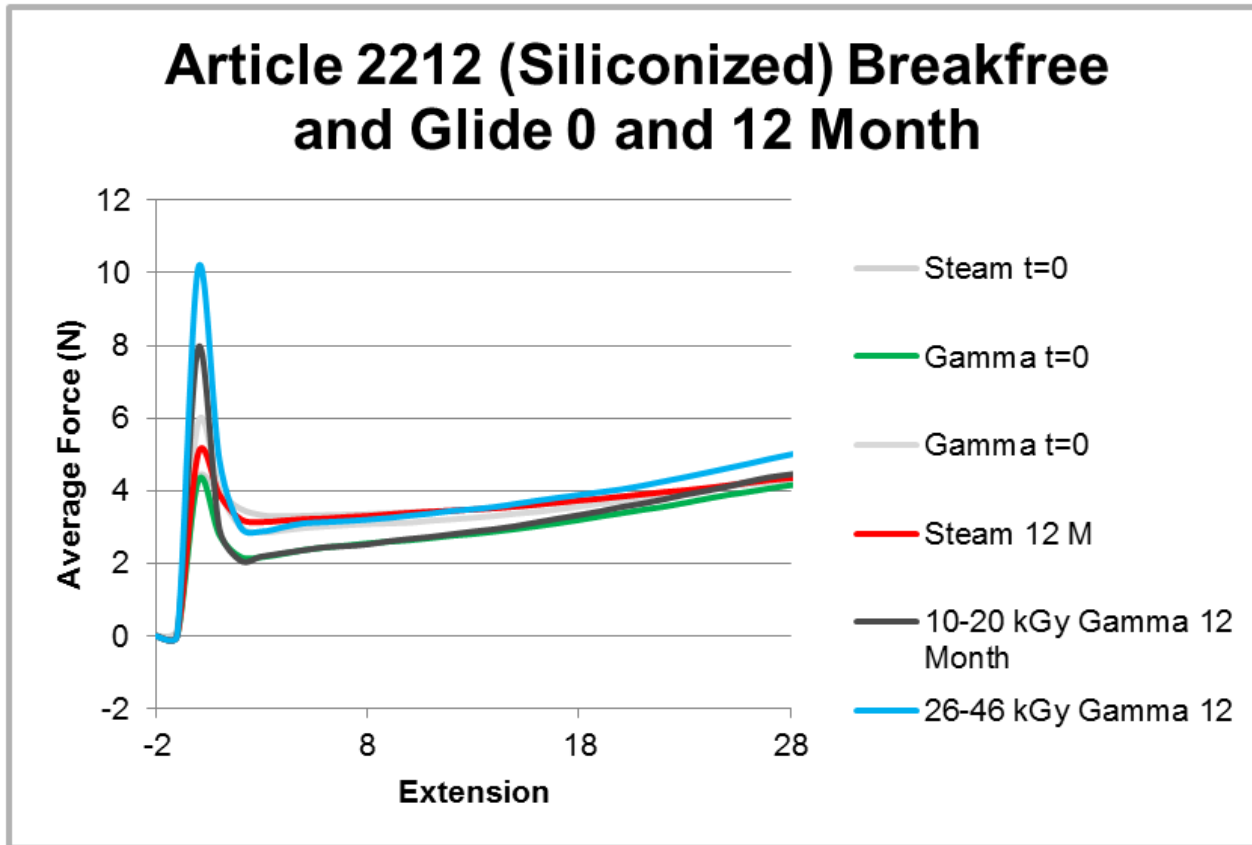
Assembled
on nested
syringes

Ready-to-Use Steam vs Ready to Use Gamma for Plungers



Functionality – Steam versus Gamma

1 mL long Plunger - Break Loose and Gliding Force at 0 and 12 Month

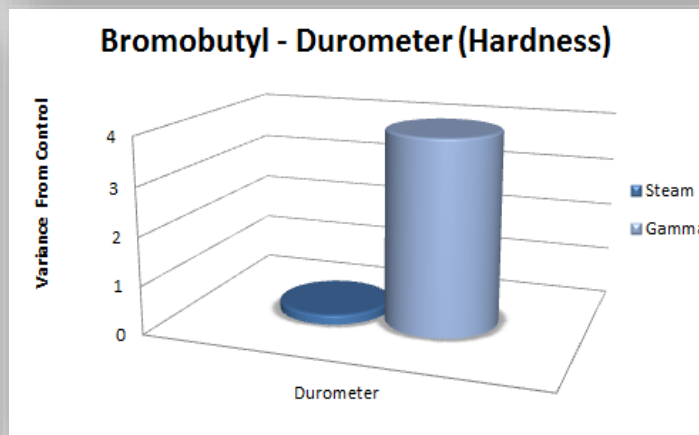
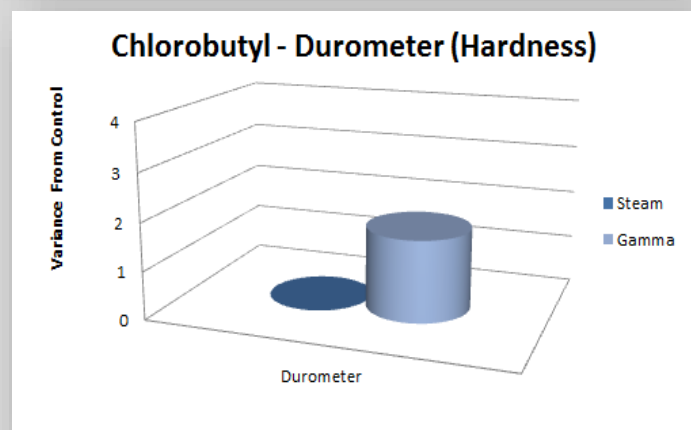
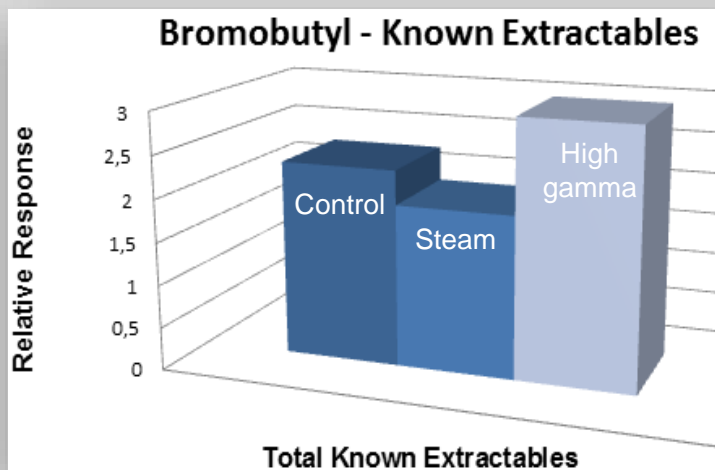
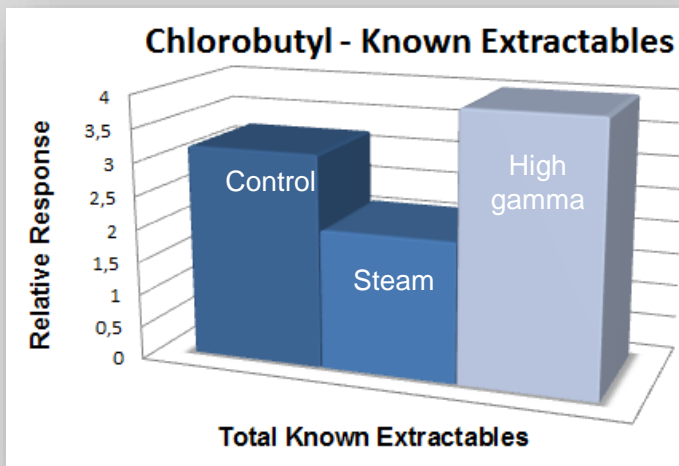


Key findings:

- Steam treated plungers improve functionality due to lower and more consistent break loose forces

Ref.: TR 2011/140

Physical and Chemical Characteristics Steam versus High Gamma



Key findings:

- High gamma shows twice the amount of known extractable

- Hardness is significantly increasing after high gamma treatment

Secondary Packaging - Flexibility for Filling Needs

Drug Development and Life Cycle Management Require Multiple Packaging Formats
Prescreens, Process Validations, Clinical Trials, Commercial fill-finish



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*

Global Comparison of Elastomer Chapters

usp U.S. Pharmacopeia	European Pharmacopeia 10 th Edition	JP Japanese Pharmacopeia	PHARMACOPOEIA OF THE PEOPLE'S REPUBLIC OF CHINA
<ul style="list-style-type: none">• Development of a new chapter addressing functionality tests USP <382>• Including E&L	<ul style="list-style-type: none">• Revision of Heavy Metals / Elemental Impurities and methods• Plastics materials & additives	<ul style="list-style-type: none">• Deletion of pyrogen and hemolysis test• Addition of cytotoxicity test	<ul style="list-style-type: none">• Ongoing revisions in all topics with a strong attention to the global revision process and discussion

Overview of Relevant USP Chapters



Glass Containers

- 1660
- 660

Elastomer Components

- 381
- 382**
- 1381
- 1382**

Plastics Materials & Packaging

- 1661
- 661.1
- 661.2

Polymer Manufacturing Components

- 1665
- 665

E&L

- 1663
- 1664
- 232*
- 233

Particles

- 1787
- 1788
- 1790
- 787
- 788
- 789
- 790

Chapters > 1000 informational
 Chapters < 1000 mandatory if required by monograph

- <231> has been deleted
- ** will be official 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

Secondary Packaging



Packaging Materials

High-quality packaging materials

- Reduction of particle load of primary packaging → tighter specification
- Ease of use
- Pinhole resistant – physical – stress
- Plastic cartons & plastic pallets



Ready-to-Use Packaging Solutions

Bulk Packaging System (Gamma)



Not commercially available – Under Development
Tub Nested Plungers



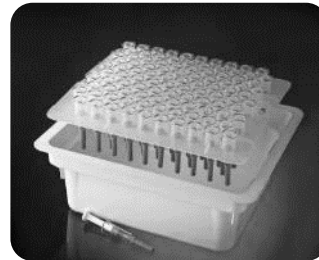
STERILIZABLEBAG™
Packaging System Small Pack or Commercial



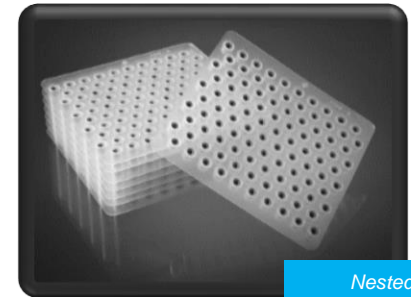
Sartorius Stedim Biotech (SSB)
110mm BioSafe™ System
(Steam and Gamma)



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



Nested Packaging System (Gamma)



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

**Thank you very
much for your
attention!**

*Any Thoughts?
Any Questions?*

Christa.Jansen-Otten@westpharma.com

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