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for a healthier world™

Elastomeric Closures for Pre-filled Syringes and Cartridges

Hands-on Training Course, PDA Universe of Prefilled Syringes

Friday 10th November 2017 – [90 min]

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**Elastomeric Components for Syringes and Cartridges
Formulations, Requirements, Films & Coatings, E&L,
Case Study and Designs**

**Different Manufacturing Technologies for Elastomeric
Components for Pharmaceutical Use – Video**

Sterilization and Packaging



Cartridge Components



[Multilayer] lined seals

Solid plungers

Syringe Components



Tip caps and needle shields

Syringe accessories



Cartridge

Single/Multiple Dose
Device mandatory



Pen application



Prefilled Syringe

Single Dose
Manually or Device



Auto-injector application

Single dose

Typical Fill Volume: 0.5mL – 10mL

Drug Content Format

Liquid

Packaging Components

Barrel (glass, COC, COP)

Plunger (piston, stopper)

Tip cap for luer

Needle shield or rigid needle shield for needle syringes

Plunger rod

Backstop or finger flange extender



Available in bulk or Ready-to-Use (RU) format



Single or multiple dose

Typical Fill Volume: 0.25mL – 3mL

Drug Content Format

Liquid, powder / lyo

Package Components

Container (glass or polymer)

Plunger

Lined seal

Device

Pen system

Disposable needles



Available in bulk or Ready-to-Use (RU) format

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



Risks for Container Closures

Potential Risks with High Regulatory Focus



- Preservation of drug or biologic
 - Chemical incompatibility
 - Leachables formation
- Variability in quality of container closure systems
 - Particle levels
 - Visual defects
- Reliability with device delivery
 - Dimensional control
 - Functionality
- Sterile component availability
 - Various fill-finish requirements
 - Equivalent quality in bulk, nest and port bags

- Sealing properties and 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



What we Measure

Why it Matters

Hardness (Durometer)

Can affect physical attributes of the elastomer (coring, breakloose and extrusion, compression and CCI)

Crosslink Density (% Swelling)

Can predict gross compatibility issues

Barrier Properties (O₂ 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

Main pharmacopoeia chapters that reflect elastomeric primary packaging of pharmaceuticals

- **Ph. Eur. Chapter 3.2.9**

- Rubber Closure for Containers for Aqueous Parenteral Preparations, for Powders and Freeze Dried Products

- **USP Chapter 381**

- Elastomeric Closures for Injections (also Chapter 1; Chapter 87 and 88)

- **JP 16th edition Chapter 7.03**

- Test for rubber closures for aqueous solutions

Extractable

Compounds removed from individual components of the packaging system under appropriate solvent and temperature conditions

→ exaggerated conditions

Leachable

Compounds that migrate from the container/closure (c/c) system of the drug or biologic product under normal conditions of use or during stability studies

→ normal conditions

■ 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

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.





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

Ozone Cracking



Frosting (Bloom)



Typical modern rubber formulations

7028/55 Gray

Does not crack

7025/65 Gray

Not made with natural rubber!



Film – sheet (e.g. PTFE, ETFE) that is laminated to elastomeric component during the molding process,

- Barrier function e.g. FluroTec[®] film

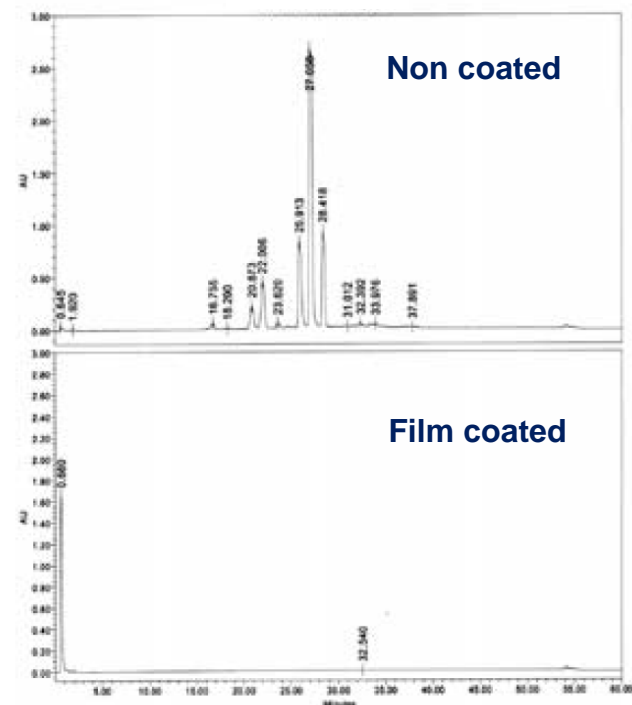
Coating – liquid or vapor that is sprayed, tumbled or vapor deposited onto the elastomeric component

- Lubricity e.g. B2-coating
- Lubricity and barrier function

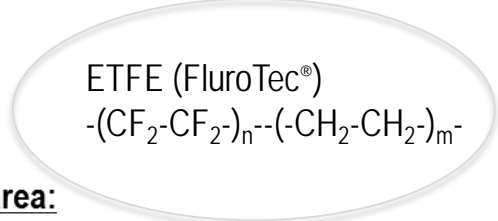
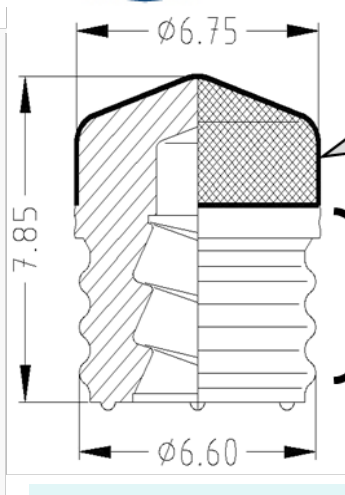
Fluoropolymer films (FluroTec[®] Film)

- Applied during the compression molding process
- Barrier from leachables and extractables
 - Minimize interaction between elastomer and drug ingredients
- Superior functional performance
 - Provides lubricity without the need for silicone oil
 - Ensures predictable piston release and travel forces
- Reduces adsorption of drug product

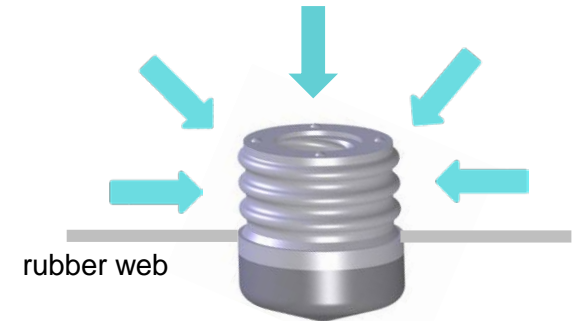
HPLC/PDA Overlay –
Time 6 Months, 50% Ethanol



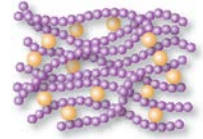
Most marketed biopharmaceuticals use fluoropolymer-coated component technology (FluroTec[®] film)



B2- 40 Coating

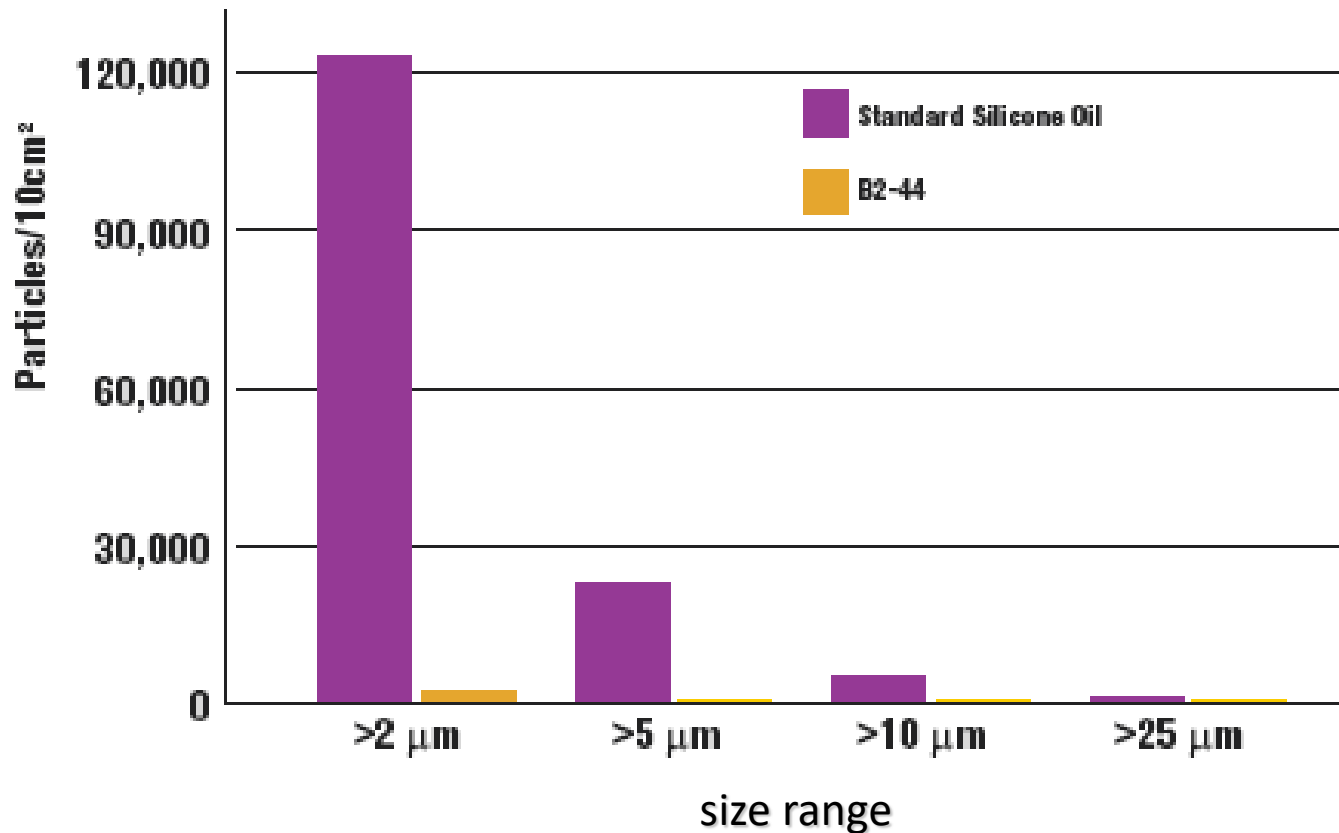


- Cross-linkable high molecular weight polydimethylsiloxane coating
- Applied to the surface of rubber stoppers and syringe components
- Low levels of silicone oil extractable
- Reduced particulate count
- Enhanced machinability
- Does not alter chemical and biological stopper/plunger properties



Lubricity Coatings

B2 Coating → Sub visible Particles



- 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

Prefillable Syringe Components



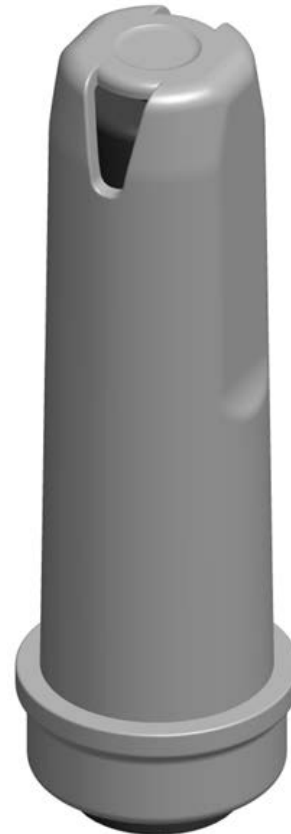
RNS 1/2" [13 mm]

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



RNS 5/8" [16 mm]

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



Rigid Needle Shield

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 un-shield when used with auto-injectors

Appearance

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

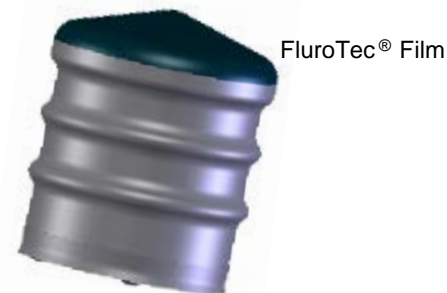
Rigid Needle Shields are the preferred closure for staked needle syringes

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



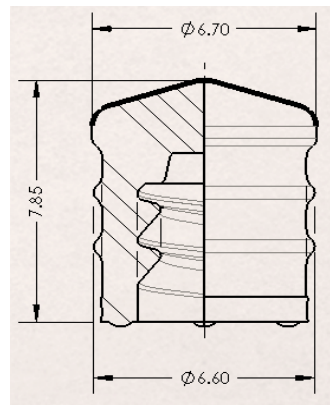
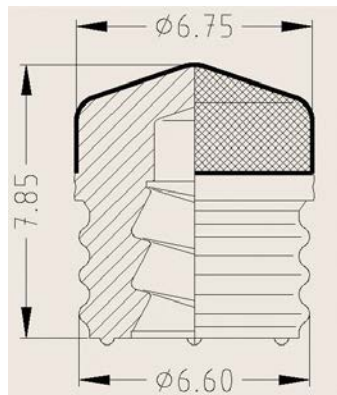
Plungers with coating and B2



Plungers without coating (with silicone)

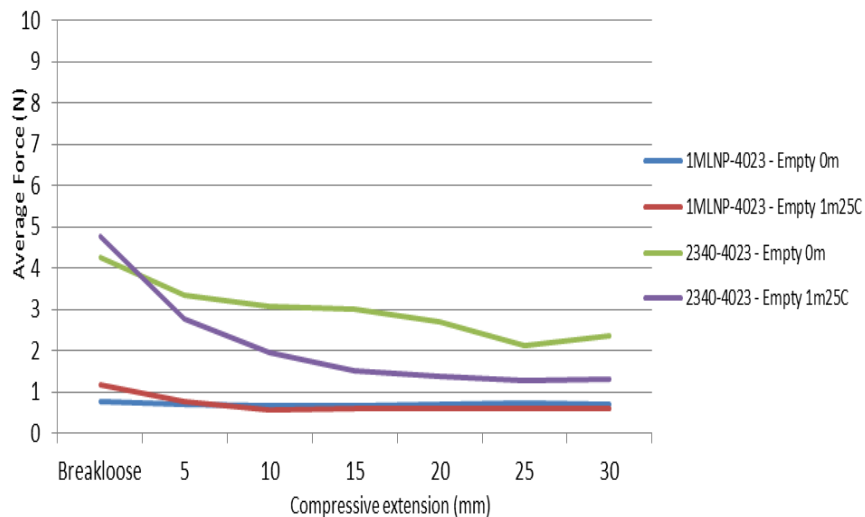


Common 1 mL Long
Fluoropolymer coated
plunger design → 2340

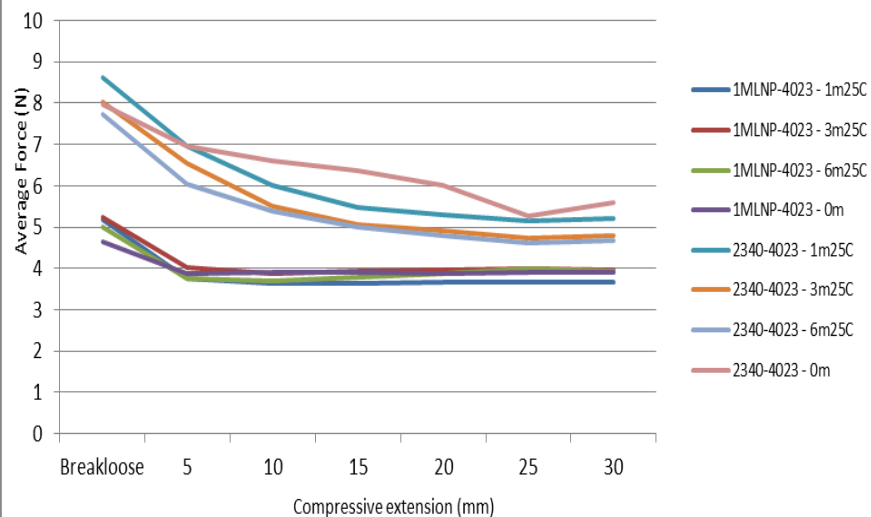


New generation 1 mL Long
fluoropolymer coated plunger
design – 1mL NP (1 mL Long
NovaPure[®] plunger

Empty 1 mL Long syringe_Break Loose and Gliding Forces



Water Filled 1 mL Long syringe_Break Loose and Gliding Force

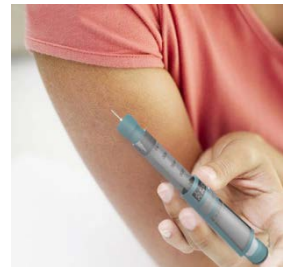




Prefillable Cartridge Components



- Common drug products in cartridges
 - Type I insulin and dental anesthetics - Majority of Applications
 - Human growth and interferon – Specialty
- Historically customers process cartridge components
 - 1.5ml and 3.0ml solid plungers
 - 8mm monolayer lined seals
 - 8mm laminate lined seals
- Evolving patient needs driving combination products
 - Self administration with ease of use
 - Dose accuracy and patient compliance

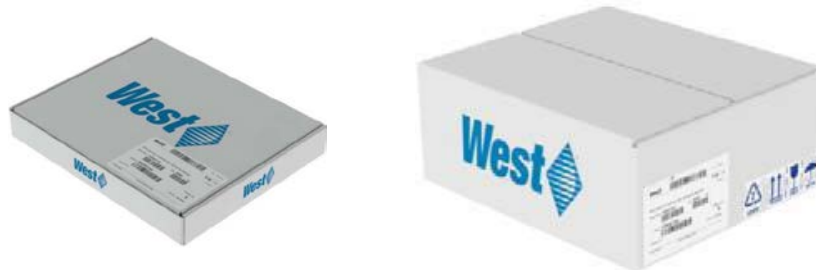


- Multiple designs on the market in different sizes, colors, rubber formulations
- Often customized





- Validated particle levels in specified size ranges
- Optimized silicone oil on plungers for device functionality
- Lined seals for multi-dose (laminated technology)
- Steam sterilized for lower levels of potential extractables
- Market proven elastomer formulations
- Flexibility of package options



Washing and sterilization can be sources of:

- Elastomer component loose particles

- Aluminum shell lacquer and metal particles

Elastomers impact reseal and coring issues

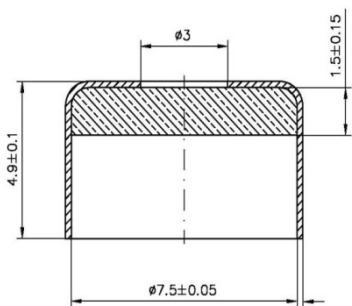
- Interaction of needle gauge and number of punctures

Silicone oil impacts functional performance

- Consistency controls breakloose and extrusion



8 mm Cartridge Lined



8 mm monolayer
Bromo - or Chlorobutyl
formulation

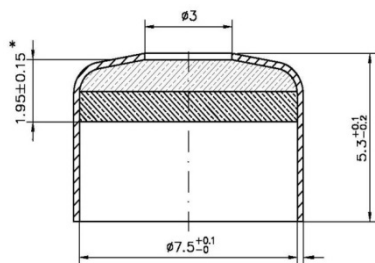
4432/50 or 4023/50 Gray

< 5 Punctures

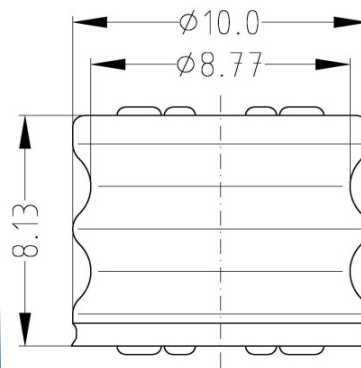
8 mm bi-layer [laminate]
Polyisoprene and Halobuty
formulations

4480/40 cream//7778/40
grey

> 5 Punctures

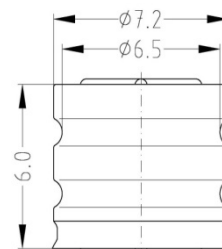


Solid Cartridge Plunger



3 mL Solid Cartridge Plunger

Available in State of the Art
Bromo -and Chlorobutyl
formulations

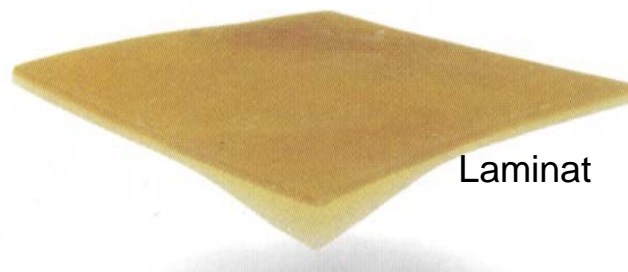
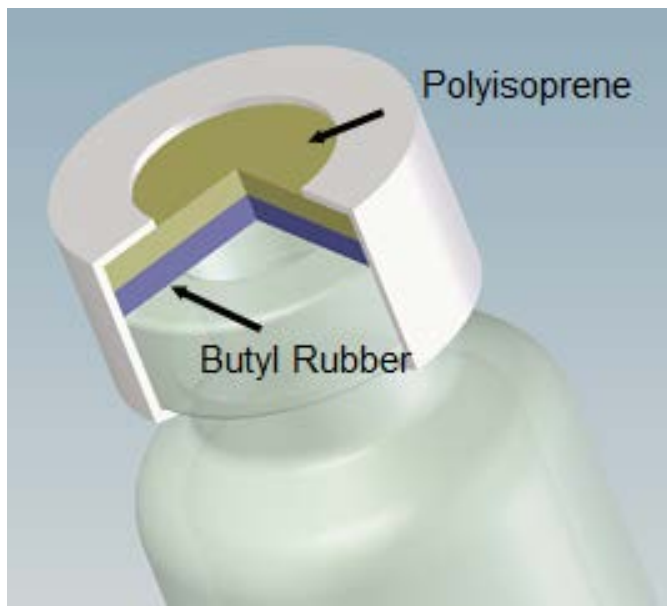


**1,5 mL Solid Cartridge
Plunger**

Available in State of the Art
Bromo -and Chlorobutyl
formulations

Laminated discs:

- Combination of low coring + good compatibility
 - Product contact side → Butyl Rubber
 - Non-Product contact side → Synthetic Polyisoprene



Different 'shapes' need different molding technology:

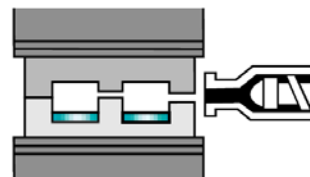
Compression Molding (CM)

Plungers, stoppers, disks....



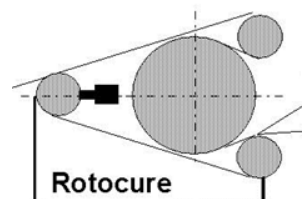
Precision Injection Molding (PIM)

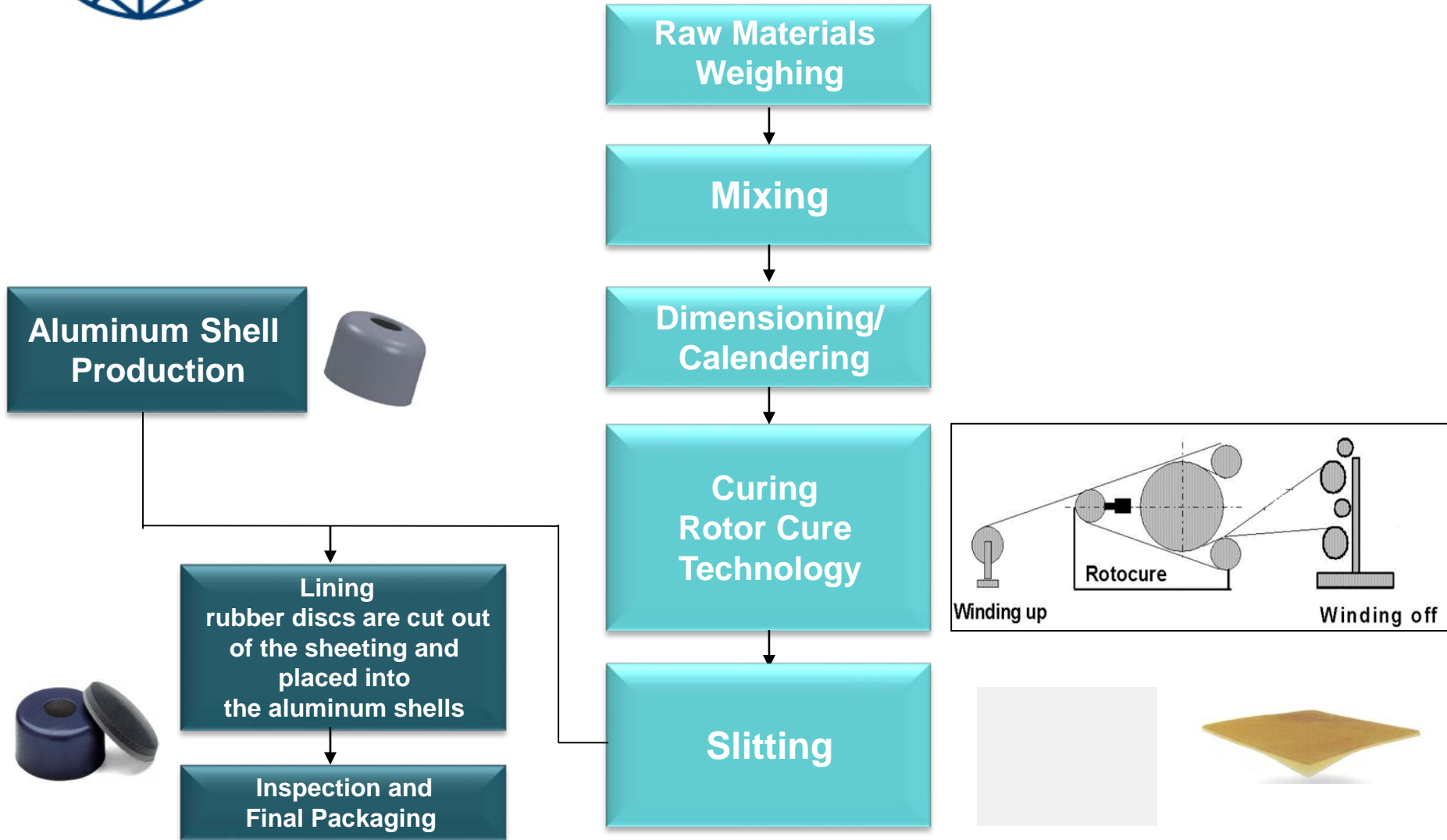
Needle shields ...

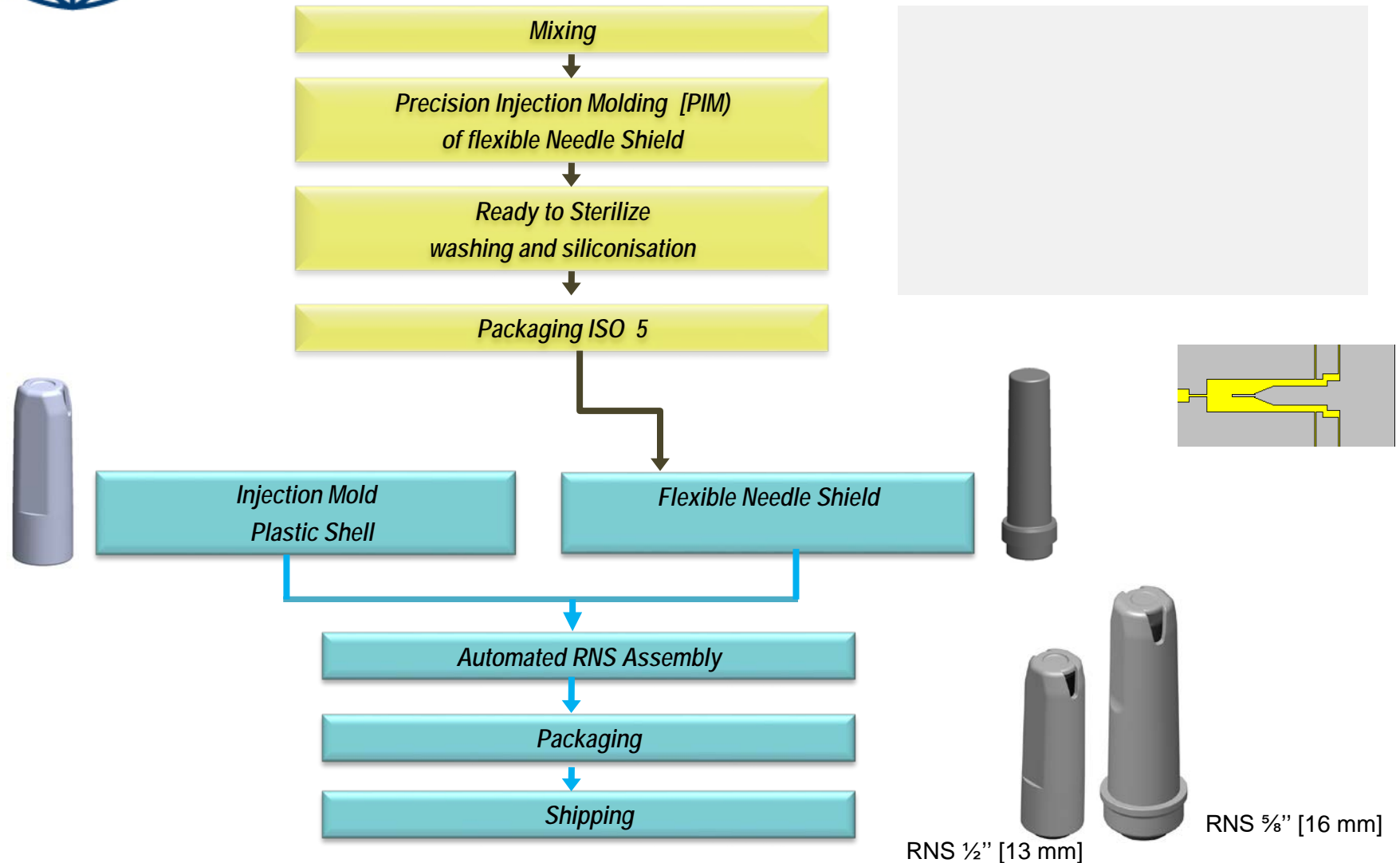


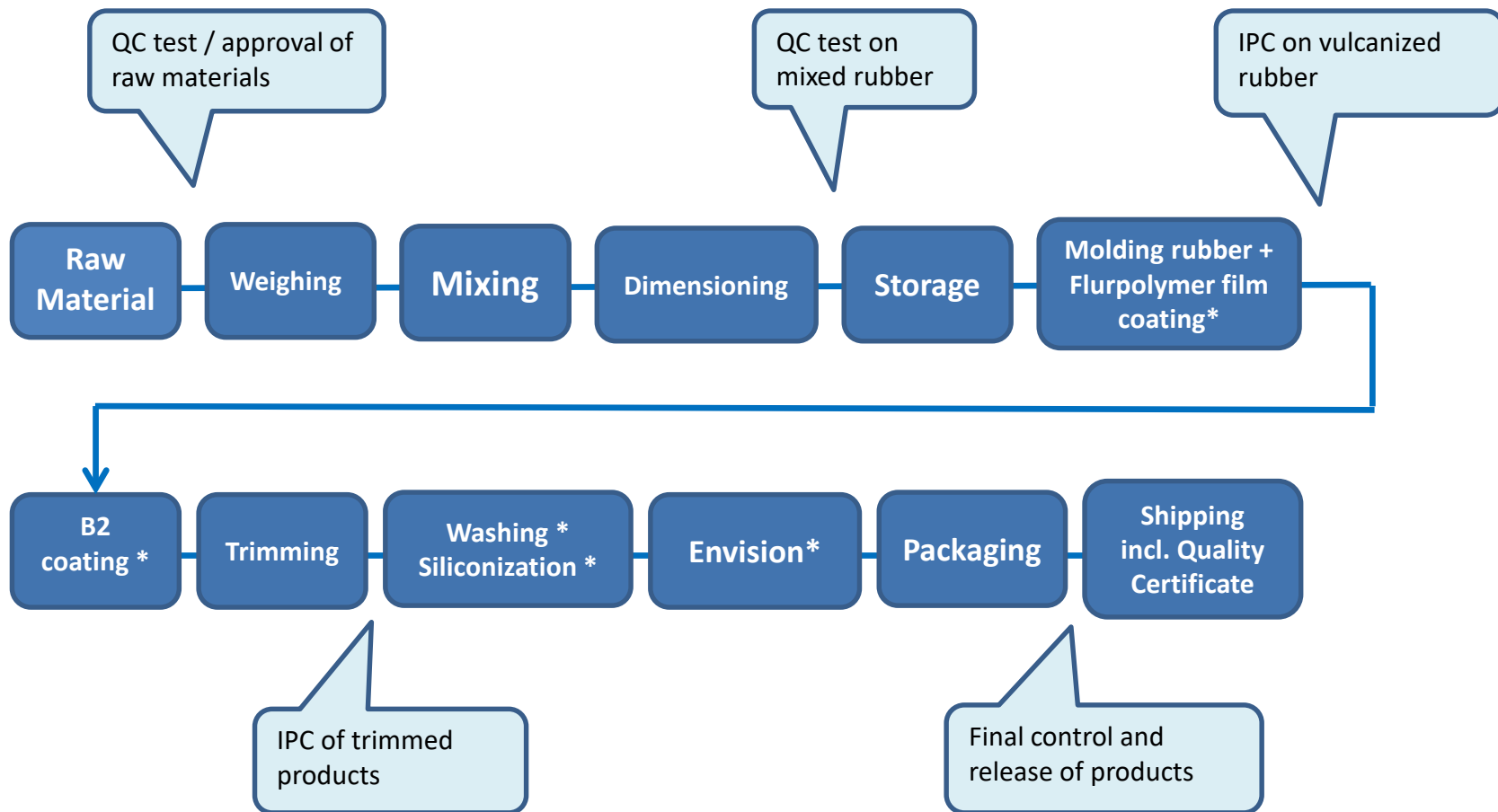
Rotocure (Sheeting Material)

Lined seals...



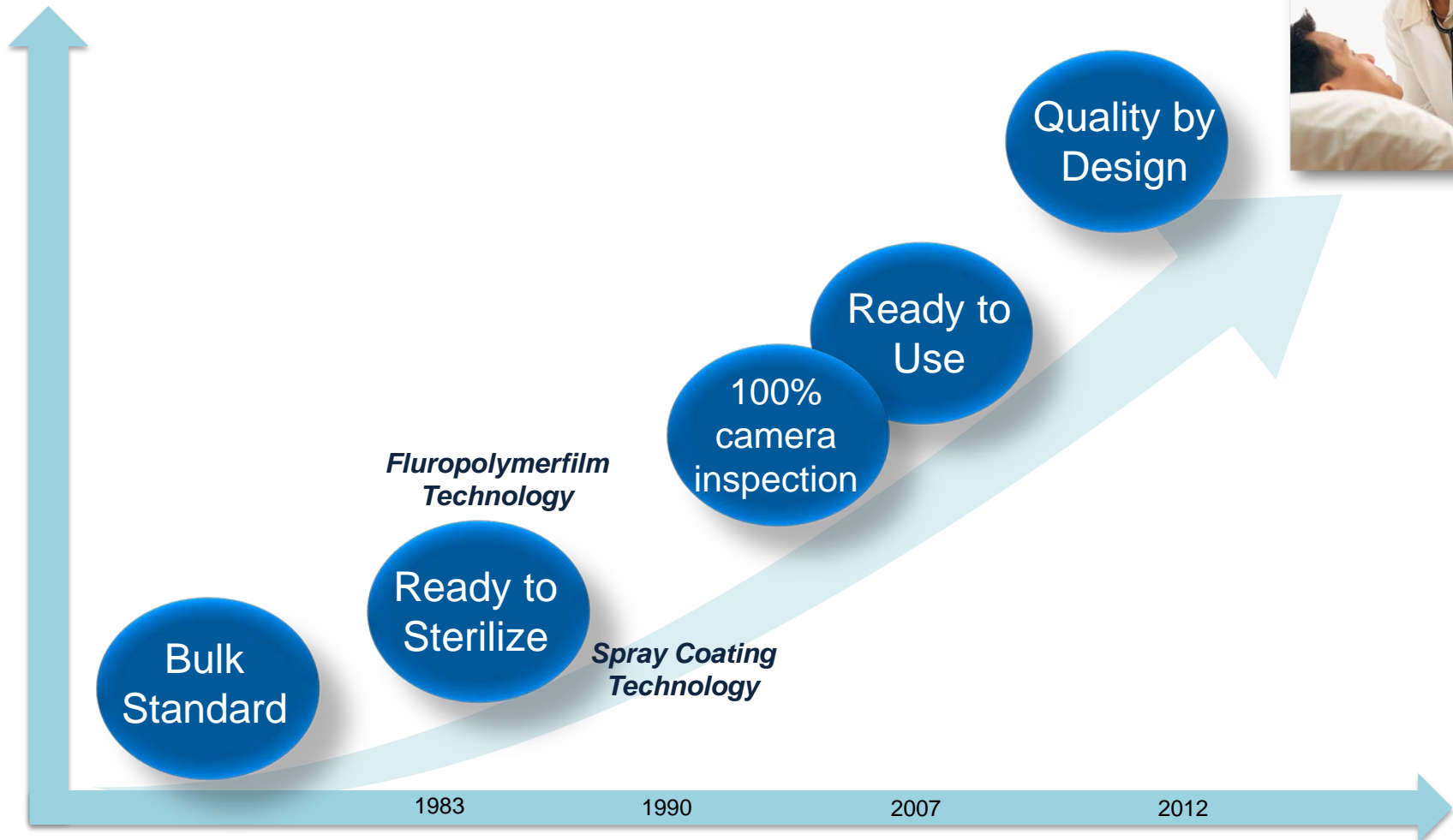


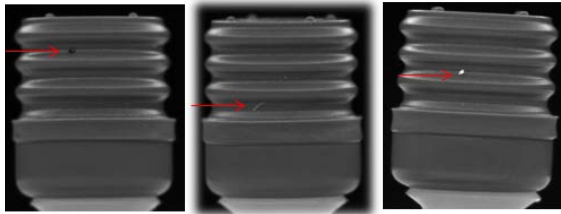




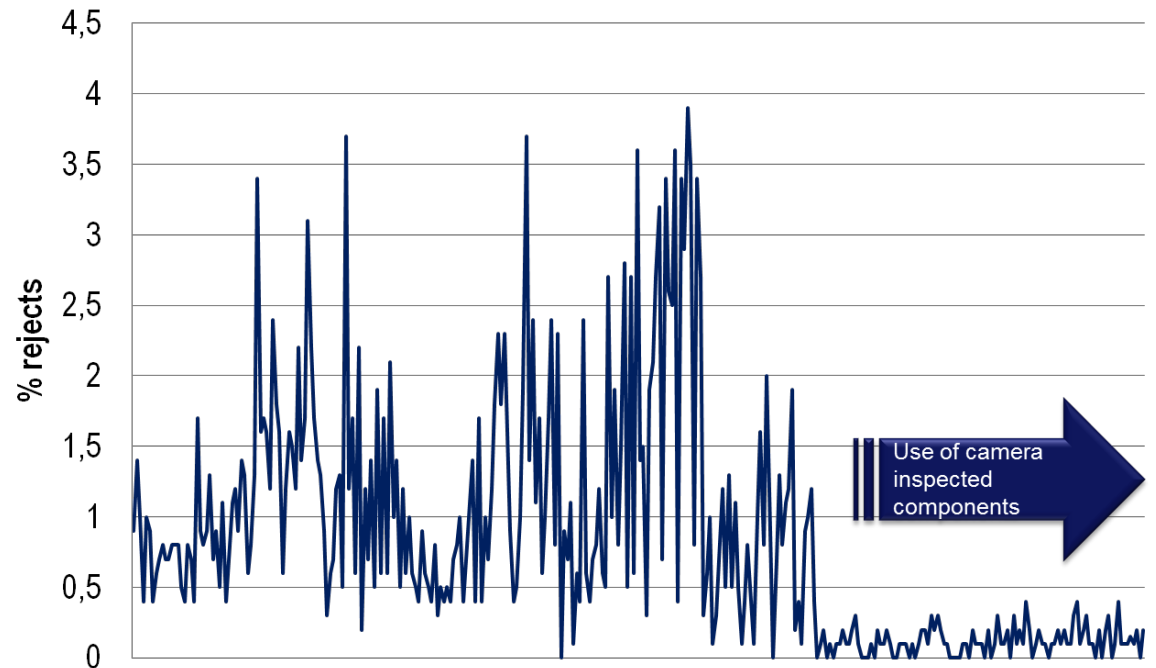
* optional upon request







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



Feedback loop for continuous improvement!

- Bioburden: ≤ 5 CFU/100 cm² (pre-sterilization)
- Endotoxin: ≤ 0.10 EU/mL
- Particles: ≤ 2.5 PCI (three size ranges)
- B2 or surface silicone oil level (each lot)



Biosafe[®] aseptic transfer equipment is for Isolators, RABS and cleanrooms

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



RU Plungers

Low Gamma sterilization
10–20 kGy

Steam
sterilization

Bag/portbag

Nest

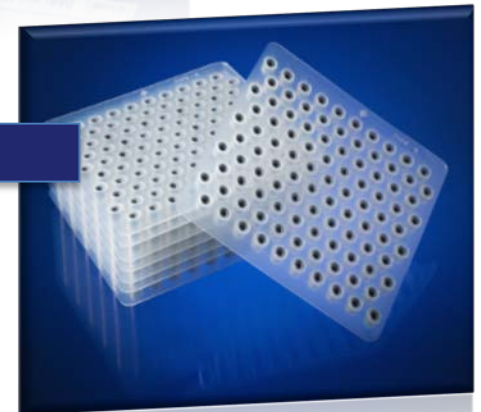
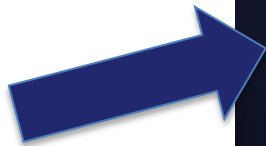
Steribag

Portbag

High-quality packaging materials

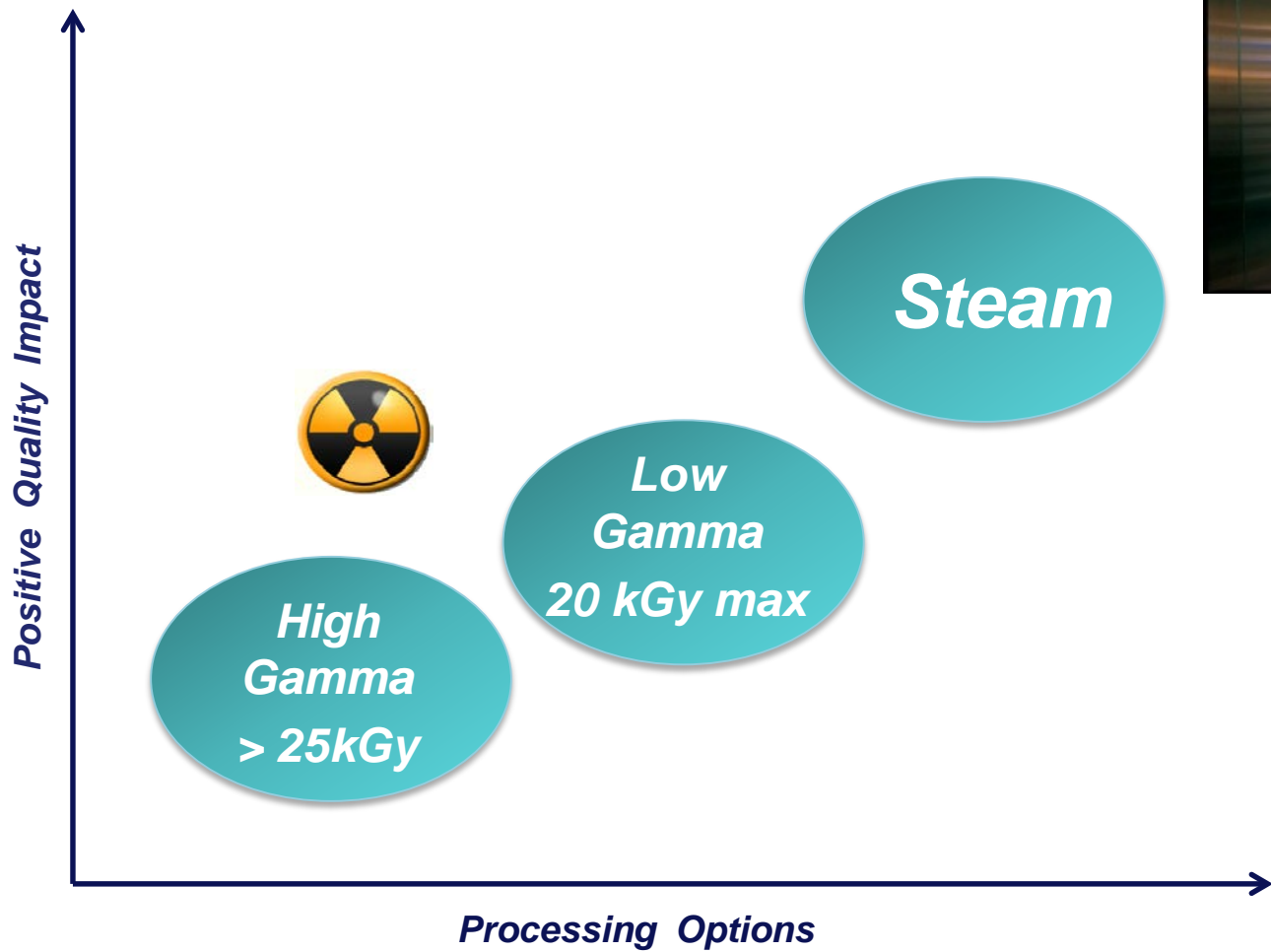
- Reduction of particle load of primary packaging → tighter specification
- Ease of use
- Pin hole resistant – physical – stress
- Plastic cartons & plastic pallets



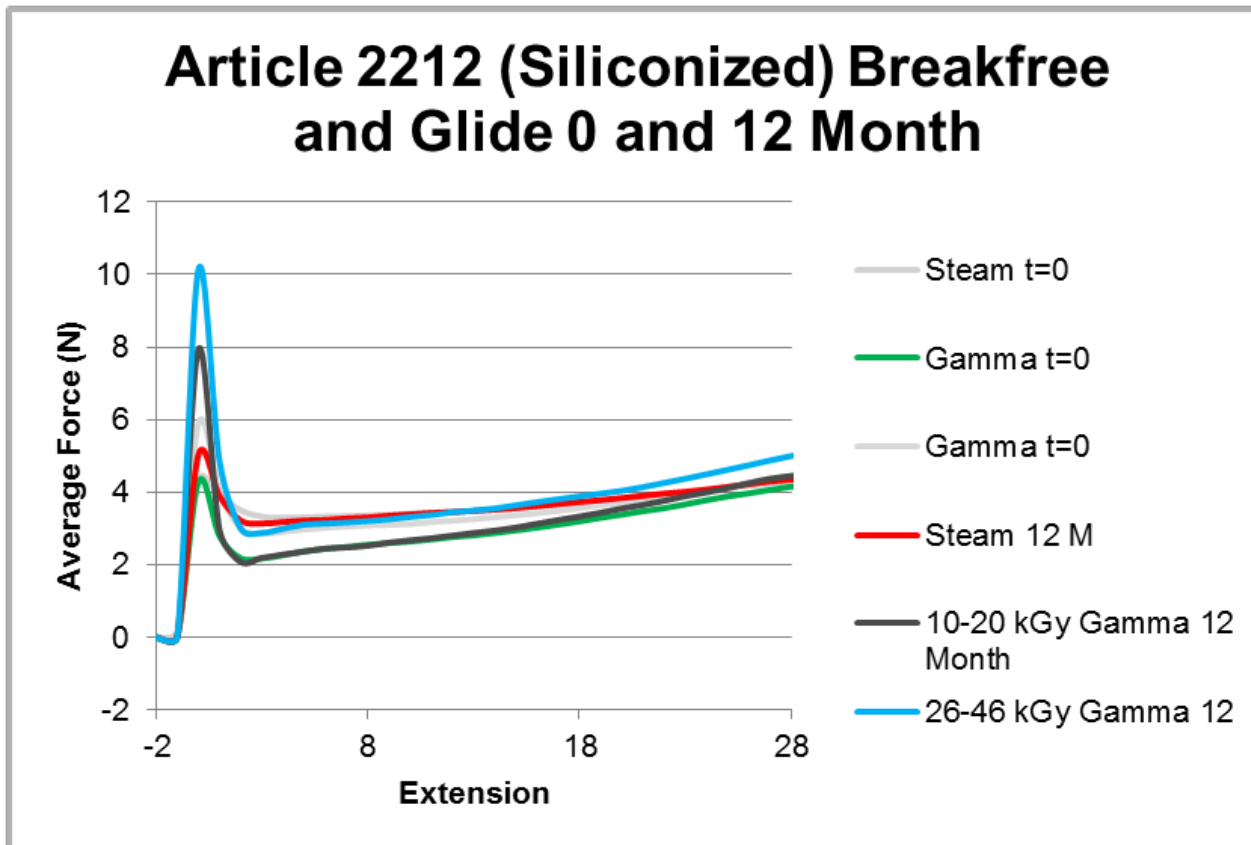


- Multiple packages for industry requirements
- No plunger preparations is required
- Available with 100% automated verification

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



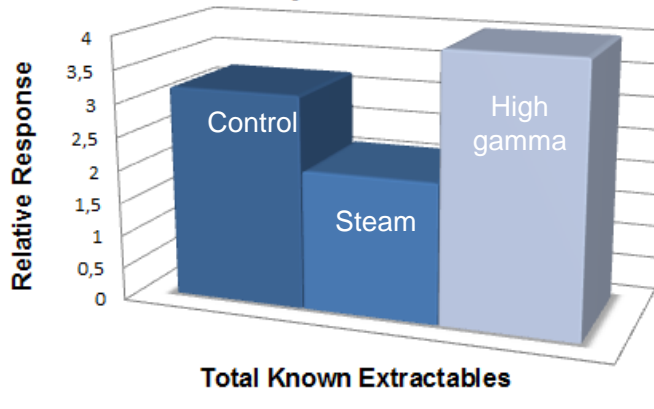
1 mL long Plunger - Break Loose and Gliding Force at 0 and 12 Month



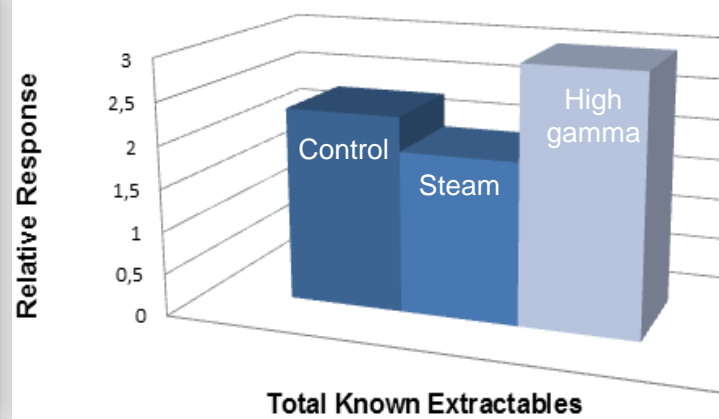
Key findings:

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

Chlorobutyl - Known Extractables



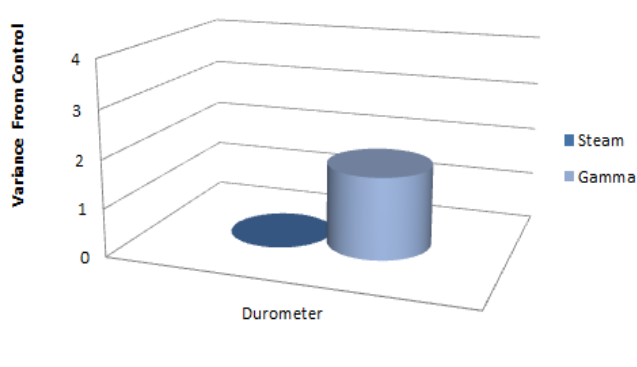
Bromobutyl - Known Extractables



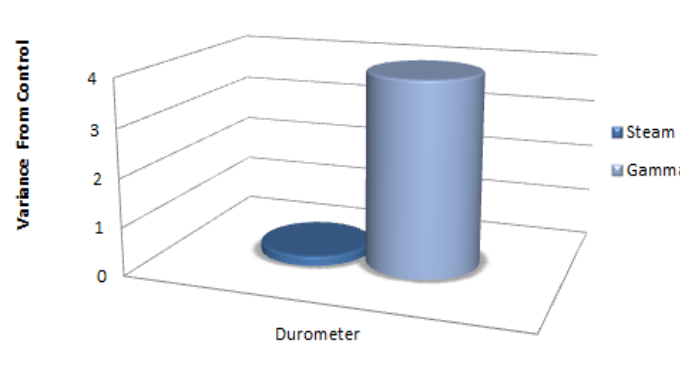
Key findings:

High gamma shows twice the amount of known extractable

Chlorobutyl - Durometer (Hardness)



Bromobutyl - Durometer (Hardness)



Hardness is significantly increasing after high gamma treatment

The Ready-to-Use steam sterilized plungers can mitigate risk for chemical and physical deterioration through an optimized steam sterilization cycle that, when compared to high-dose gamma irradiation may:

- ✓ **Minimize impact on elastomer physical characteristics, and chemical oxidation and degradation during shelf life**
- ✓ **Decrease the number and lower the levels of extractables, with less potential for interaction between the plunger and the drug product**
- ✓ **Improve prefilled syringe functionality due to lower and more consistent break-free forces**



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

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