All about Pre-filled Syringe Systems

From Initial Development to Final Fill Finish

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PDA Parenteral Drug Association

West

GERRESHEIMER

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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

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

Risks for Container Closures Systems – Potential Risks with High Regulatory Focus

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

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

Elastomer Physical Properties

What we Measure	Why it Matters
Hardness (Durometer)	Can affect physical attributes of the elastomer (coring, break loose and extrusion force, compression and CCI)
Crosslink Density (% Swelling)	Can predict gross compatibility issues
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

Definitions Extractable and Leachable

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

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

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	Heavy metals, Zinc, Ammonium, Volatile Sulfides	✓	✓	✓	✓
Functionality Tests	Fragmentation, self-sealing, …	✓	✓	—	✓

Global Comparison of Elastomer Chapters

USP	European Pharmacopeia	JP Japanese Pharmacopeia	PHARMACOPEIA OF THE PEOPLE'S REEPUBLIC OF CHINA
- Separating material characterization from functionality Tests - Including E&L	- Revision of Heavy Metals / Elemental Impurities and methods - Plastics materials & additives	- Deletion of pyrogen and hemolysis test - Addition of cytotoxicity test	Ongoing revisions in all topics With a strong attention to the global revision process and discussion

Justification for <381> Modernization

New Title:

“Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems”

to address diversity of elastomeric components and applications:

Included, but not limited to, vials, bottles, prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), injection ports for flexible bags and infusion sets, and plungers for single-use syringes.

Separate physicochemical from functionality testing

Proposed Revisions for <381>

<381> Elastomeric Closures For Injections

<381> Elastomeric Components Used in Injectable Pharmaceutical Packaging Delivery Systems

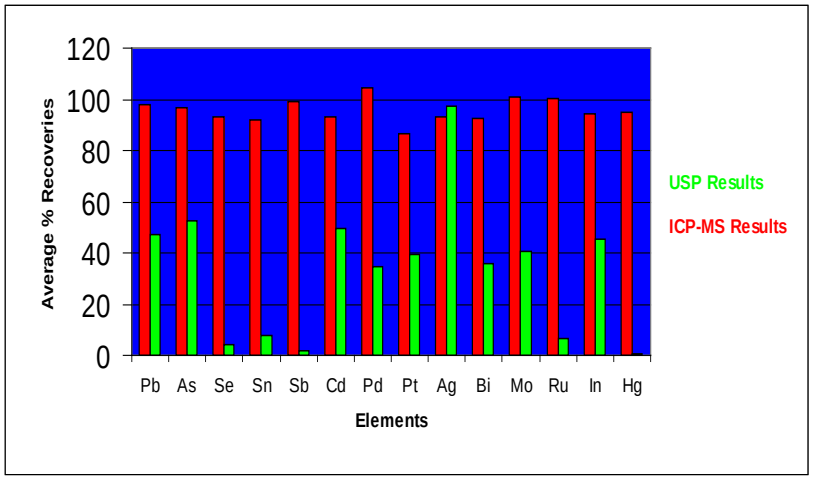
- Identification
- Biological Activity
- Physico-chemical Tests
- Extractable Metals

<382> Elastomeric Closure Functionality in Injectable Pharmaceutical Packaging Delivery Systems

- Needle and Spike Access Tests
- Plunger Tests
- Tip Cap and Needle Shield Tests

Addressing Extractable Elements in <1381>

Method is verified and elements consistent with ICH Q3D



USP Metal Impurities Initiative 2009
Darrell R. Abernethy, MD, PhD,Chief Science Officer, USP

Specific elements of interest

Antimony, arsenic, cadmium, cobalt, copper, lead, lithium, mercury, nickel, vanadium, zinc
Reported in amounts greater than 0.05 µg/g converted to µg/component or < Limit of Detection

Extraction solution

Mixture of acids with stabilizers

Extraction conditions/analysis

70°C 24 hrs/ICP/MS and/or ICP OES

Extraction recovery

Report as found

Limits will depend specific drug product on risk safety/quality

Extract of Relevant ISO Standards

ISO

- **Glass Containers**
  - 719, 720
  - 4802-1, 4802-2
  - 11040-1, 11040-4
  - 8362-1, 8362-4
  - 13926-1
- **Elastomers Components**
  - 11040-2, 11040-3, 11040-5, 11040-7
  - 8362-2, 8362-3, 8362-5, 8362-6, 8362-7
  - 8871-2 8871-4, 8871-5
  - 13926-3
- **Plastics Materials**
  - 11040-6
- **Polymer Manufacturing Components**
  - 9113
  - 17855
  - 2898
- **E&L**
  - 8871-1
- **Particles**
  - 8871-3

- **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

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*

*only valid for Polyisoprene

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

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
  - Does not crack
- 7025/65 Gray

Not made with natural rubber!

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

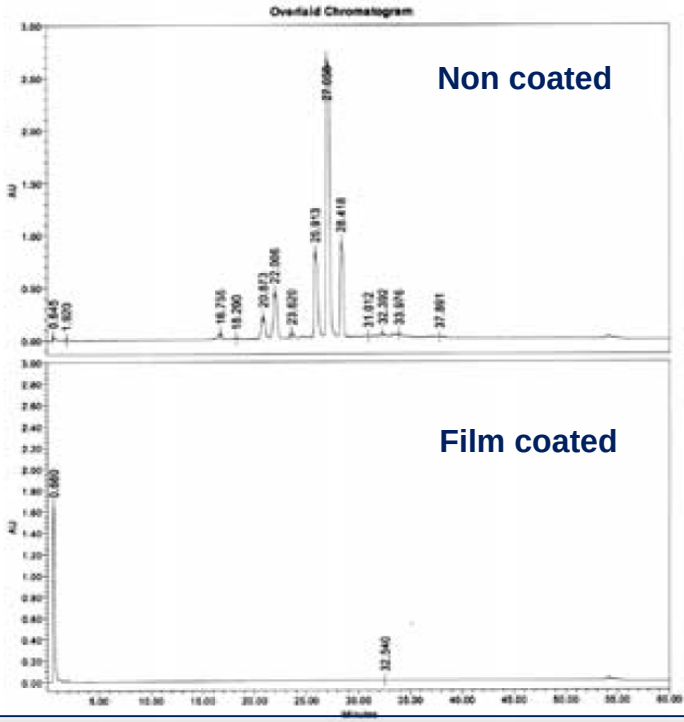
- Lubricity, e.g. B2-coating
- Lubricity and barrier function

Fluorpolymer Lamination i.e. FluroTec® Film

Fluorpolymer films

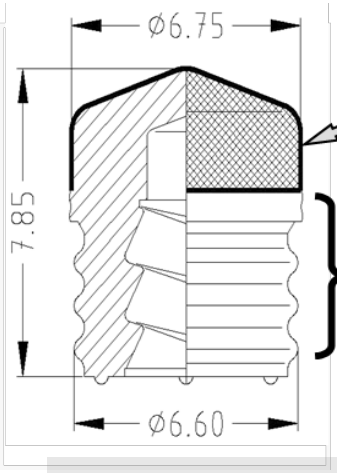
- Applied during the compression molding process
- Barrier from leachables and extractables
  - Minimize interaction between elastomer and drug ingredients
- Superior functional performance
  - Provides lubricity without the need for silicone oil
  - Ensures predictable piston release and travel forces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

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



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

Fluorpolymer Lamination

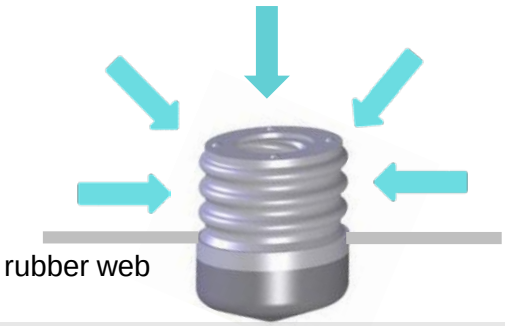


Laminated area:
Eliminates direct contact between rubber and drug

Sealing area:
- Provides good sealing
- B2 coated

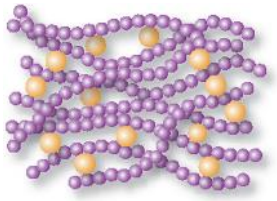
ETFE (FluroTec®)
$-(CF_2-CF_2-)_n--(-CH_2-CH_2-)_m-$

B2- 40 Coating



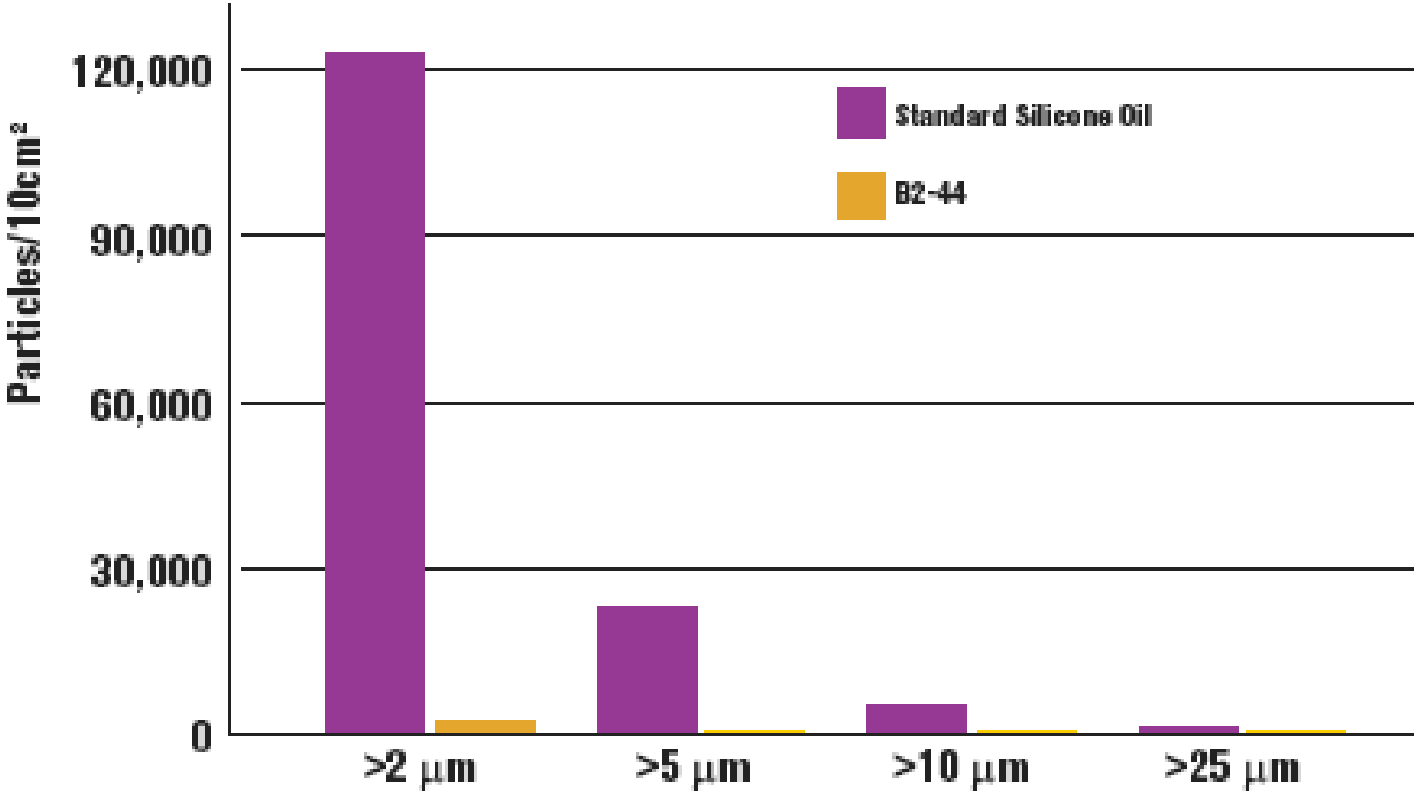
- Cross-linkable high molecular weight polydimethylsiloxane coating
- Applied to the surface of rubber stoppers and syringe components
- Low levels of silicone oil extractable
- Reduced particulate count
- Enhanced machinability
- Does not alter chemical and biological stopper/plunger properties

B2-coating vs. Traditional Silicone Oil



Lubricity Coatings

B2 Coating → Sub visible Particles



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	*Disadvantages*
▪ Commonly used ▪ Applied during wash cycle ▪ Low cost	▪ Particles/droplets may be found in drug product ▪ Silicone level may be inconsistent if process is not validated

Design Examples of Rigid Needle Shields

RNS ½" [13 mm]

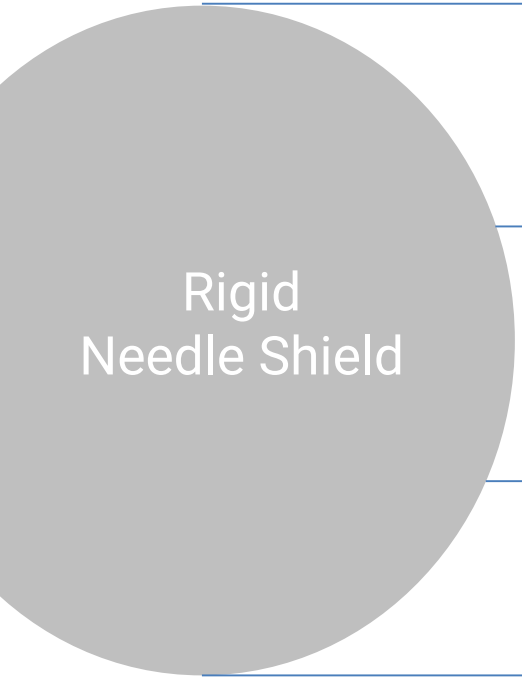
Needle length used for subcutaneous drug injection (into the tissue layer between the skin and the muscle)

RNS ⅝" [16 mm]

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

West RNS™ Rigid Needle Shields

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 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

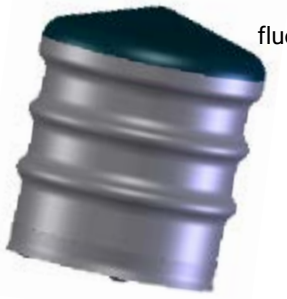
Example of Prefilled Syringe - Plunger Portfolio at West

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 mLLong 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

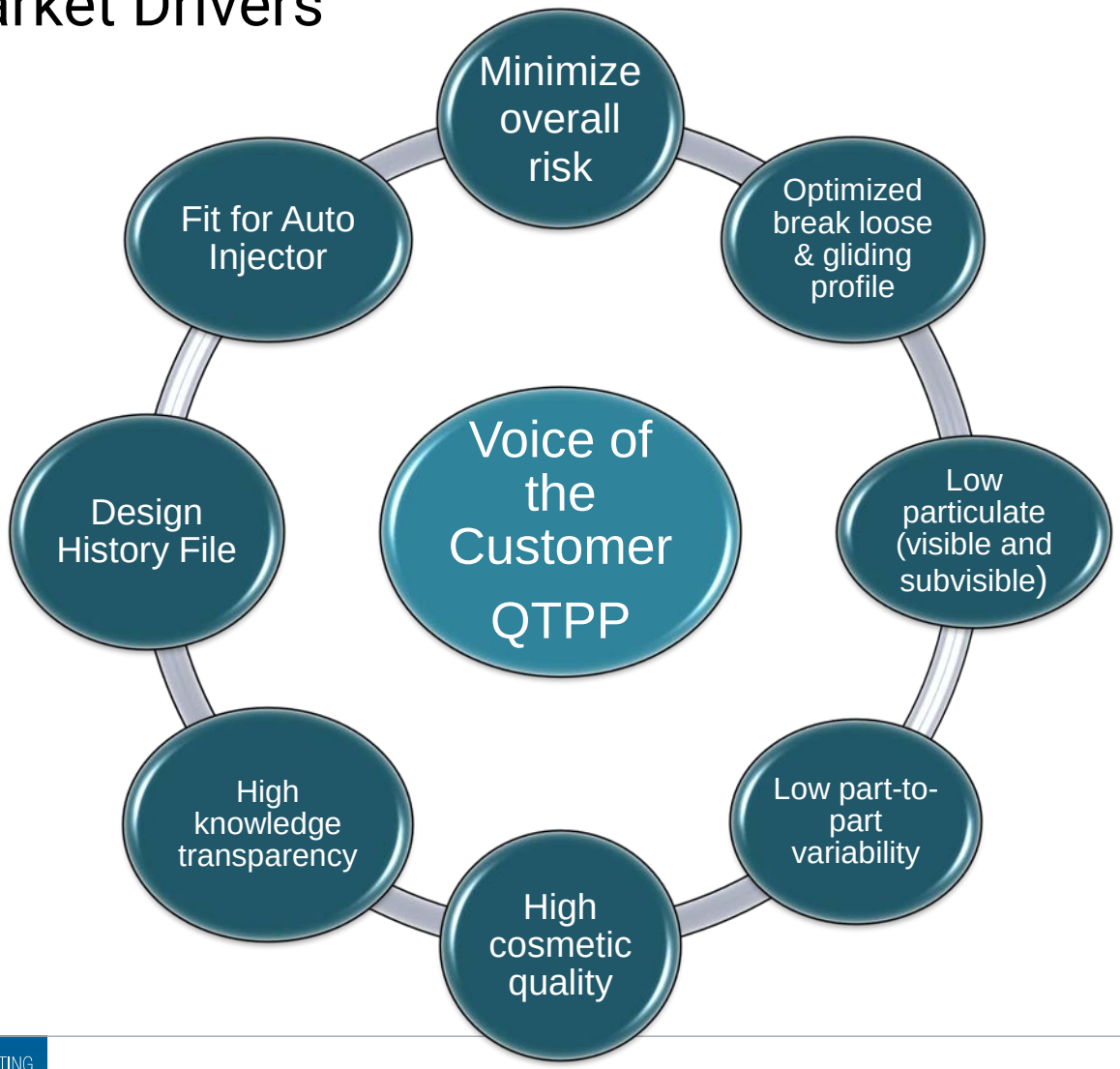
Majority of designs are customized



Plungers with coating and B2

Plungers without coating (with silicone)

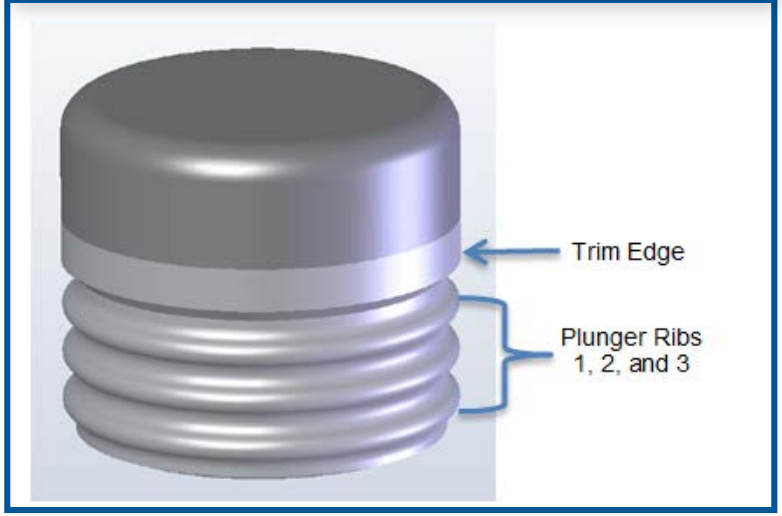
Market Drivers



Examples of Plunger Design Intent

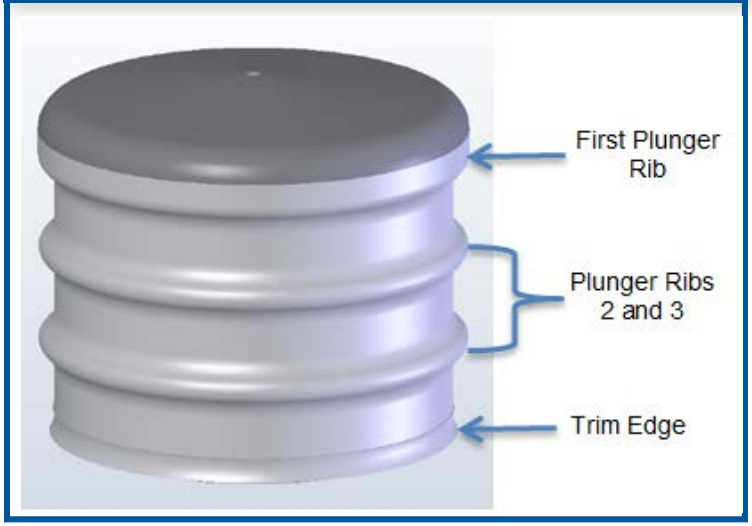
1-3 mL FluroTec®

- First rib acts as the primary seal
- Ribs 2-3 are secondary sealing ribs
- Trim edge is at the back of the plunger and is not a sealing feature



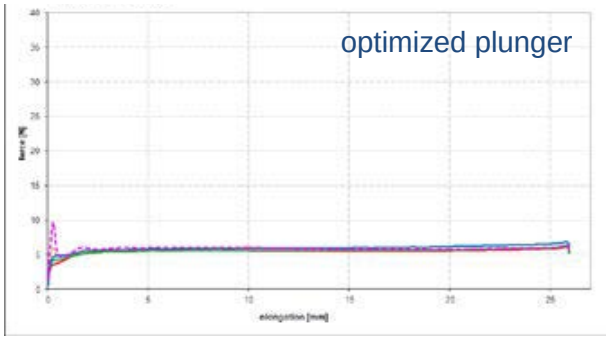
1-3 mL NovaPure®

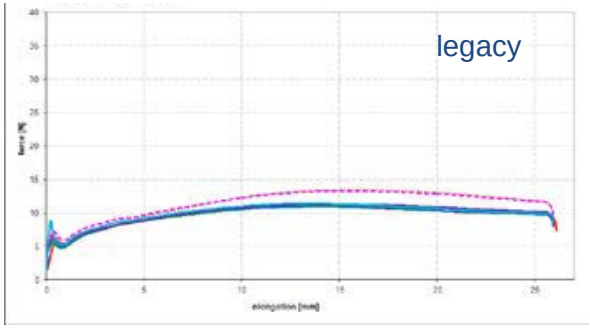
- First rib acts as the primary seal
- Ribs 2-3 are secondary sealing ribs
- Trim edge is at the back of the plunger and is not a sealing feature



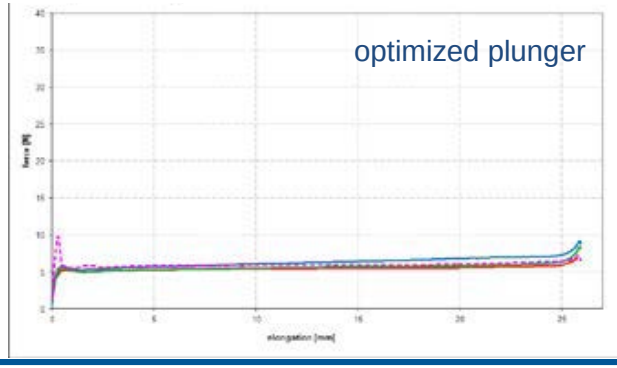
Functionality of 1 mL Long laminated Plungers

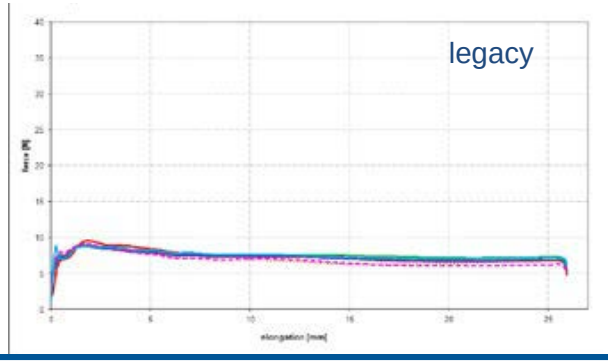
Vent tube placement





Vacuum placement





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

Graphs courtesy of Gerresheimer.

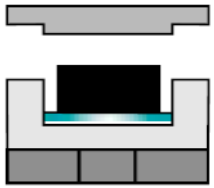
Optimized Plunger design shows:

- low break loose and gliding forces with very consistent, smooth profiles and minimal variation
- meeting functionality requirement for use with auto-injectors and other medical delivery devices.
- Neither placement nor storage conditions have a determinable influence on the optimized BLG

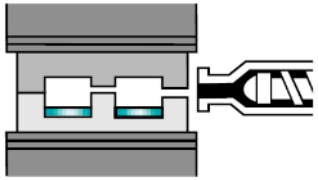
Pharmaceutical Rubber Manufacturing

Different ‘shapes’ need different molding technology:

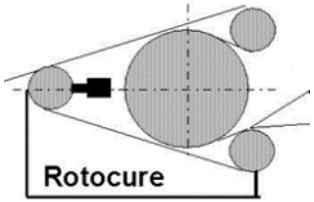
- Compression Molding (CM)
  Plungers, stoppers, disks….



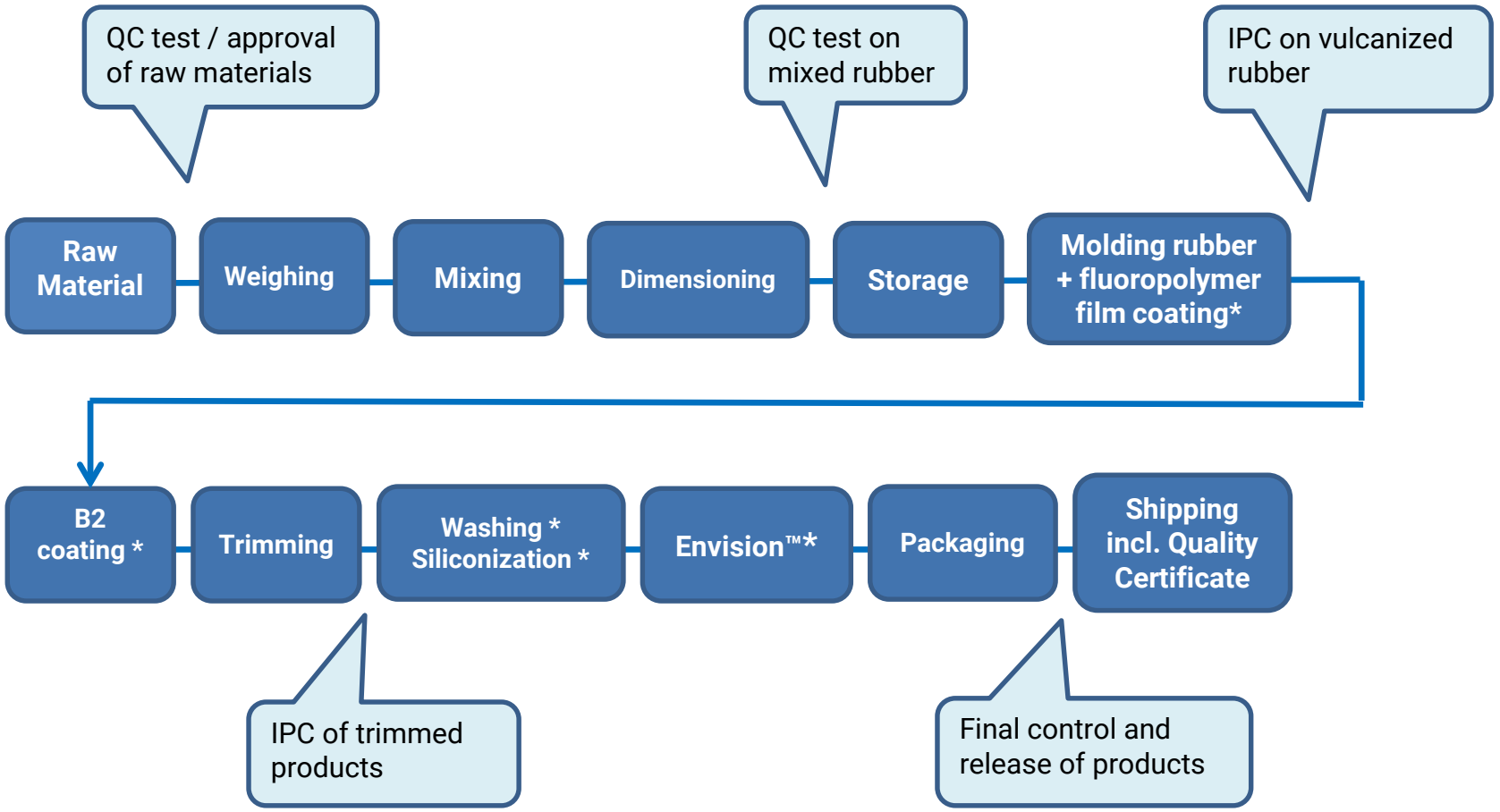
- Precision Injection Molding (PIM)
  Needle shields …



- Rotocure (Sheeting Material)
  Lined seals…



Production of Plungers Compression Molding



* optional upon request

Manufacturing Process

Internal Mixer

- Components are mixed by means of rotors that are turning
- Shearing the elastomer
- Squeezing out air
- Incorporating all material
- Critical parameters are specific for the individual formulations: rotor speed, temperature, time, filling volume, etc.

Open Mill

- The mixture is being homogenized more using 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
- Coasted into webs with defined thickness and width
- Webs are led to relax for some time

Mixing Control (Mill Control)

Curing of ISO - standard sample for testing purposes:

- Specific Gravity of test sample - per Batch
- Shore A of vulcanized sample - per Batch
- Dispersion of vulcanized sample - per Batch
- Color of vulcanized sample - per Batch
- Ash - 1 + (10) batch = every 10th batch plus first and last
- Rheology of the compound - 1 + (5) batch = every 5th batch plus first and last

Manufacturing Process

Compression Molding

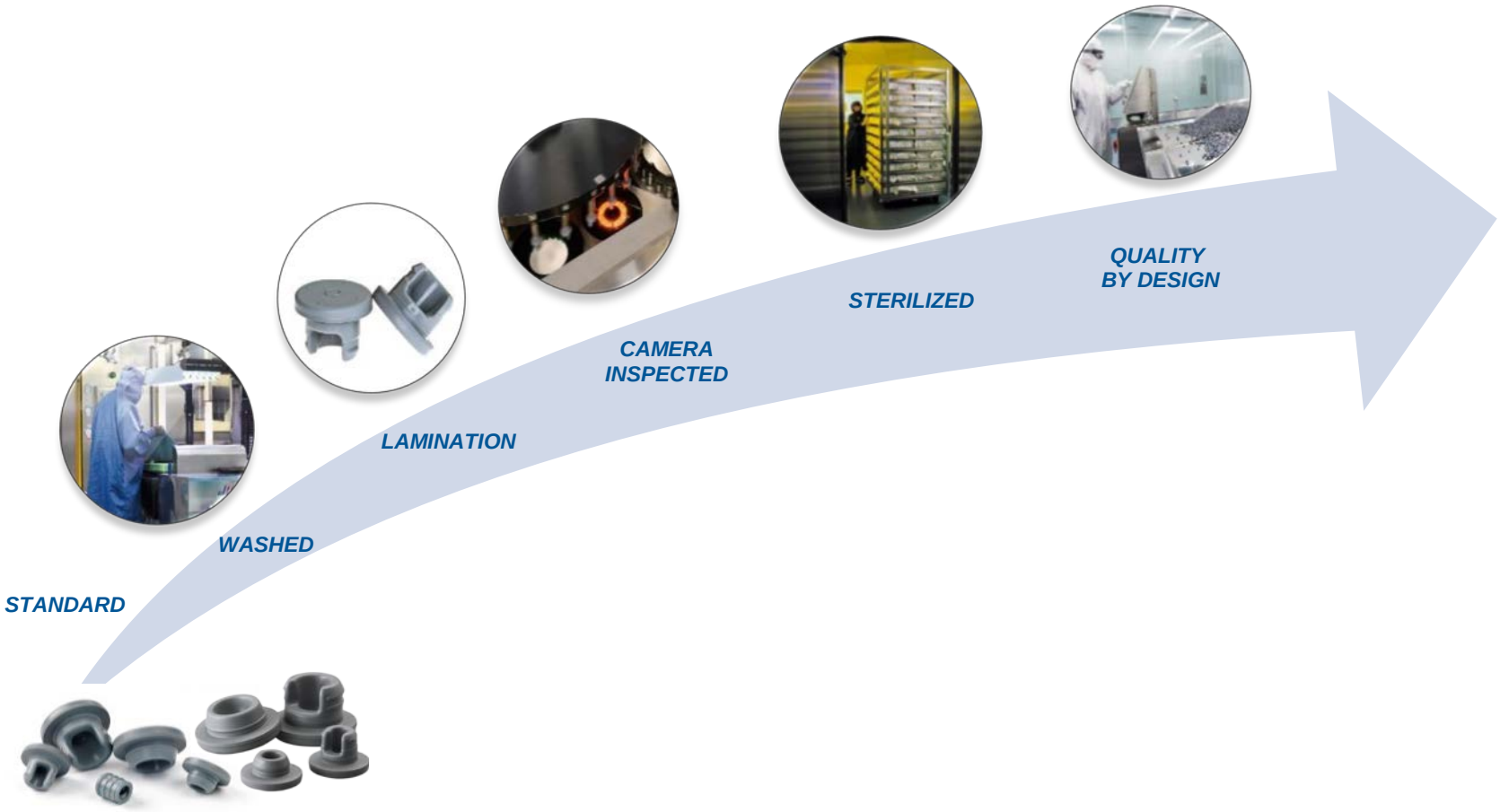
- Compression and Precision Injection Molding
- Vulcanization takes place
- Critical parameters are specific for the individual formulations: press speed, temperature, time, vacuum, etc.

Trimming

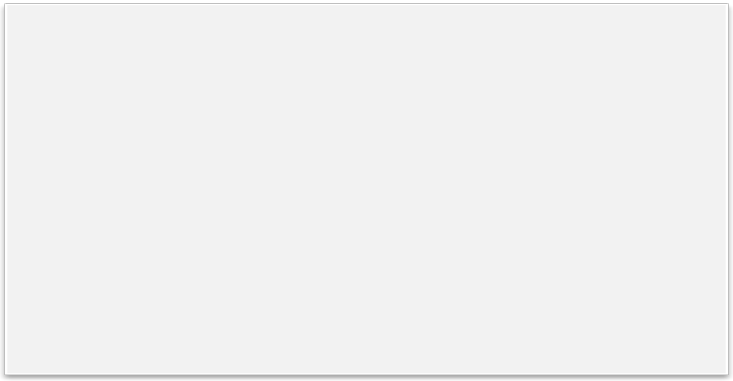
- Trim presses designed for cleanroom manufacturing
- Enhanced trim dies to lower particle contamination
- Automated control of web positioning
- Automated web spraying for lubrication

- Single parts transferred to Washing operations

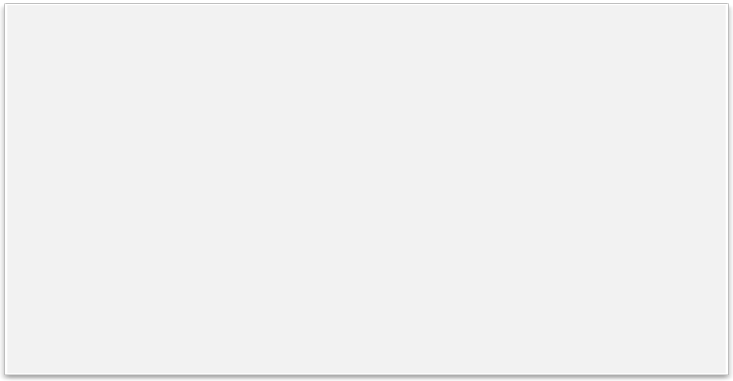
Differentiated Solutions: Increasing Quality & Inspection



Final Inspection: Sampling, Packing and Release Testing

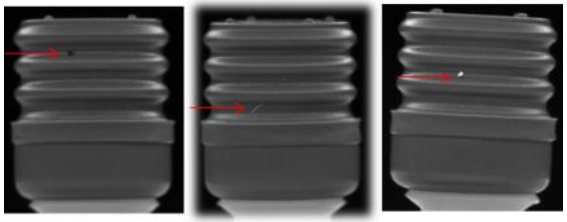


- Evaluation of sample size according to ISO 2859
- Visual check according to the defect evaluation list for rubber parts
- Defect / individual characteristics
- Dimensional Inspection

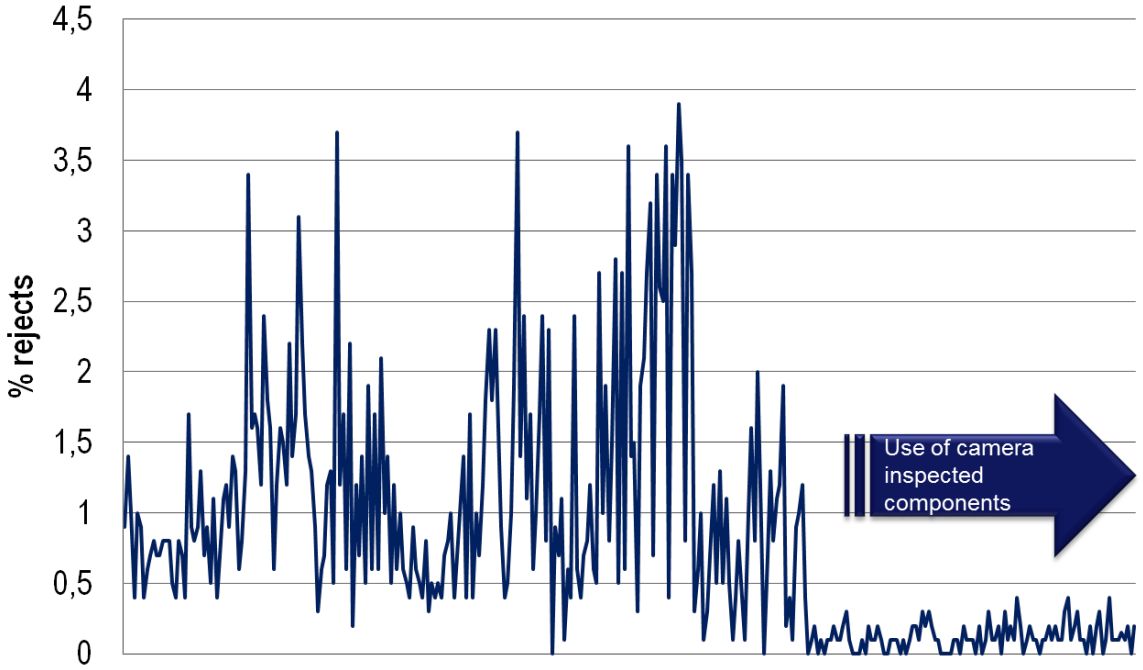


- AQL Samples
- Customer Samples
- Retain Samples
- Test Samples

Production of Plungers Compression Molding



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

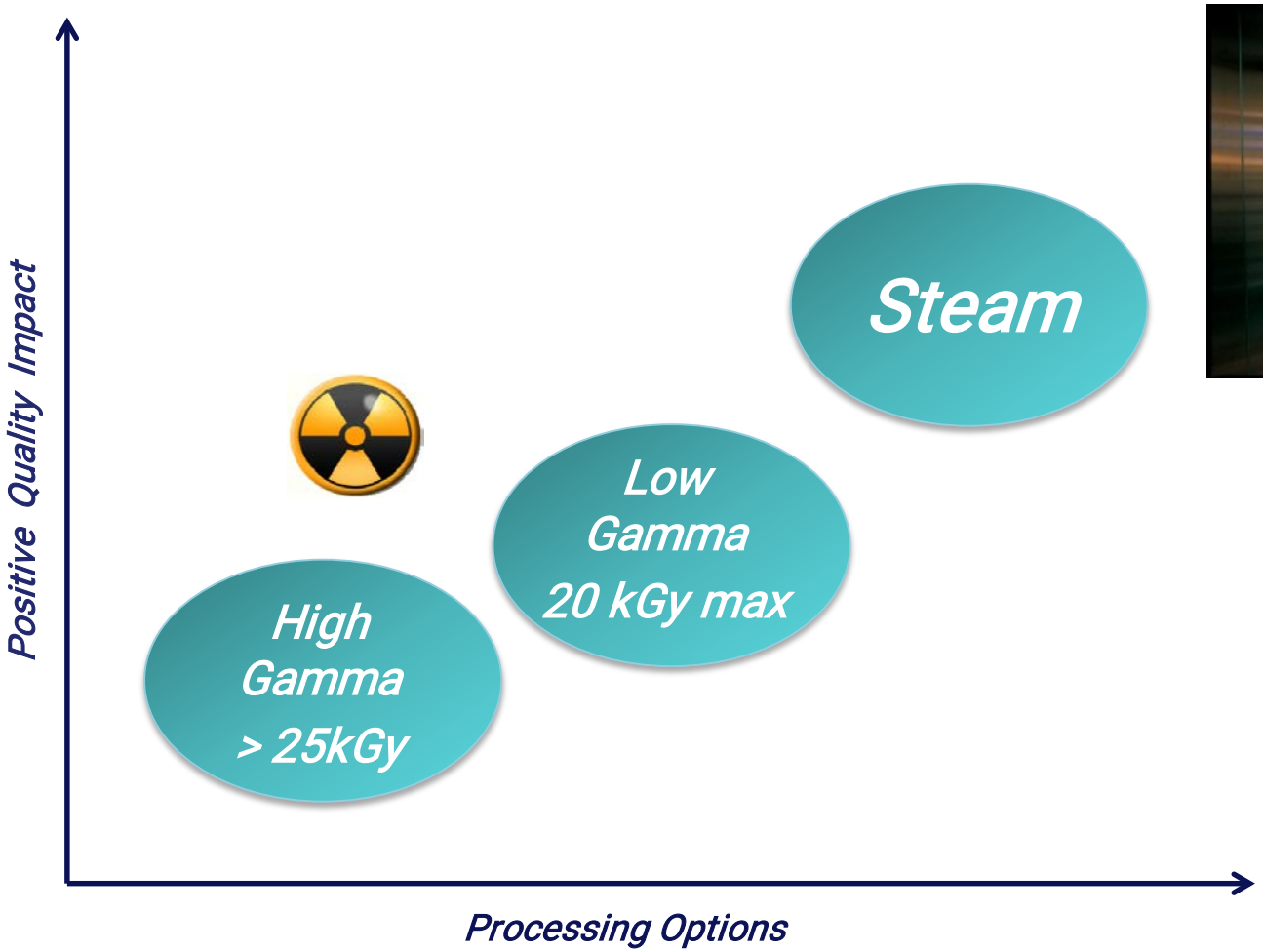


Feedback loop for continuous improvement!

Manufacturing Process

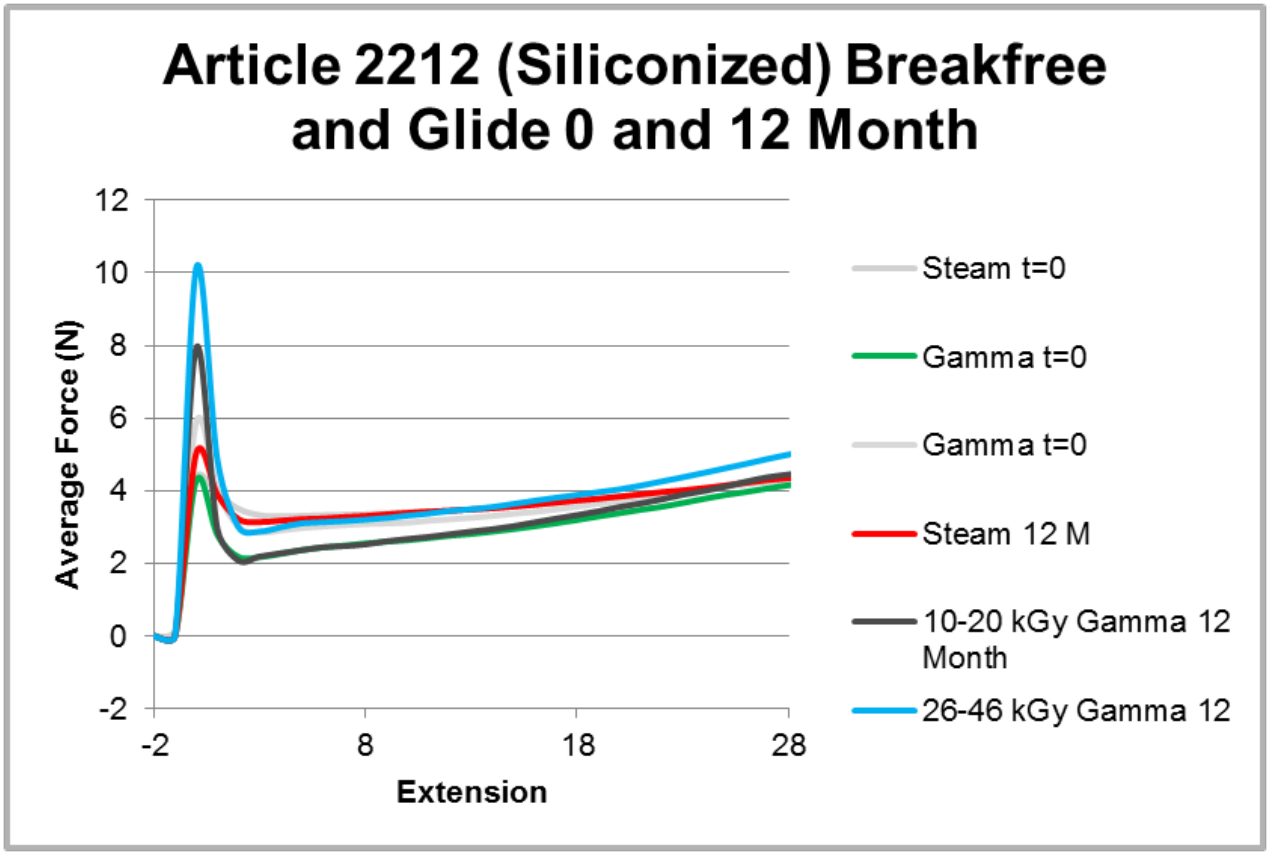
Typical Sterilization Treatments for Elastomeric Components

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



Functionality – Steam versus Gamma

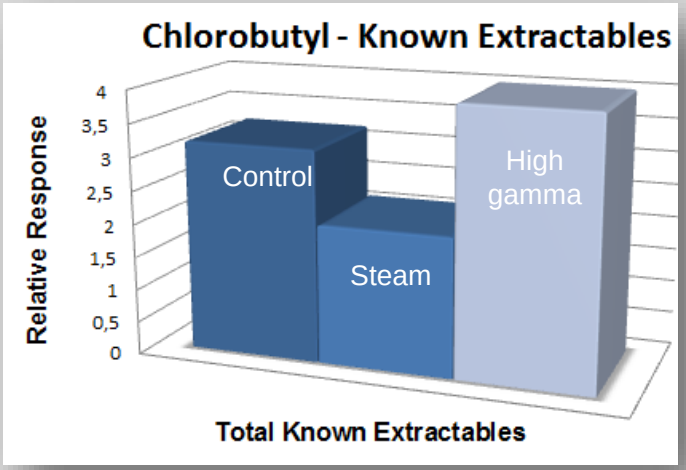
1 mL long Plunger - Break Loose and Gliding Force at 0 and 12 Month

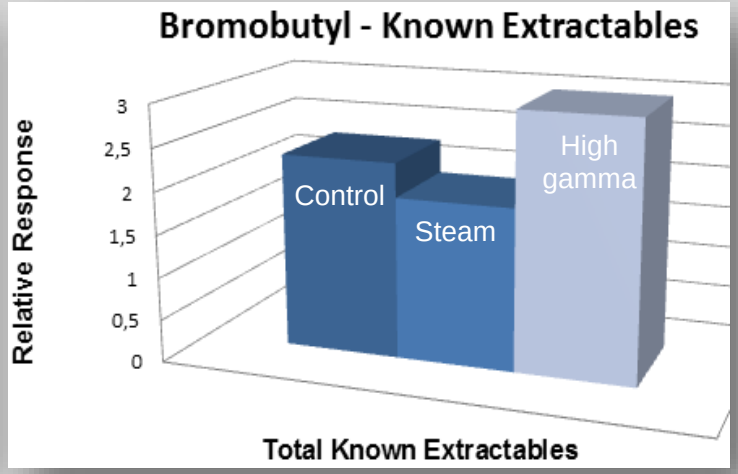


Key findings:

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

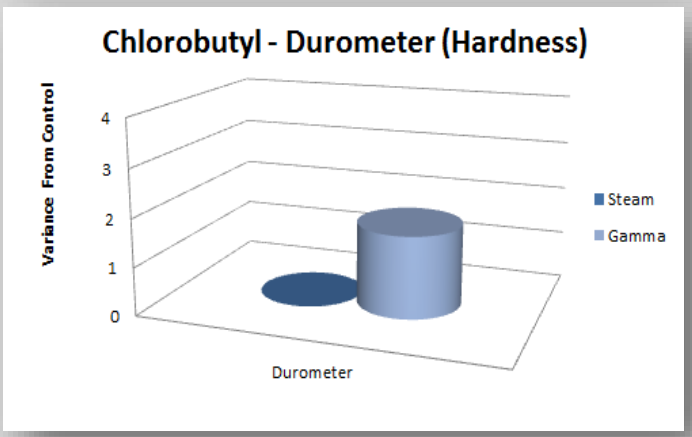
Physical and Chemical Characteristics Steam versus High Gamma

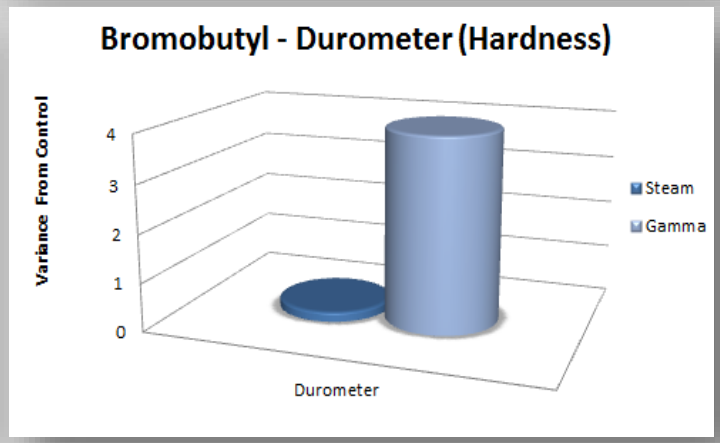




Key findings:

- High gamma shows twice the amount of known extractable





- Hardness is significantly increasing after high gamma treatment

Packaging Materials

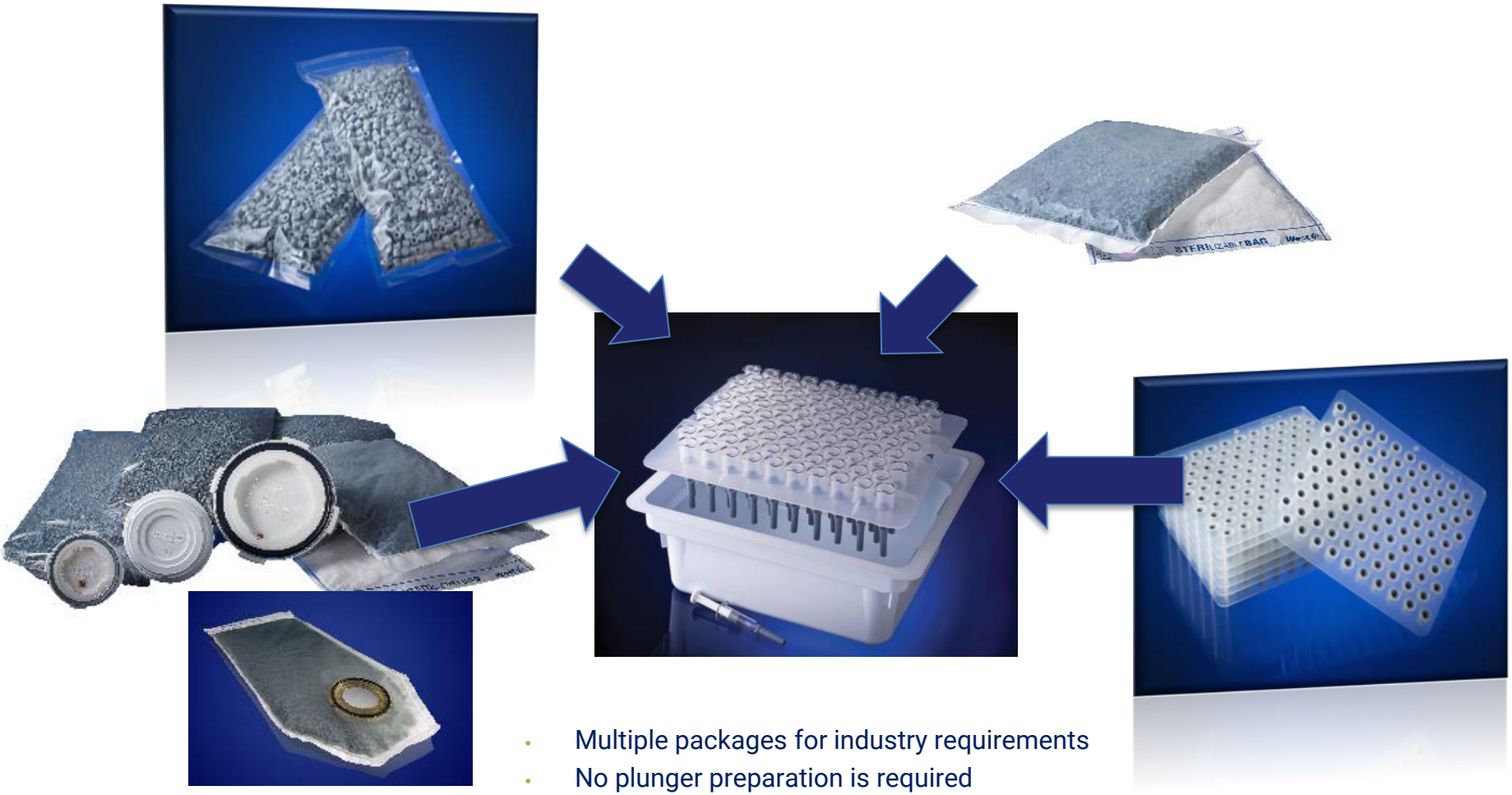
High-quality packaging materials

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

Flexibility for Filling Needs

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

Ready-to-Use Packaging Solutions



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