



Test Methods for Prefilled Syringes

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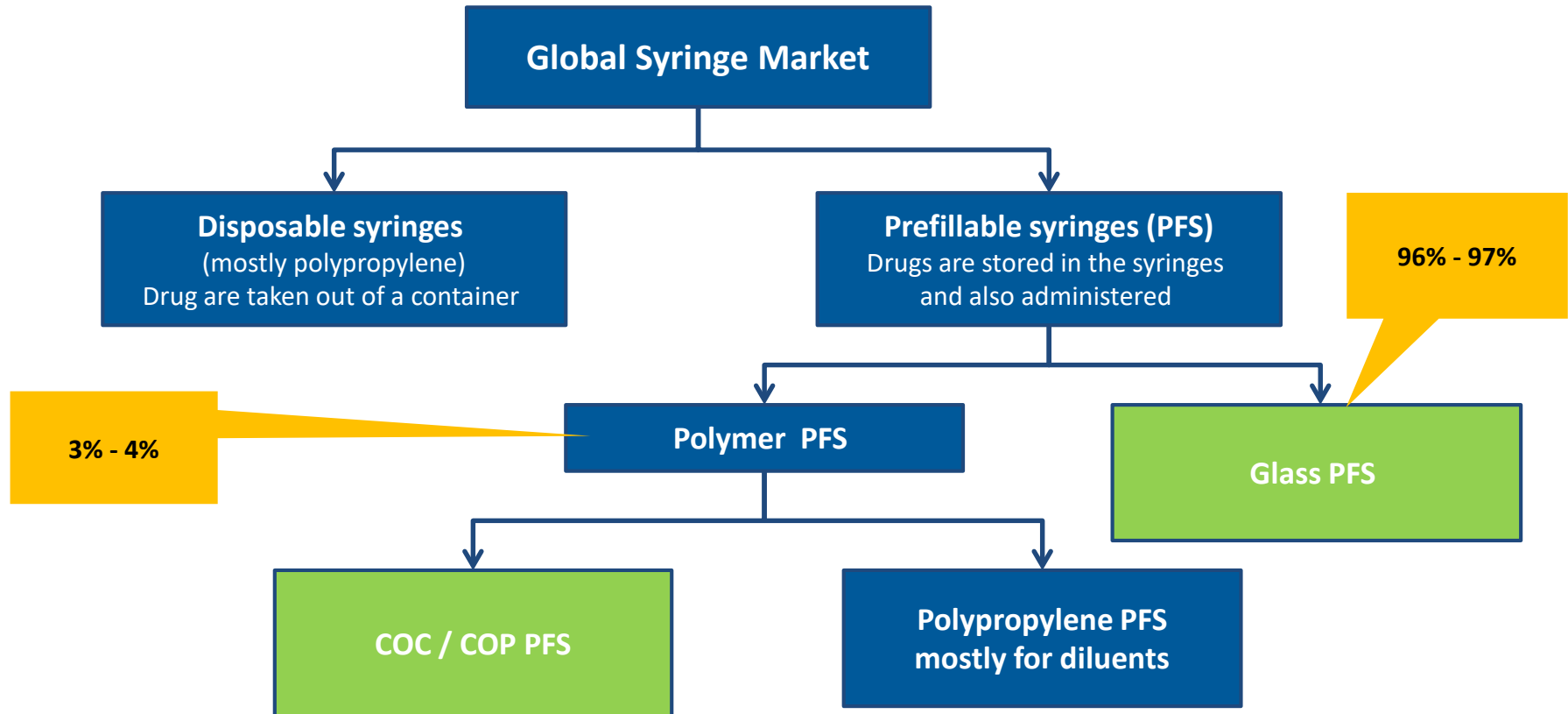
Roman Mathaes PhD, Senior Group Leader, Lonza Drug Product Services

- **Introduction to Syringe Systems & Components**



Prefilled Syringes

Syringe Market Overview - General



Notes:

COC: Cyclic Olefin Copolymer

COP: Cyclic Olefin Polymer

Definition of Prefilled Syringes

When we are talking about syringes,
we are talking about **Prefilled Syringes!**

Bulk Syringes

Bulk syringes unsterile and were delivered packed in Rondo trays.



Prefilled Syringes

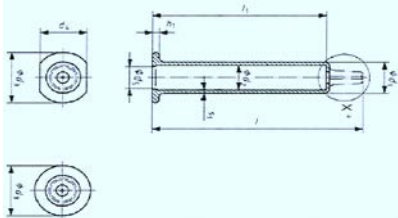
Pre-Sterilized syringes are delivered in tub and nest and are ready for filling at customers.



Materials for Syringe Systems

Glass Formats up to 20ml,

GLASS



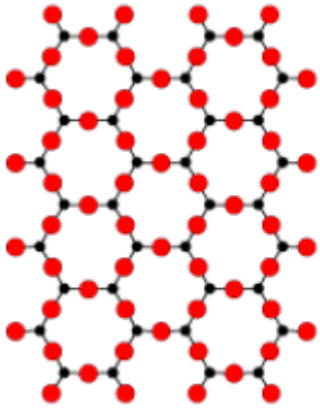
Syringe Size	OD [mm]	OD ± [mm]	ID [mm]	ID ± [mm]
0.5 ml	6.85	0.10	4.65	0.10
1ml lg	8.15	0.10	6.35	0.10
1 – 3 ml	10.85	0.10	8.65	0.20
5 ml	14.45	0.10	11.85	0.20
10 ml	17.05	0.20	14.25	0.20
20 ml	22.05	0.20	19.05	0.20

ISO 11040-4 specified Outer & Inner Diameter Dimensions

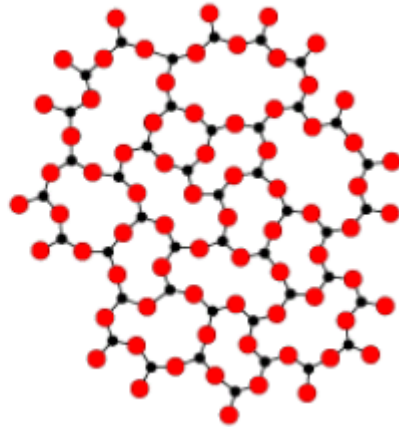


Outer Diameter: 1ml std $9,2 \pm 0.1\text{mm}$

Materials for Syringe Systems: Glass

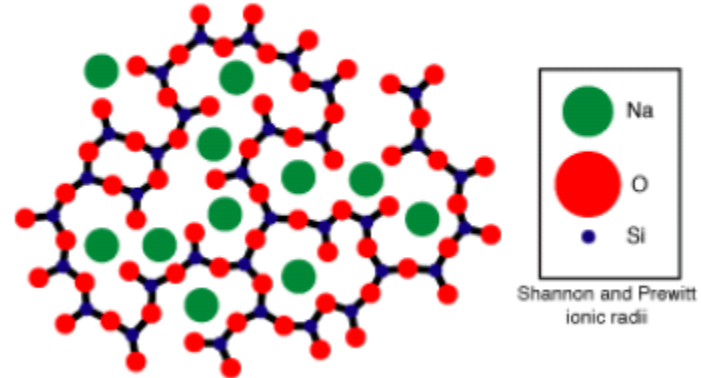


Quartz crystal
MP >2000° C



Quartz glass
MP ~1700° C

Proposed Structure of Sodium Silicate Glass
after Warren and Bischoe (1930's)



- Mixture of crystalline oxides, carbonates, etc.
- Glass is a “frozen super cooled liquid”
- Glass is an inorganic melt, cooled down and solidified without crystallization.
- Considered solid below ~500°C, without defined melting point because of its amorphous structure.
- Composed of:
 - Network former : SiO_2 (SiO_4^{4-})
 - Network modifiers to lower melting point - Na_2O , B_2O_3 , PbO
 - Stabilizers to improve durability - CaO , Al_2O_3
 - Colorants as needed - Fe_2O_3 - TiO_2 & many others

Materials for Syringe Systems: Glass

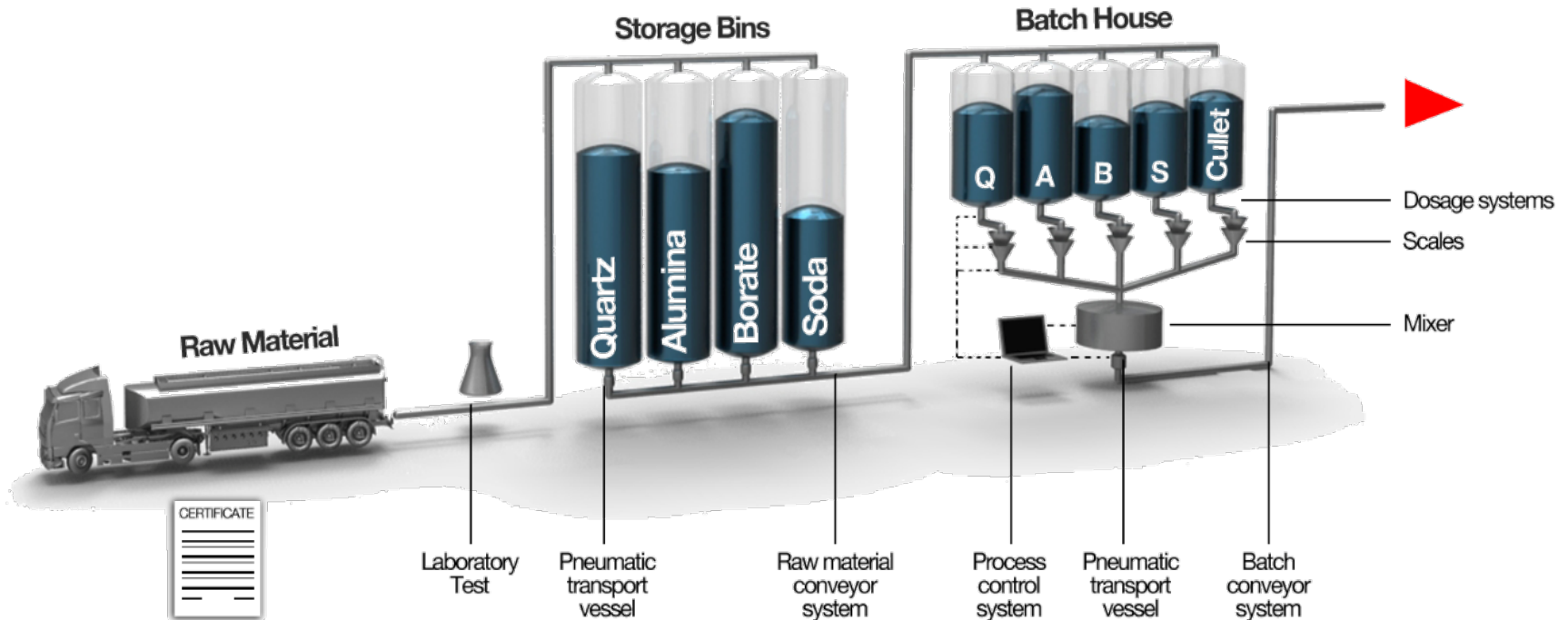
CORNING



Non limitative list

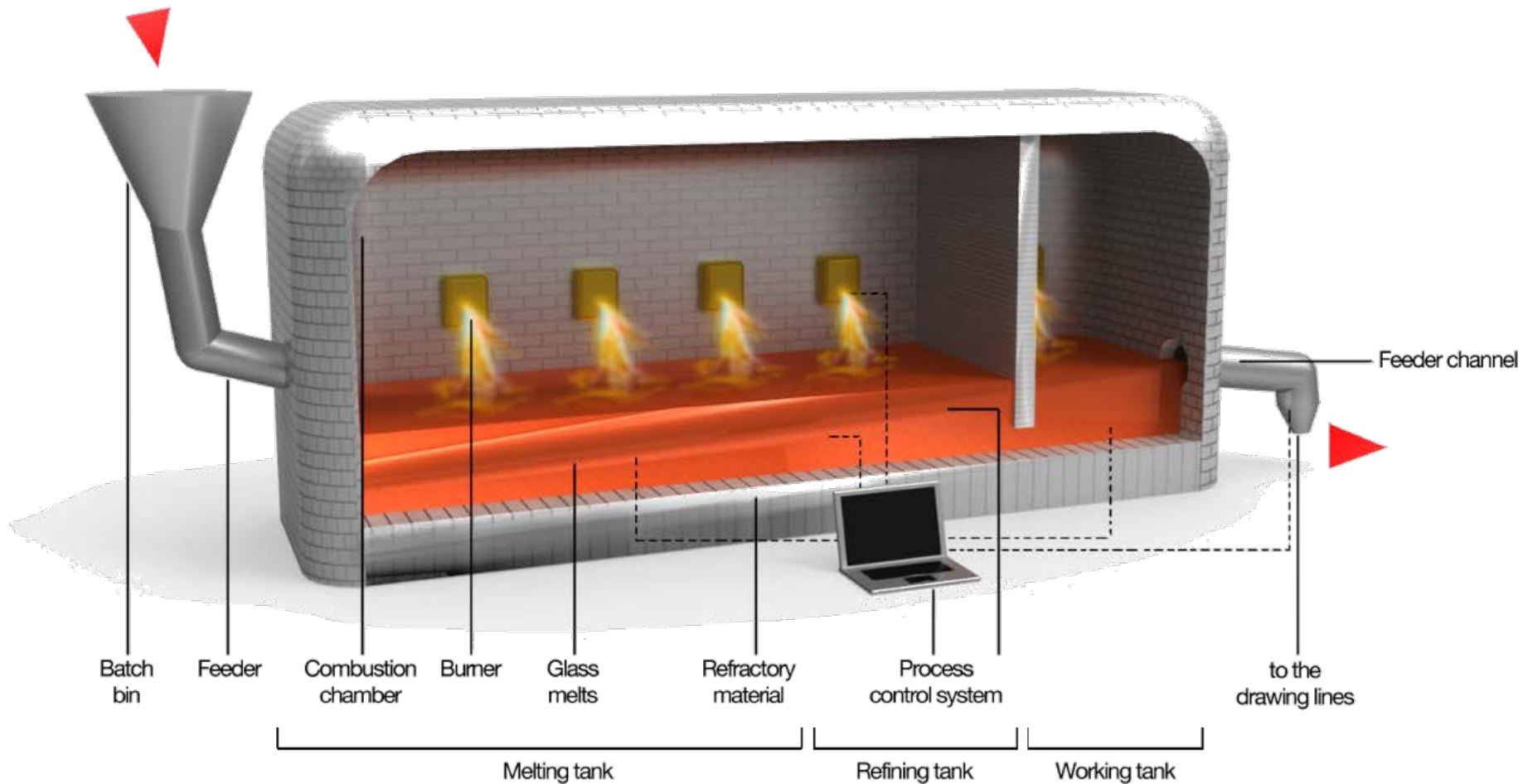
Logos taken from companies webpages

Tubing Manufacturing Process



Graphic is courtesy of SCHOTT Pharmaceutical Systems

Tubing Manufacturing Process



Graphic is courtesy of SCHOTT Pharmaceutical Systems

Tubing Manufacturing Process



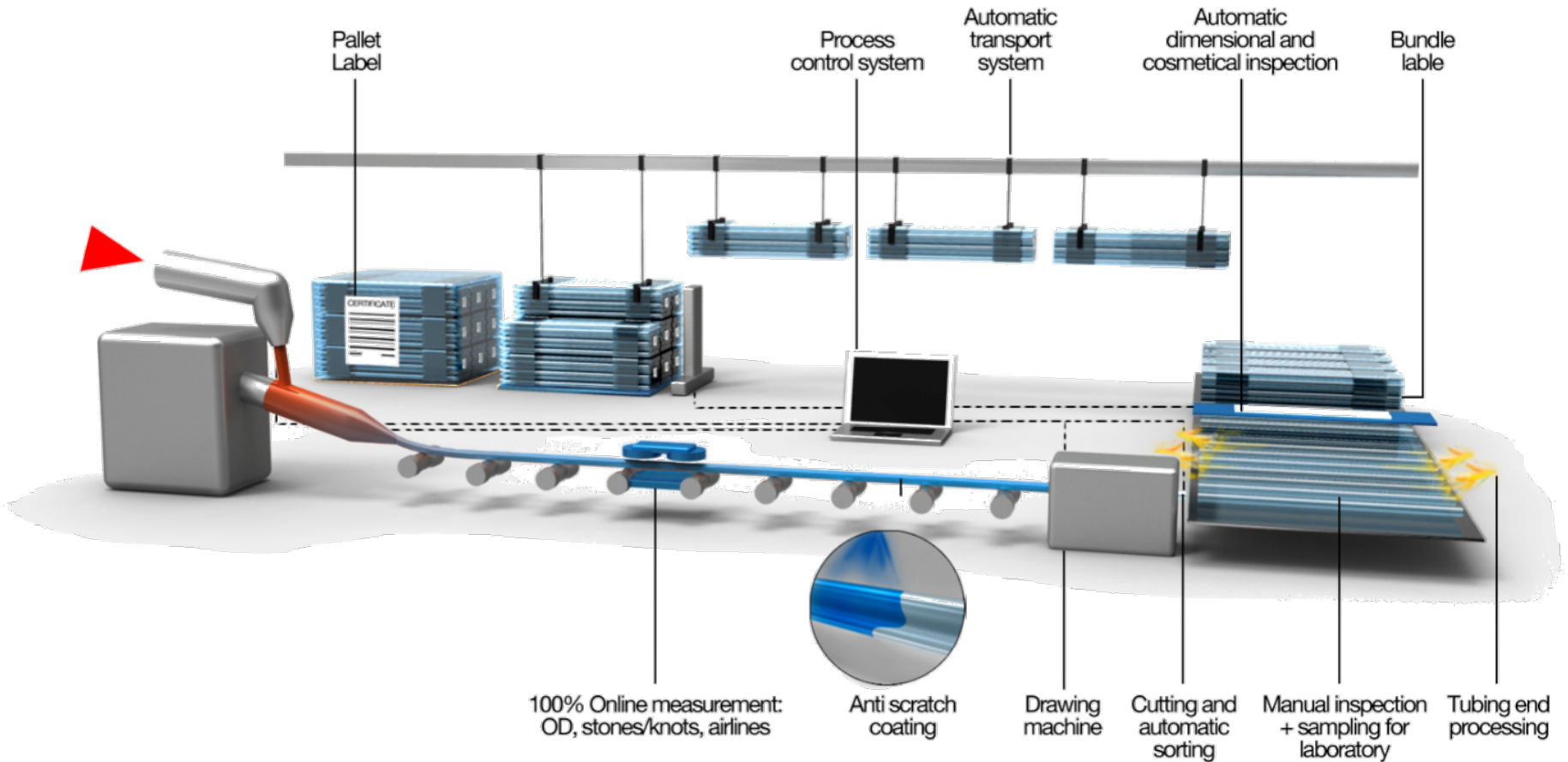
Melting tank



Danner Mandrel

Graphic is courtesy of SCHOTT Pharmaceutical Systems

Tubing Manufacturing Process



Graphic is courtesy of SCHOTT Pharmaceutical Systems

Key Player Glass Syringes



GERRESHEIMER



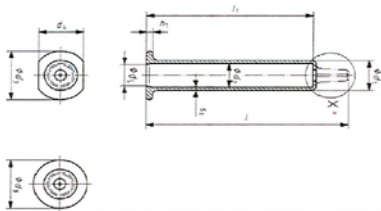
Non limitative list

Logos taken from companies webpages

Materials for Syringe Systems

Polymer Formats up to 100ml

POLYMER



Syringe Size	OD [mm]	OD ± [mm]	ID [mm]	ID ± [mm]
0.5 ml	6.8 – 8.2 6-8 – 9.4*	0.10	4.6 – 4,8	0.10
1ml lg	8.1 – 9.4	0.10	6.3 – 6,5	0.10
1 – 3 ml	10.8 - 11.4	0.10	8.5 – 8,75	0.10
5 ml	14.4 - 15.0	0.10	11.7 –12.2	0.10
10 ml	16.6 - 18.0	0.10	14.1 –14.7	0.10
20 ml	21.2 - 22.7	0.15	18,9 –19.1	0.15
50 ml	29.2 – 32.3	0.2	26.4 – 29.3	0.2
100 ml	35.2 – 35.5	0.2	31.8 – 32.2	0.2

ISO 11040-6 specified Outer & Inner Diameter Dimensions in Ranges

Materials for Syringe Systems: Polyolefines

Cyclic Olefin Copolymer (COC) and Cyclic Olefin Polymer (COP)

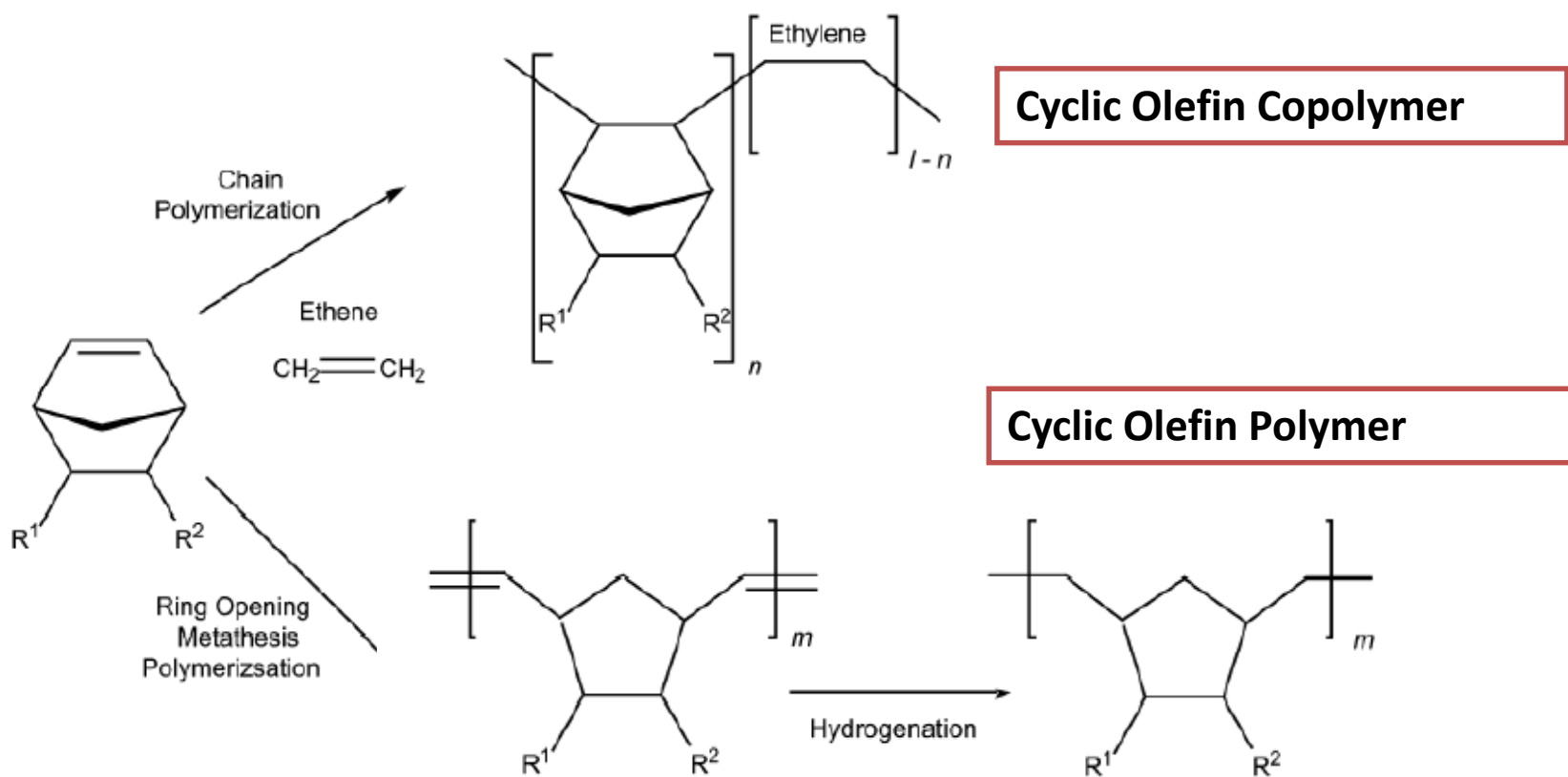
- Amorphous polymer
- Relatively new class of polymers
- Wide variety of applications in films, lenses, medical devices
- No commodities (price)



Logos taken from companies webpages
Pic is courtesy of SCHOTT Pharmaceutical Systems

Materials for Syringe Systems: Polyolefines

Cyclo Olefine Copolymer (COC) and Cyclo Olefine Polymer (COP) are closely related

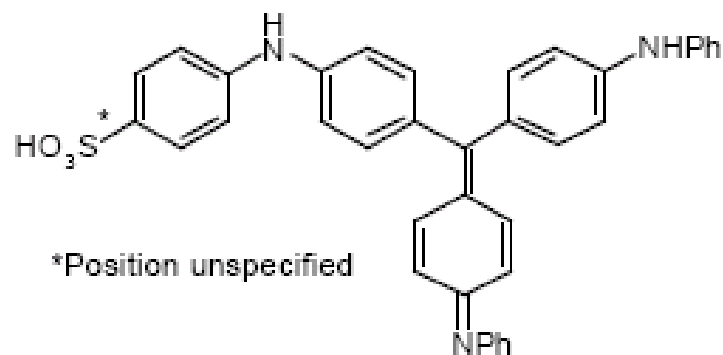
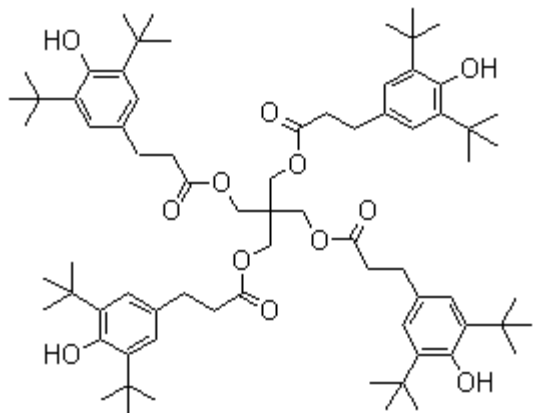


Non limitative list

Materials for Syringe Systems: Polyolefines

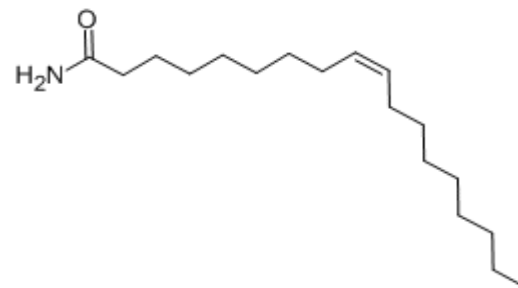
Stabilizer : Irganox 1010

Pentaerythritol Tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate)



Colorant: Ultramarine Blue

Slip additives: Oleamide, Erucamide



Materials for Syringe Systems: Polyolefines



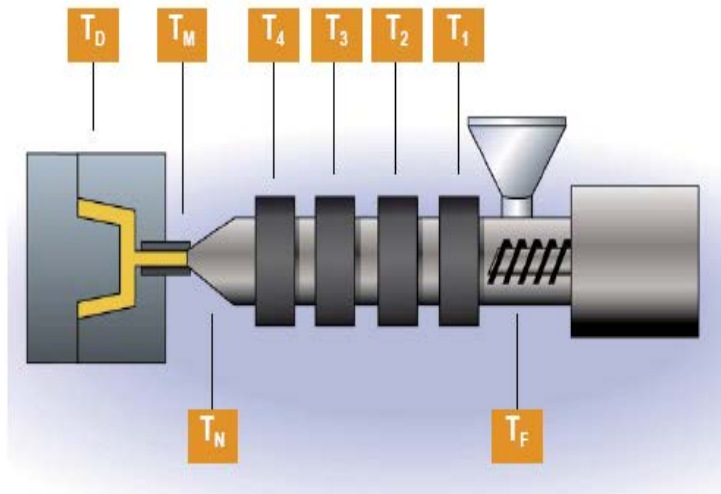
ZEON

Company	Name	Type
Japan Synthetic Rubber	Arton™	COC
Mitsui Chemicals	APEL™	COC
Topas Advanced Polymers	Topas®	COC
Zeon Corp	Zeonex	COP

Non limitative list

Logos taken from companies webpages

Manufacturing Process: Injection Molding



Processing temperature $T_F = < 100 \text{ }^\circ\text{C}$
 $T_1 = 230\text{-}260 \text{ }^\circ\text{C}$
 $T_2 = 240\text{-}270 \text{ }^\circ\text{C}$
 $T_3 = 250\text{-}280 \text{ }^\circ\text{C}$
 $T_4 = 260\text{-}290 \text{ }^\circ\text{C}$
 $T_N = 240\text{-}300 \text{ }^\circ\text{C}$
 $T_M = 240\text{-}300 \text{ }^\circ\text{C}$

Mold-temperature: $T_D = 95 - 130 \text{ }^\circ\text{C}$

Max. residence time $< 15 \text{ min}$; short interruption to cycle: reduce $T_x = 170 \text{ }^\circ\text{C}$!

Injection pressure: $P_{Sp} = 500 - 1100 \text{ bar}$ (specific)

Hold on pressure: $P_N = 300 - 600 \text{ bar}$ (specific)

Back pressure: $P_{St} = 150 \text{ bar max.}$ (specific)
 Screw speed: $n_s = 50 - 200 \text{ rpm}$
 Injection speed: moderate to fast (50 mm/sec - 150 mm/sec)
 Nozzle type: free - flow

- Note:
- Shrinkage is dependent on processing conditions and part design. Typical shrinkage values are 0,4 - 0,7%
 - Topas Advanced Polymers recommends only external heated hot runner systems.
 - For molded parts with especially high requirements to the surface quality we recommend to choose the highest possible mold temperature.

Key Players Polymer Syringes

Prefillable Polymer Syringe Offerings

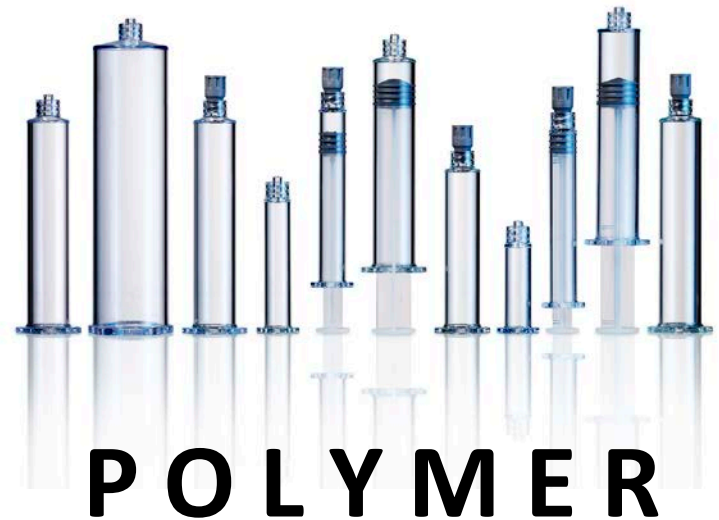
Company	Resin	Brand
Becton Dickinson	COP	BD Sterifill™ SCF™
Gerresheimer Taisei Kako	COP	ClearJect™
Schott Schweiz	COC	SCHOTT TopPac®
SiO ₂ Medical Products	COP	Barrier Coated Systems
Terumo	COP	Playjex™
West (Daikyo)	COP	CZ® RU system

What Material is the BETTER Choice ?

GLASS



vs.



POLYMER

Advantages and Disadvantages of Materials

Polymer Vs. Glass



Vs.



Feature	Polymer	Glass
Absence of Heavy Metal's	👍	
Breakage Resistance	👍	
Design Space / customizing	👍	
Discoloration by radiation		👍
Haze Formation		👍

Advantages and Disadvantages of Materials

Polymer Vs. Glass



Vs.



Feature	Polymer	Glass
Integrated Luer Lock	👍	
Low E & L Profile	👍	
„long term“ experience		👍
Multiple Supply Source		👍
Permeability (gases)	👍	👍

Advantages and Disadvantages of Materials

Polymer Vs. Glass



Vs.



Feature	Polymer	Glass
Sterilization Possibilities	👍	
Siliconization (free silicone)	👍	
Temperature Resistance		👍
Tolerances	👍	
Tungsten Free	👍	

Sterilization Methods

Method	COC/COP	Glass
Autoclave 121° C, 20 min ¹⁾	yes	yes
Gamma irradiation, 25 kGy ²⁾	yes	<u>no</u>
Electron radiation ²⁾	yes	<u>no</u>
X-Ray ²⁾	yes	<u>no</u>
Heat tunnel 280° C, 5 min	<u>no</u>	yes
Ethylene oxide	yes	yes

1) Minimal change in transparency and color, maintains mechanical properties

2) Maintains mechanical properties, no influence on transparency, some color change

Rubber Components for PFS

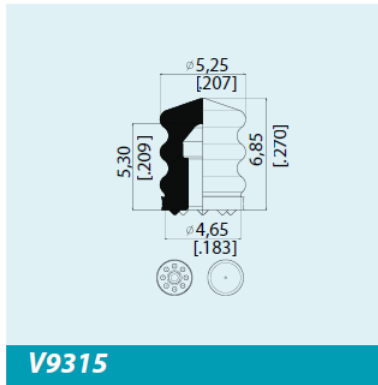
Major Suppliers for PFS Rubber Components

1. **Aptar Stelmi:** <http://www.aptar.com/pharma/injectables/>
2. **Datwyler:** <http://sealing.datwyler.com/de/industry-solutions/health-care.html>
3. **West:** <http://www.westpharma.com/en/Pages/Default.aspx>

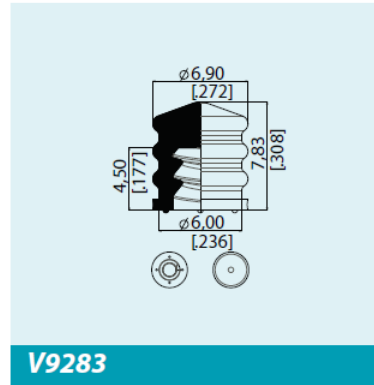
Rubber Components for PFS

TYPICAL PRODUCTS

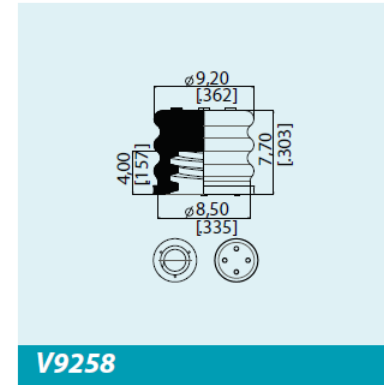
0.5 ml



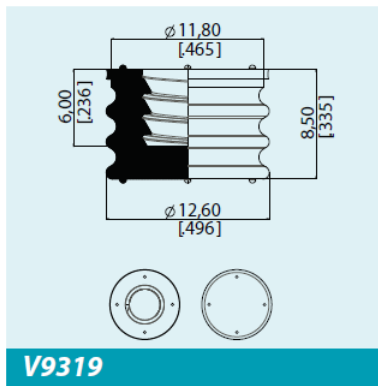
1 ml long



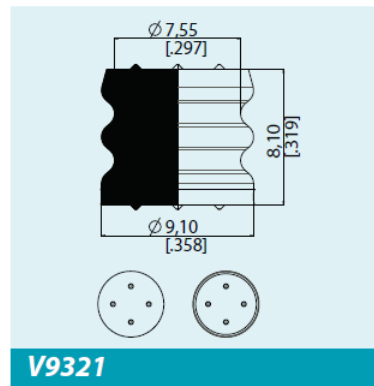
1 - 3 ml



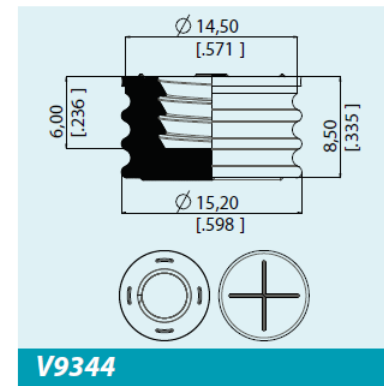
5 ml



Dual chamber plunger



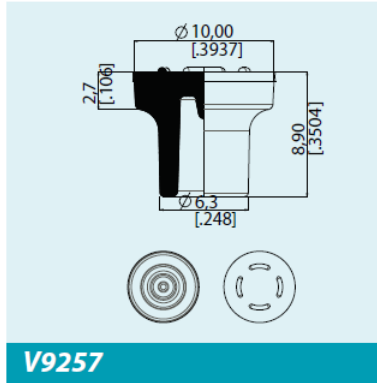
10 ml



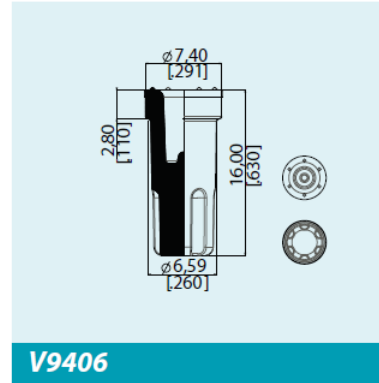
Drawings taken from Datwylers product brochures

Rubber Components for PFS

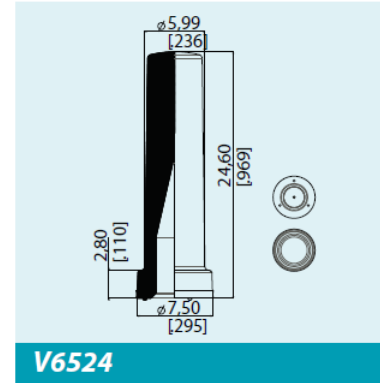
Mushroom Tip Cap



Ribbed Tip Cap



1/2" Needle Shield



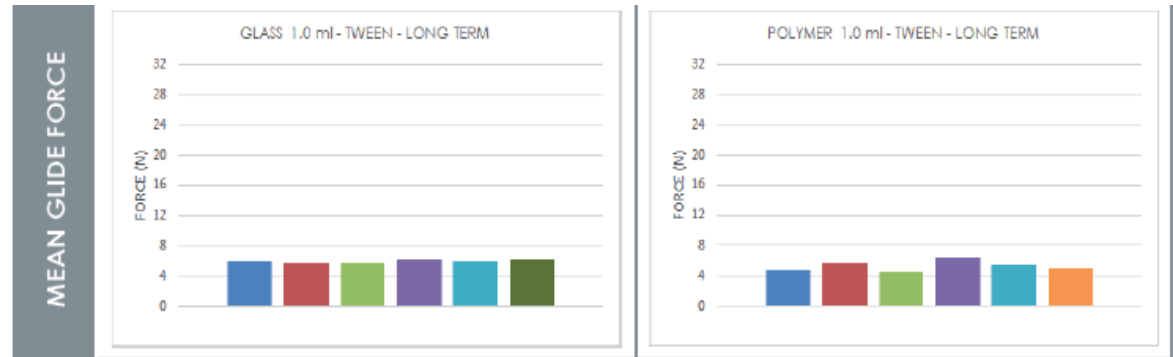
Drawings taken from Datwylers product brochures

Pic is courtesy of SCHOTT Pharmaceutical Systems

Alternative to Standard Rubber



	CHARACTERISTICS
MATERIAL	THERMOPLASTIC ELASTOMER - EVOPRENE G970
BIOCOMPATIBILITY	ISO 11040-5, ISO 10993-5, 1999, USP 27, NF 22, 2004 - CLASS VI70°C
STERILIZATION	GAMMA IRRADIATION, STEAM (relaxed), NONE - by customer choice
BREAK LOOSE & GLIDE FORCES	ISO 11040-8 Annex E
CONTAINER CLOSURE	ASTM F1929
PERMEABILITY	ICH Q1A(R2)
EXTRACTABLES	DS/EN ISO 8871-1:2005



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QUESTIONS ?