Connecting People, Science and Regulation

PDA Workshop

Development and Manufacturing of Pre-filled Syringes

Vienna, Austria - Friday November, 10th 2017

Glass Pre-filled containers

Alessandro Morandotti
(Ompi)

Connecting People, Science and Regulation

Agenda

- Chemical, physical and functional properties
- Manufacturing overview
- Quality Trends

Definition of Pre-filled Syringes

Bulk Syringes

Bulk syringes unsterile and were delivered packed in trays.

Pre-fillable Syringes

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

Other options

Syringes are not the only product that can be supplied Ready-To-Fill

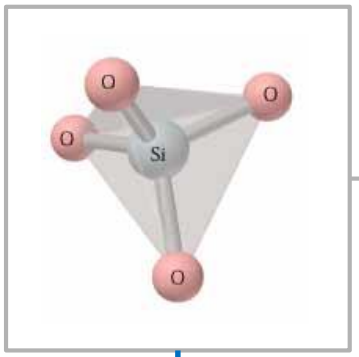
Vials

Cartridges

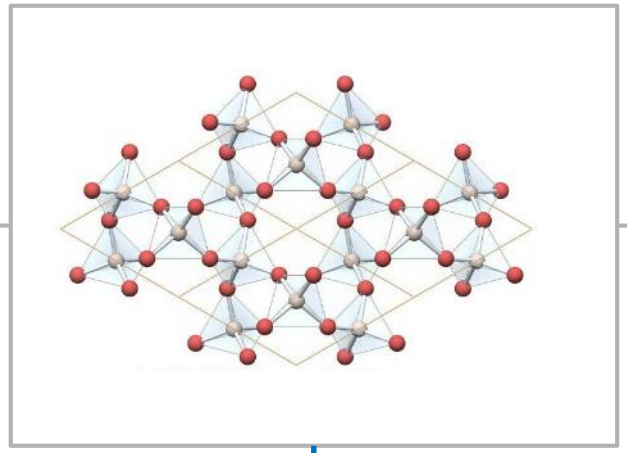
Materials for Syringe Systems

GLASS

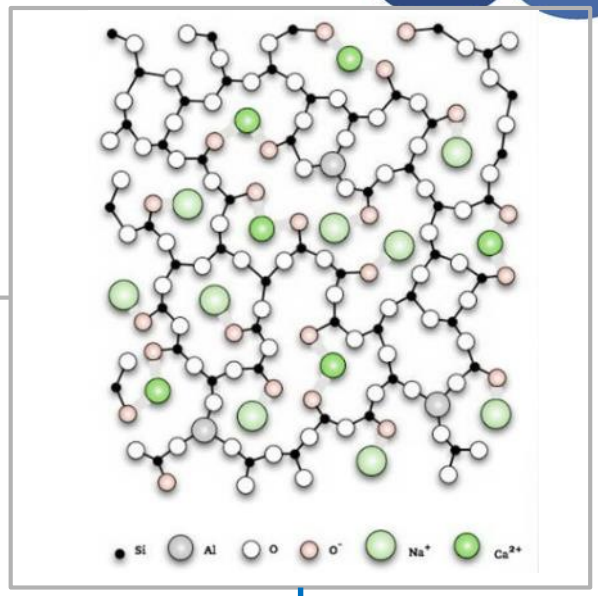
Materials for Syringe Systems: Glass



Silica: basical unit



Silica: cristal, long range order **(Quartz)**



Silica: short range order **(Glass)**

- Glass is non-crystalline solid material obtained by cooling a supercooled liquid.
- It is a non organic material.
- It has an amorphous structure, obtained with solidification without crystallization.

In industry, glass is the result of chemical combination of raw materials available in nature, synthetic elements and glass cullet

Glass composition and types

Glass for Parmaceutical purposes is composed by:

Network former: SiO_2

Network modifiers: Na_2O, K_2O, B_2O_3

Stabilizers to improve durability: CaO, Al_2O_3

Colorants (amber glass): Fe_2O_3 - TiO_2

Neutral glass is a borosilicate glass containing significant amounts of boric oxide, aluminium oxide, alkali metal oxides and/or alkaline earth oxides in the glass network. Due to its composition, neutral glass has a high hydrolytic resistance and a high thermal shock resistance.

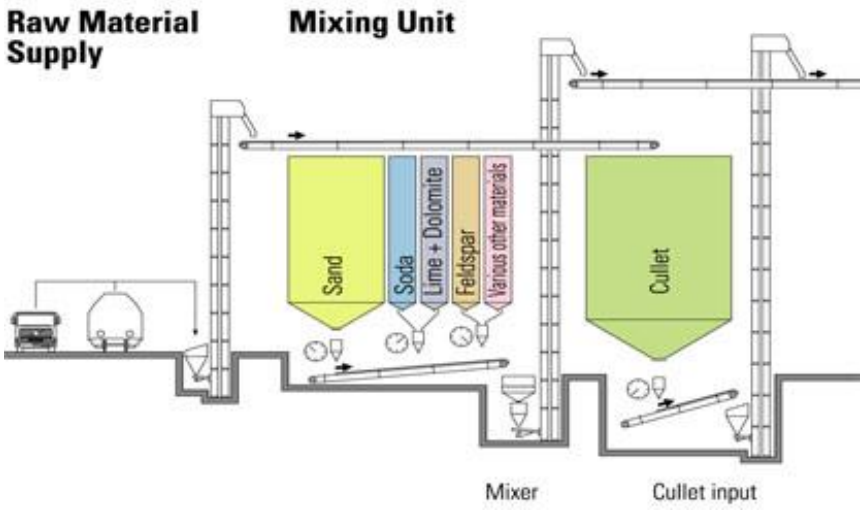
Soda-lime-silica glass is a silica glass containing alkali metal oxides, mainly sodium oxide, and alkaline earth oxides, mainly calcium oxide, in the glass network. Due to its composition, soda-lime-silica glass has only a moderate hydrolytic resistance.

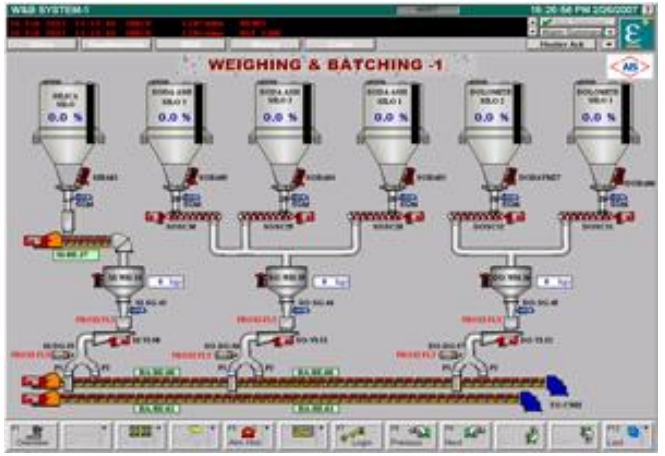
	BOROSILICATE GLASS (Neutral glass)		SODA-LIME GLASS
	Exp. 3.3 group	Exp. 5.1 group	Exp. 7.8 – 9.5
SiO_2	80 - 82	69 - 75	70 - 75
B_2O_3	12 - 13	7 - 12	0 - 1
Al_2O_3	2 - 3	5 - 8	2 - 4
Na_2O / K_2O	3 - 5	7 - 11	12 - 16
CaO / MgO / BaO	0	1.5 - 4	10 - 15
Working Point	1250 – 1260 °C	1110 – 1170 °C	1015 – 1045 °C
Transition Temperature	525 – 555 °C	545 – 570 °C	525 – 540 °C

Tubing Manufacturing Process

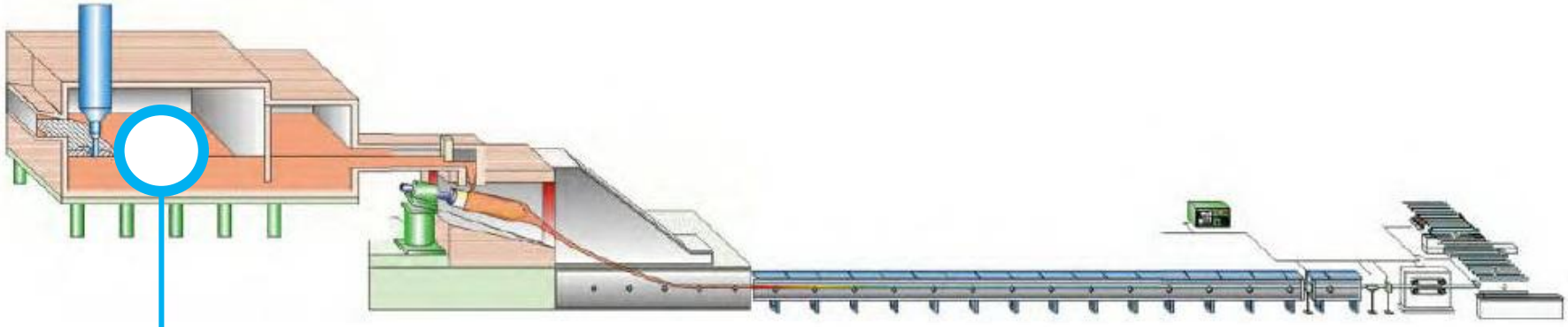
THE BATCH HOUSE

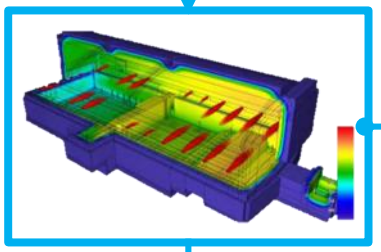
Raw materials are dowloaded in sylos and then mixed with cullet to obtain the right batch formulation





Tubing Manufacturing Process

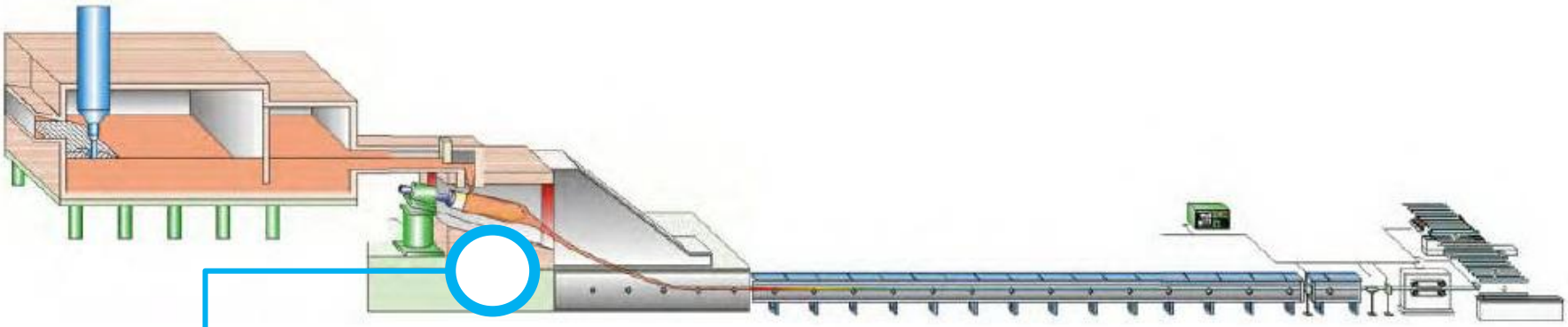




THE FURNACE

The batch formulation is melted in the furnace: a lot of chemical reactions among the chemical elements start and, at the end of the process, glass is ready to be formed as tube

Tubing Manufacturing Process

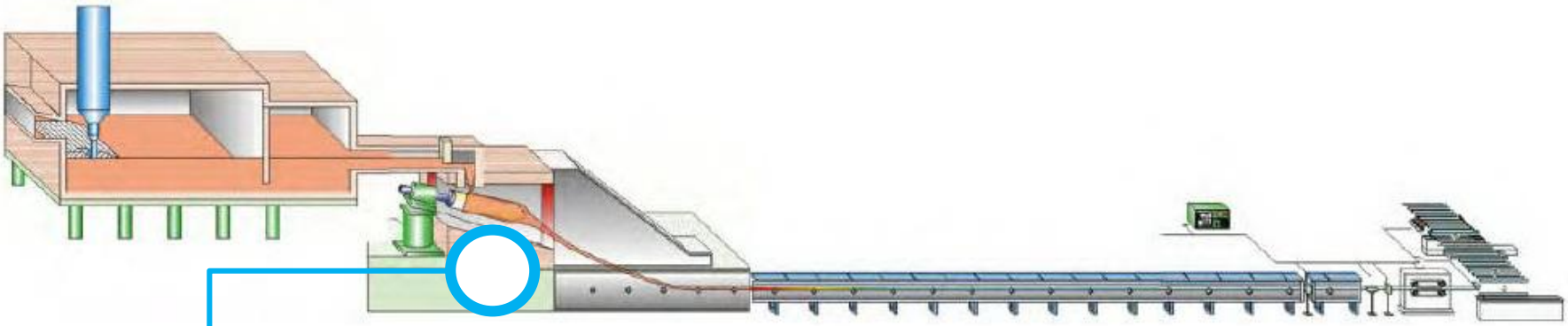


FORMING SYSTEMS

Danner Mandrel

- Rotating system
- T glass ≈ 1200˚ C
- Flexible: big range of sizes can be produced, from 2 mm OD up to 60 mm
- Widely used in Europe and Asia

Tubing Manufacturing Process

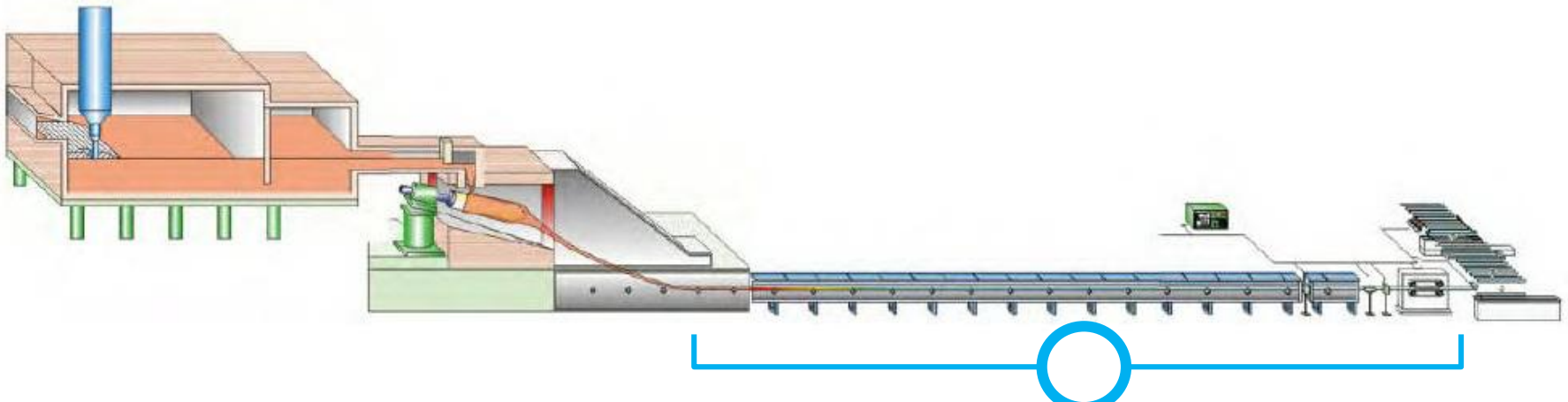


FORMING SYSTEMS

Vello Mandrel

- Not rotating system
- T glass ≈ 1000° C
- Mostly used in US

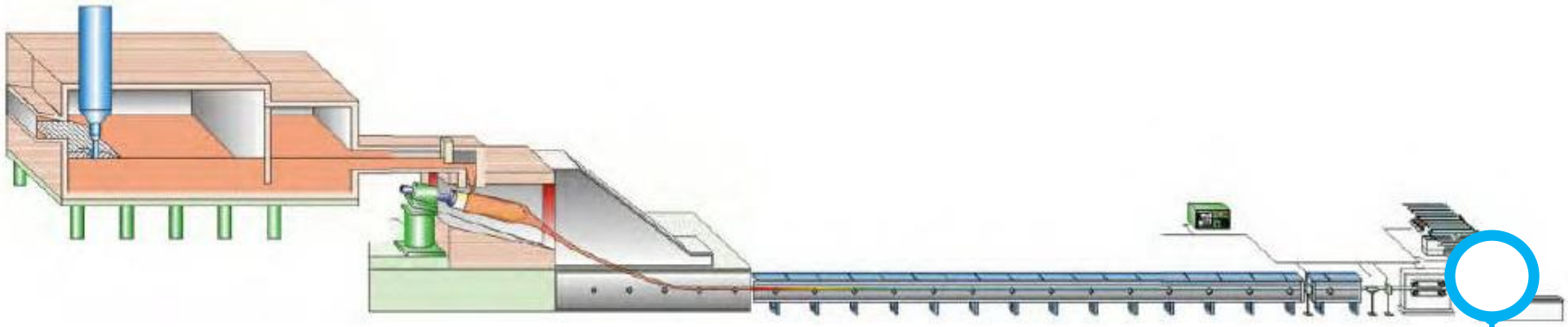
Tubing Manufacturing Process



PULLING LINE AND CUTTING SYSTEM

- The tube is drawn for around 50 m to cool down
- Several inspection systems check the quality of the tube (visual and dimensional parameters) with automatic rejection in case of failure
- High speed rough cutting system

Tubing Manufacturing Process



TRIM, GLAZING AND FINAL PACKAGING

- The ends of the tubes are trimmed to obtain a flat surface
- Ends are glazed with flames
- Tubing are packed in bundles

SCHOTT
glass made of ideas

Nippon Electric Glass Co., Ltd.

NIPRO

CORNING

Non limitative list

ISO 11040-4 Syringes

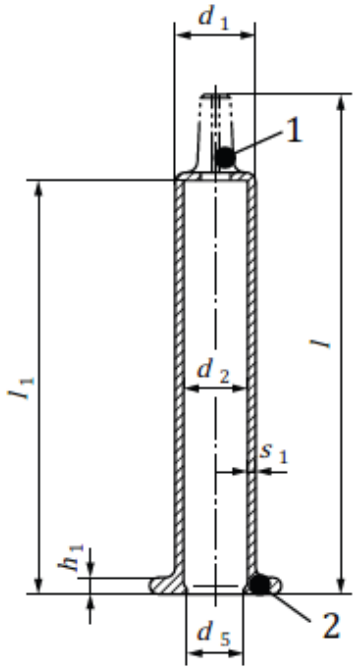


Table 1 — Syringe barrel dimensions (see Figure 1)

Dimensions in millimetres

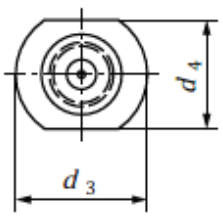
Nominal volume	Glass barrel										Finger flange					
	d_1		d_2		d_5	l_1		l^c		$s_1{}^c$	h_1		d_3		d_4	
ml	nom	tol	nom	tol	min.	nom.	tol.	nom.	tol.	≈	nom.	tol.	nom.	nom.	nom.	tol.
0,5	6,85		4,65	±0,1	4,40	47,6		57,5		1,1	1,8	±0,5	13,4	±0,4	10,5	±0,4
1[a]	8,15		6,35		6,05	54		64,0	±0,5	0,9	1,9		13,8		11	
1[b]	10,85	±0,1	8,65		8,25	35,7	±0,5	46,7		1,1	2,2		17,75		14,7	
2	10,85		8,65		8,25	49		60,0		1,1	2,2		17,75	±0,75	14,7	
2,25	10,85		8,65		8,25	54,4		66,6	±0,75	1,1	2,2	±0,5	17,75		14,7	±0,5
3	10,85		8,65	±0,2	8,25	72,2		84,4	±1,0	1,1	2,2		17,75		14,7	
5	14,45		11,85		11,45	66,7	±0,75	80,0	±0,75	1,3	2,4		23		19,5	
10	17,05	±0,2	14,25		13,85	87,25		100,5	±1,0	1,4	2,5	±0,6	27	±1	21,5	
20	22,05		19,05		18,40	96,8		114,9	±1,0	1,5	3,1		32,25		25,9	±0,6

[a] Long version.

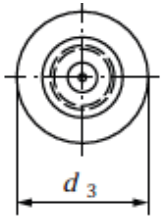
[b] Short/standard version.

[c] Dimension on total barrel length and wall thickness are for information only.

Dimensions in millimetres



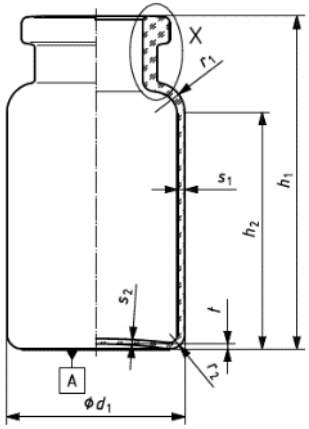
a) cut-flange



b)round flange

c) small-round flange

ISO 8362-1 Vials



Dimensions in millimetres

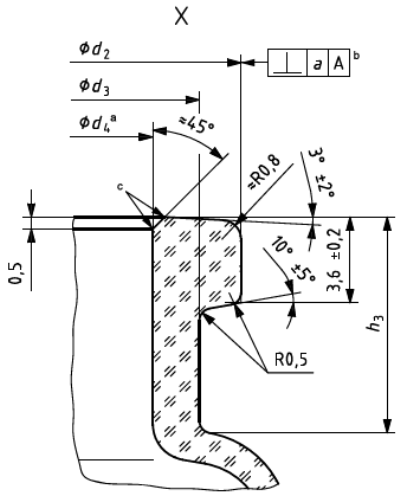
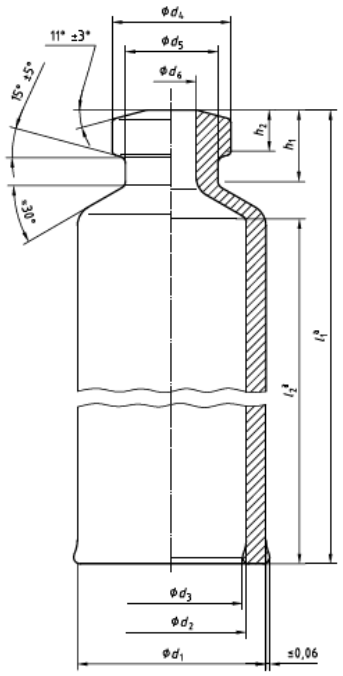


Table 1 — Dimensions, overflow capacity and mass

Size designation of injection vial	Overflow capacity ml	tol	a mm	d_1 mm	tol.	d_2 mm +0,2 −0,3	d_3 mm max.	d_4 mm ± 0,2	h_1 mm	tol.	h_2 mm min.	h_3 mm	tol.	r_1 mm =	r_2 mm =	s_1 mm	tol.	s_2 mm min.	t mm max	Mass g =
2R	4	± 0,5	1	16	± 0,15	13	10,5	7	35	± 0,5	22	8	± 0,5	2,5	1,5	1	± 0,04	0,6	0,7	5
4R	6								45		32									6,1
6R	10		1,2	22	± 0,2	20	16,5	12,6	40		26	8,5		3,5	2			0,7		8,3
8R	11,5								45		31									9,4
10R	13,5	± 1		24					45		30	9		4,0						10,2
15R	19								60		45									12,8
20R	26	± 1,5	1,5	30	± 0,25		17,5		55	± 0,7	35	10	± 0,75	5,5	2,5	1,2	± 0,05		1	17,4
25R	32,5								65		45									20
30R	37,5								75		55									22,7

ISO 13926-1 Cartridges



[a] Lengths l_1 and l_2 shall be agreed upon between manufacturer and customer.

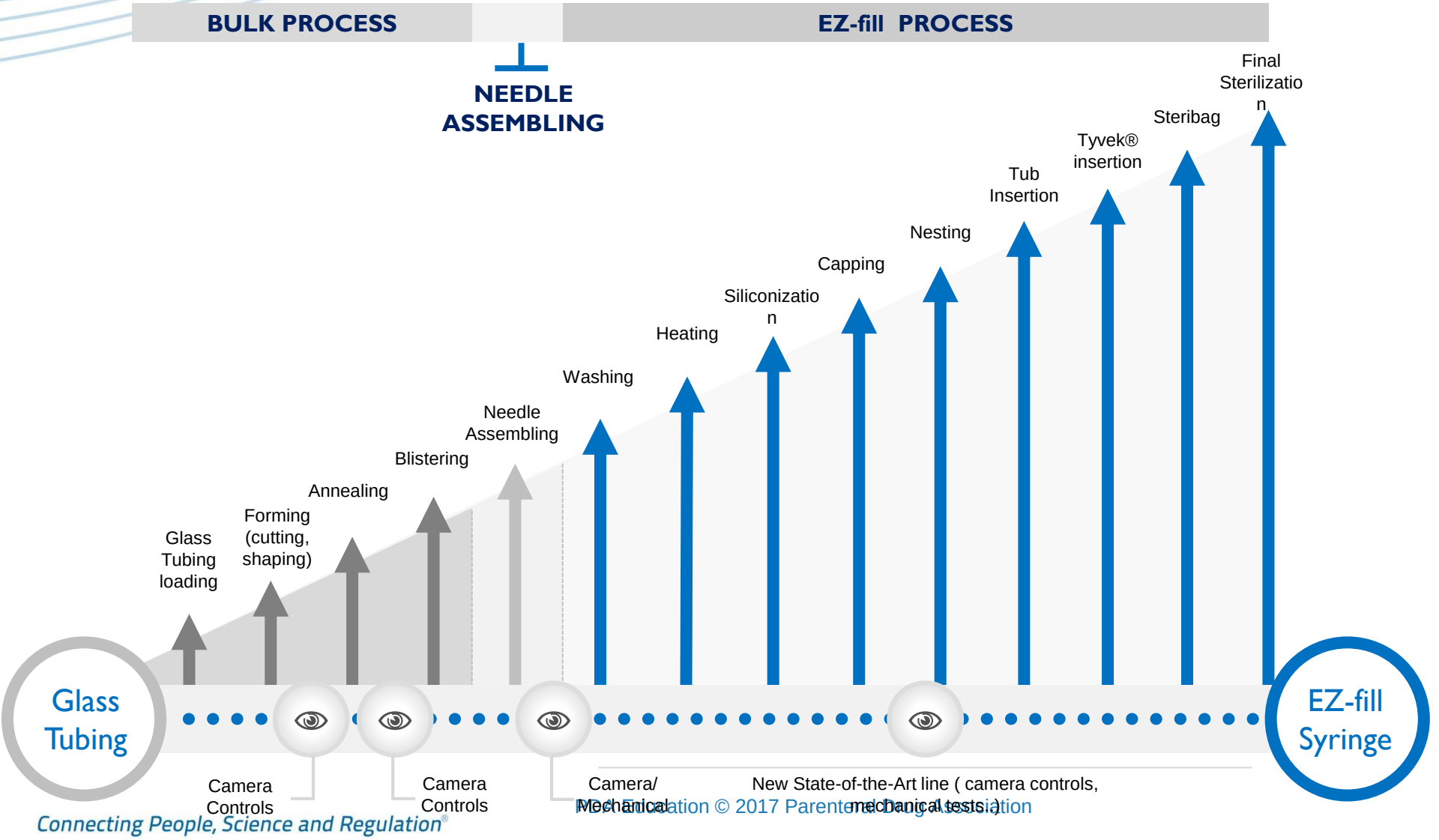
Figure 1 — Configuration of glass cylinders for pen-injectors

Table 1 — Dimensions of glass cylinders for pen-injectors

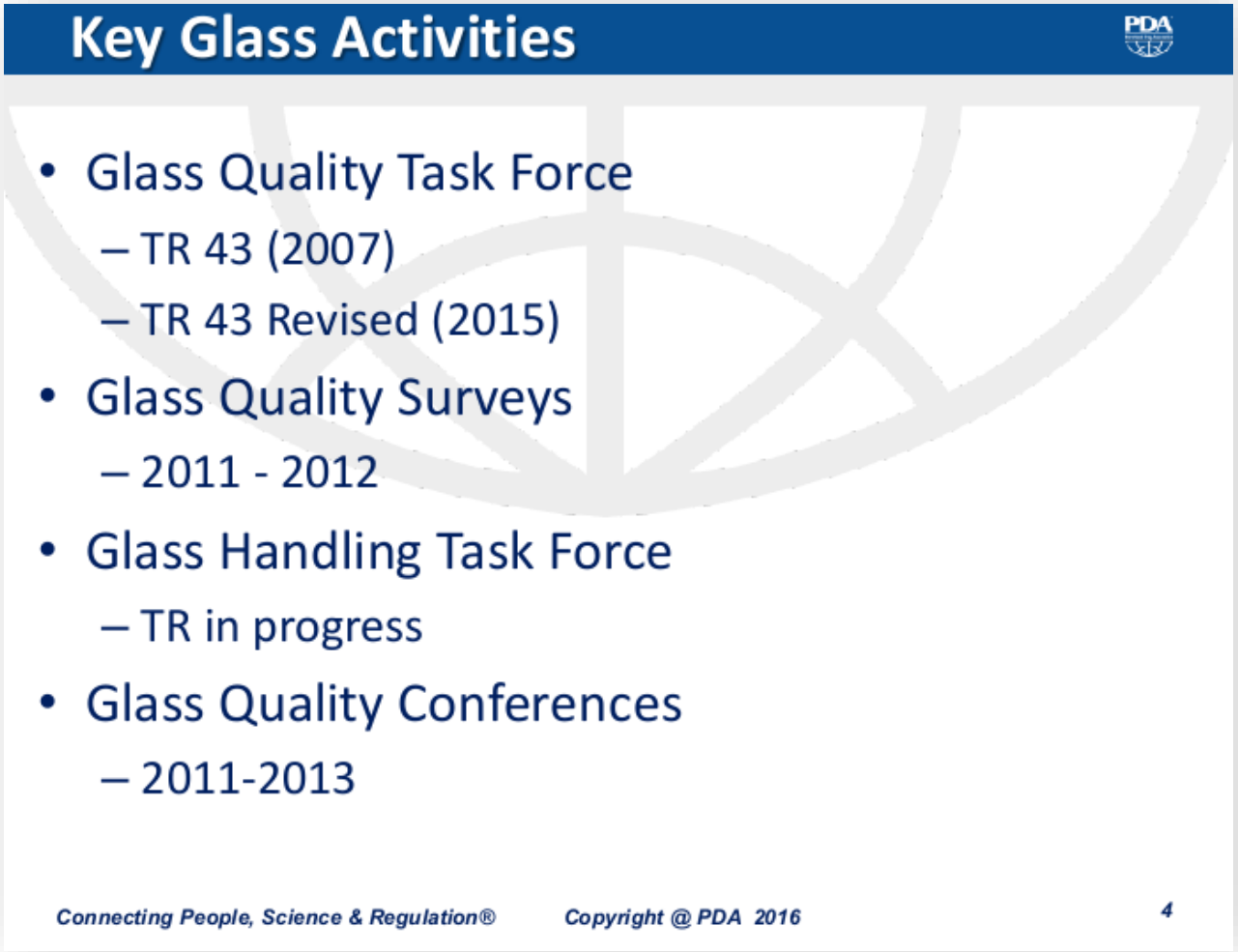
Dimensions in millimetres

d_1	tol. ±	d_2	tol. ±	d_3 min.	d_4	tol. ±	d_5	tol. ±	d_6	tol. ±	h_1	tol. ±	h_2	tol. ±
8,65	0,1	6,85	0,1	6,55	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,85	0,1	8,65	0,1	8,35	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
10,95	0,15	9,25	0,1	8,95	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
11,60	0,15	9,65	0,1	9,35	7,15	0,2	5,5	0,35	3,15	0,2	5,0	0,20	2,9	0,1
14,00	0,15	12,00	0,15	11,65	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15
14,45	0,15	11,85	0,15	11,50	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15
18,25	0,15	16,05	0,15	15,50	9,5	0,2	7,6	0,35	4,5	0,2	5,0	0,50	2,9	0,15

ISO 13926-1 Cartridges



Regulatory Inspection Trends



Regulatory Inspection Trends

PDA
Parenteral Drug Association

SYRINGE GLASS LEXICON

PDA Glass Task Force
June 17, 2013

PDA Glass Task Force
Syringe Glass Lexicon 1

Broken, Finger Grip

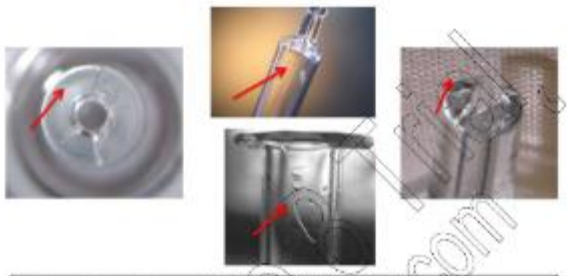
Location: Finger Grip (a.k.a. Flange) Class: Major A

Large fragment of glass missing from finger grip.

PDA Glass Task Force
Syringe Glass Lexicon 16

Crack

Location: General Class: Critical

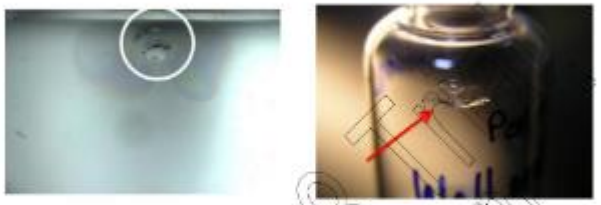


Fracture that penetrates completely through the glass wall.

PDA Glass Task Force
Syringe Glass Lexicon 31

Bruise, (a.k.a Bump Check)

Location: General Class: Major A if >0.5mm; or Minor <0.5mm



A surface mark that is usually crescent shape caused by a mechanical impact or glass-to-glass contact.

PDA Glass Task Force
Syringe Glass Lexicon 17

Regulatory Inspection Trends

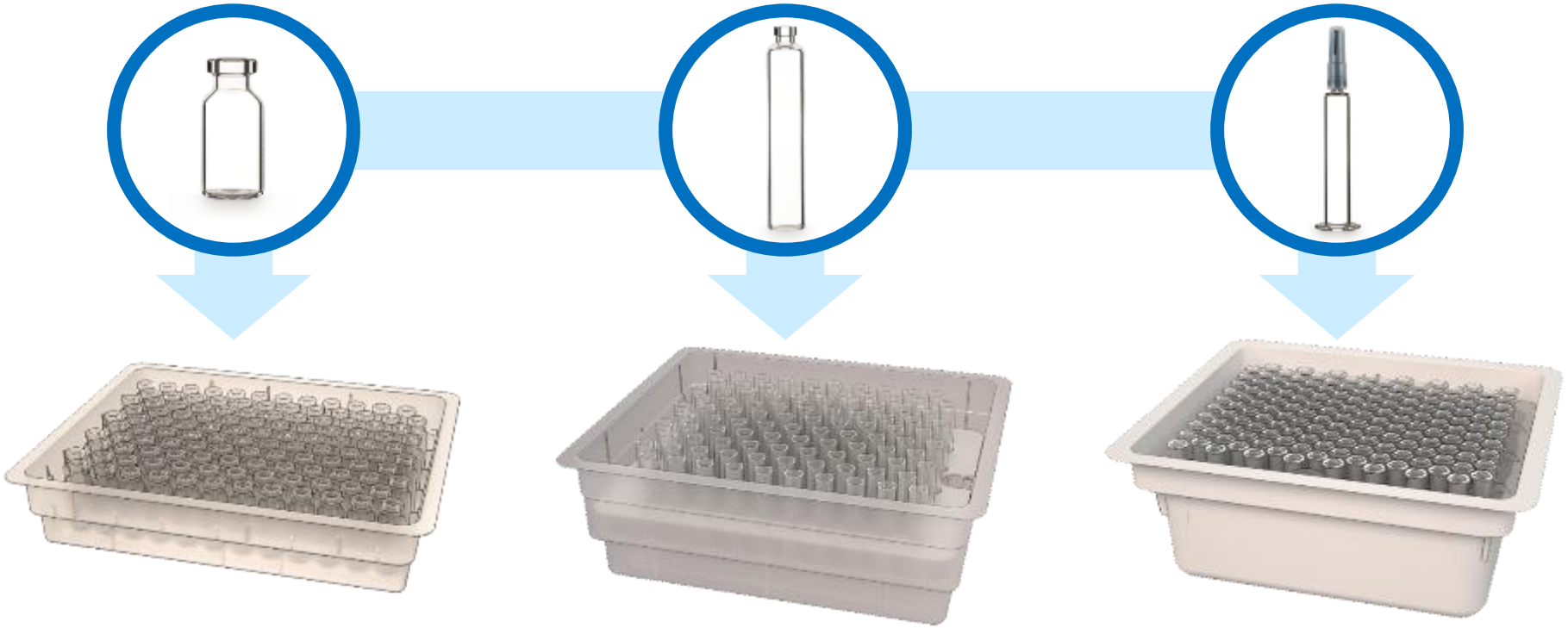
Handling packaging components in primary and secondary production steps needs to address physical material characteristics of glass & polymer

Quality by design

No glass-to-glass contact

Regulatory Inspection Trends

Secondary packaging of glass and polymers containers to be improved for maintaining expected quality and performances



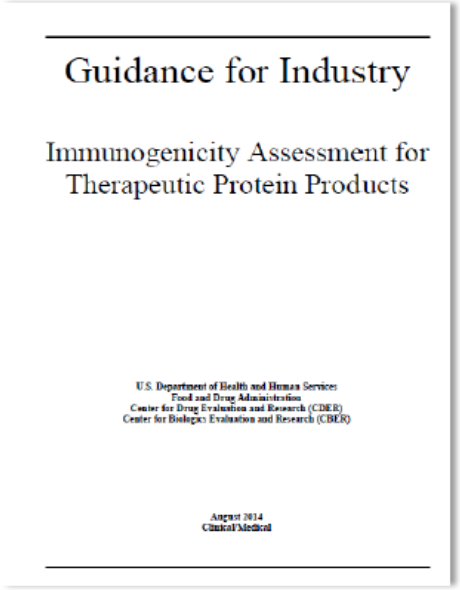
Regulatory Inspection Trends

- US FDA Guidance 2014[4)]

  Immunogenicity assessment

  Section 8 – container closure interactions

  - Glass and air interfaces can denature proteins >> aggregation
  - Glass vials known to delaminate at higher pH
  - Silicone oil-coated syringe can denaturate proteins >> aggregation
  - Leached materials as a source for enhanced immunogenicity (e.g. organic compounds of vulcanization, metals/tungsten)


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

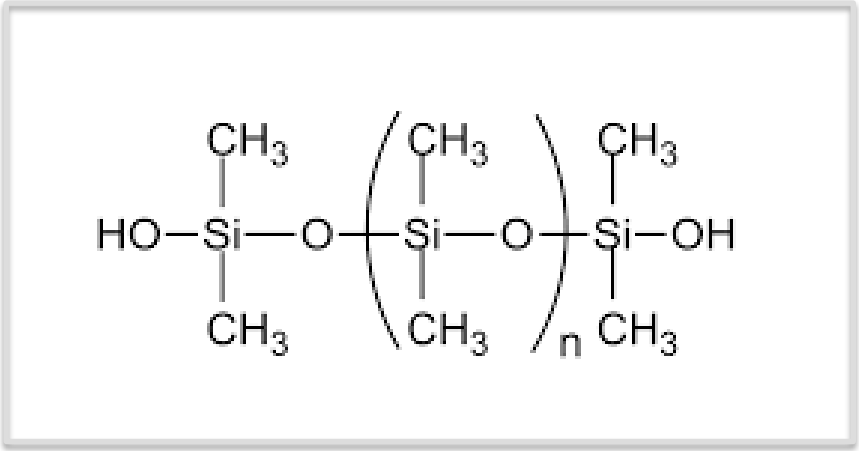
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

4) US FDA Guidance for Industry – Immunogenicity Assessment for Therapeutic Protein Products – August 2014

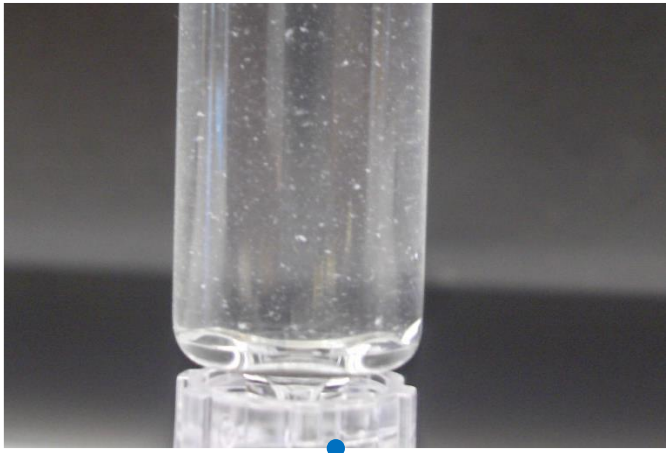
Regulatory Inspection Trends

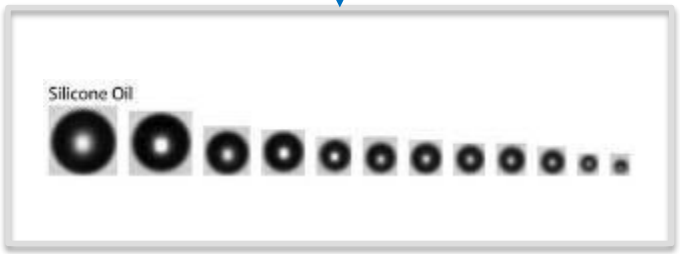
Drug Compatibility with Packaging



Polydimethylsiloxane

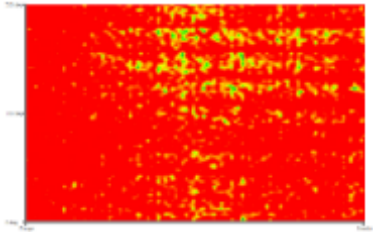
- Particle Generation
- Induction of Protein Aggregation



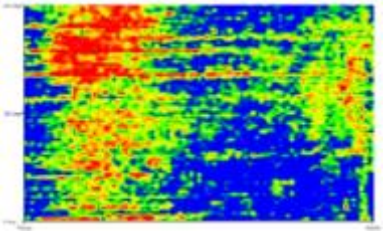


Regulatory Inspection Trends

Nice to have instruments became a must for deeper detail on silicone distribution

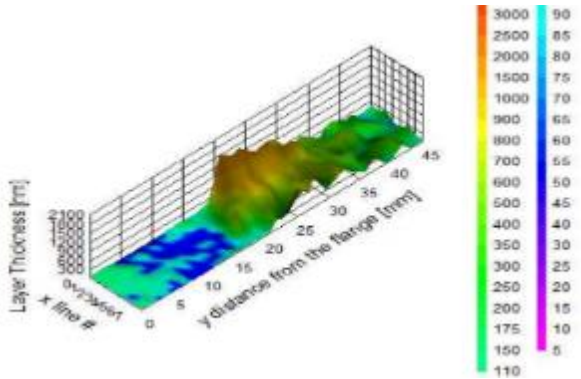


Good Coverage.
Red = 100% coverage



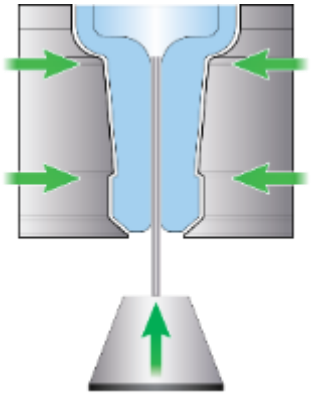
Bad Coverage.
Blue = Lack of silicone (Dry spots)

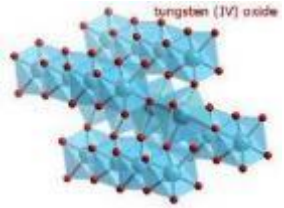
Heat Map with ZebraSci instrument to detect silicone coverage



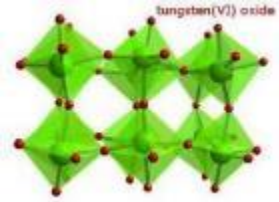
Rap-Id technique to determine silicone thickness on the barrel

Regulatory Inspection Trends



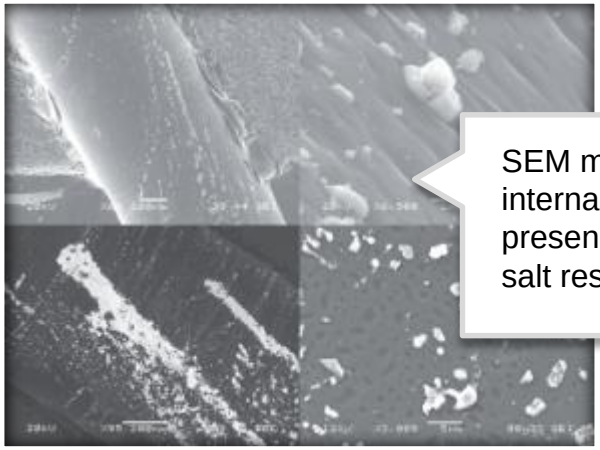


Blue Oxide Crystals



Yellow Oxide Crystals

Used Tungsten Pin



SEM micrograph of internal cone surface: presence of tungten salt residues

- Particle Generation
- Induction of Protein Aggregation

Solutions

- Low tungsten process
- Tungsten free process

Connecting People, Science and Regulation

Any question?

PDA
Parenteral Drug Association

Connecting People, Science and Regulation

Thank You for Your Attention!