



# ADVANCED PROCESSES, CONTROLS AND INSPECTION INNOVATIONS FOR PREFILLED SYRINGES

The US FDA mainly regulates prefilled syringes under pharma product regulations, and in the EU they are considered to be pharmaceutical components. As such, the glass supplier becomes the starting point in the pharma customer production chain. Glass container suppliers thus share responsibility for the drug integrity and efficacy with the pharma company. As Dr Andrea Sardella, R&D Manager at S.P.A.M.I. explains, this has put great pressure on glass converters for providing a well controlled production process with the same quality level as in the remaining part of the pharmaceutical chain.

The Stevanato Group sterile syringes production facility – EZ-Fill™ – started with an in-depth risk analysis of the glass converting and sterilisation process and ended with the implementation of several new controls and the redesign of some line components.

## TUBE PROCESSING

When comparing the average specifications of glass tubing suppliers with the requirements of the pharmaceutical market it may be seen that the starting quality of glass tubing can be insufficient (see Table 1).

Glass tubing particles are a relevant source of contamination for the final glass containers,

Composition (w %)	Borosilicate Glass Type I
SiO <sub>2</sub>	72.0-75.0
B <sub>2</sub> O <sub>3</sub>	10.0-11.5
Al <sub>2</sub> O <sub>3</sub>	5.0-7.0
Na <sub>2</sub> O-K <sub>2</sub> O	7.0-8.5
MgO-CaO-BaO	0.5-3.0
Working point	1260 °C
Transformation Temp.	525 °C
Thermal Expansion Coeff. (α*10 <sup>-6</sup> )	5.0

**Table 2. Chemical composition of type I borosilicate glass**

MAJOR CRITICAL DEFECTS:	Glass tubing supplier		Current Japan Quality Requirements	
	Defect definition	AQL	Defect definition	AQL
Cracks	-	0.025	-	0.01
Fissures	>2mm	0.65	-	0.1
Stones / knots	>0.5 to 0.8 mm	2.5	> 1 mm	1.0
	>0.5 to 0.8 mm and more than 10 pieces	1.0	> 1 mm	1.0
Glass particles	> 0.2 to 25mm (9 max)	0.65	> 0.3mm	0.4
	>0.5mm (1 max)	0.65		
Scratches	Longitudinal: Width>0.2 mm and length >30 mm	1.0	Length > 5mm	1.0
	Radial: wider more than 0.1mm for half of the circumference	1.0	Width > 1mm	1.0
Airlines	> 400mm	0.4	> 1 mm	0.25
	Aggregate >15mm length and width > 0.01mm	0.4		
	Width > 0.1 mm	0.4		
Surface impurities	Outer surface > 2mm	0.1	Not removable > 0.1 mm <sup>2</sup>	0.01
	Inner surface > 0.5mm	0.1	Not removable > 0.1 mm <sup>2</sup>	0.01

**Table 1: Comparison between glass tubing supplier specifications and Japanese pharmaceutical market requirements.**



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Figure 1: Syringe Machine GS36-15.

therefore a pre-processing automatic station to remove them is required together with a special loading tray system for automating the tubing insertion into the forming machine.

A precise and reliable system for the full evaluation of the tubing glass by measuring outer diameter, inner diameter, defects and paneling all along each tube is also required in order to reject “out-of-specs” tubing before the converting phase.

### FORMING MACHINE AND CLOSED-LOOP CONTROLS

The forming machine is the core business of Stevanato Group’s Engineering division, Spami, and the GS36-15 is the state of the art among our glass forming machines with its high productivity and high precision (see Figure 1).

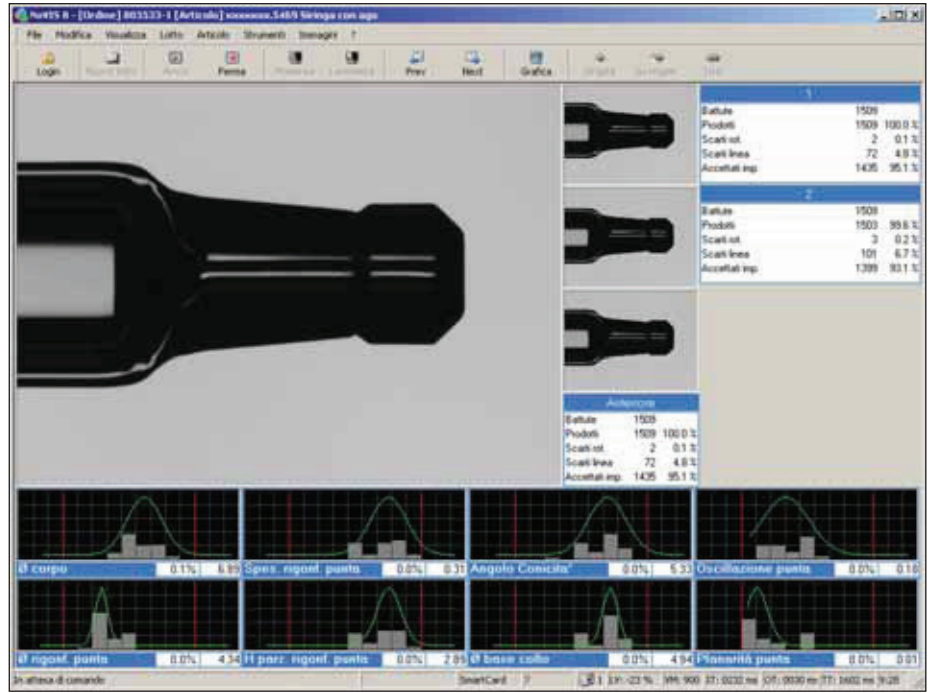


Figure 2: Novis Camera System output

All process variables are controlled and the forming tools are regulated in a closed loop between the dimensional vision system and the multi-axis electronic tool actuators for producing using the tightest possible dimensional tolerances. Figure 2 provides an example of output from the Novis camera system.

Gas flow and burner regulations are programmed and controlled by optical pyrometers in order to guarantee the most accurate control of glass converting temperature in the different machine sections.

By redesigning the cutting device we obtained a relevant reduction of particle production during tube segmentation improving the consistency of the product’s final cosmetic quality.

A very recent upgrade, driven by the ever increasing request for the best chemical

neutrality of the primary packaging for the biotech market, has been the development of new tools for funnel forming. Combined with a lower forming temperature it provides the lowest available content of Tungsten. A thermal image of optimised funnel forming is shown in Figure 3.

### AMMONIUM SULPHATE TREATMENT, COATING AND ANNEALING CONTROL

The chemical composition of a typical Type I borosilicate glass presents a percentage of about 7%  $\text{Na}_2\text{O}$ , necessary to reduce the glass melting point (see Table 2 on page 8). The heat-forming process facilitates the migration of  $\text{Na}_2\text{O}$  from the glass bulk to the surface potentially altering the hydrolytic losses of



Figure 3: Thermal image of optimised funnel forming

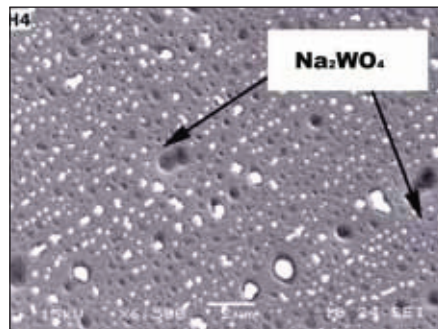
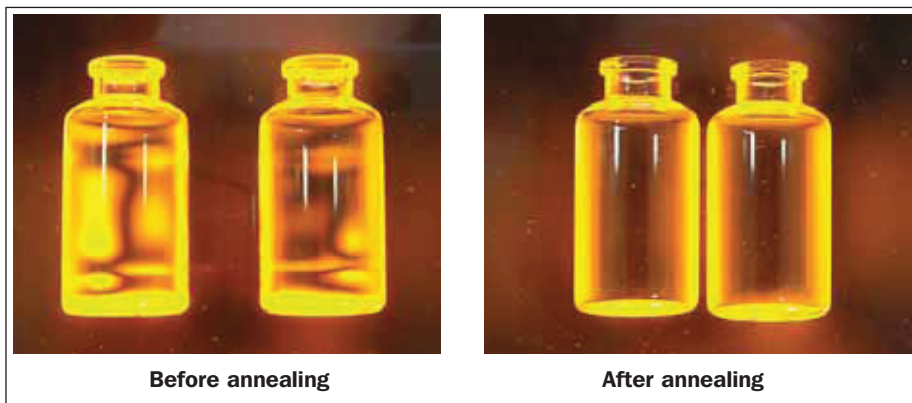


Figure 4: Scanning Electron Microscope (SEM) image of visible  $\text{Na}_2\text{SO}_4$  on syringe surface,  $\text{Na}_2\text{SO}_4$  contamination fill micro-cavities on the glass ranging from 1 to  $5\mu\text{m}$  in diameter



Figure 5: SEM image of flakes formed by delamination



**Figure 6: Effects detection due to annealing phase**

the container. The interaction of ammonium sulphate ((NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>) with Na<sub>2</sub>O at high temperatures gives rise to easily washable sodium sulphate (Na<sub>2</sub>SO<sub>4</sub>) a SEM image of which is provided in Figure 4.

The de-alkalized layer is highly beneficial to the hydrolytic resistance but if its thickness is >1μm, a delaminating effect may occur with the formation of tiny particles or flakes (Figure 5).




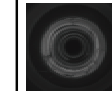

Consequently the accuracy of the sulphurisation system and the control of the temperature and concentration of the ammonium sulphate solution are critical.

To reduce even more the alkali release several SiO<sub>2</sub> coating processes can be used on the internal surface of the container.

After annealing, glass containers are inspected for residual stress presence in order to guarantee the best mechanical/thermal resistance (see Figure 6). This is particularly important in freeze-drying processes.

### LEACHABLE AND EXTRACTABLE ANALYSIS

Every batch is tested, in accordance with the sampling plan, for the quality of the inner surface of finished containers by using an alkali release test

BODY	CONE	SHOULDER	TIP	FLANGE
Contamination	Contamination	Contamination	Micro-cracks	Contamination
Air lines	Stains, dirt on the neck	Deformation		Breakages
Scratches	Folds and incision	Incisions		Deformation
Cracks	Chipped glass	Circular crack		Chipped glass
Glass fragments	Cracks on the cone	Tail heel		Cracks
Printing control	Cracks on the base of the cone			
Stains of color	Glass threads			
Dimensional	Dimensional	Dimensional	Dimensional	Dimensional
				

**Table 3: Classification of critical cosmetic defects**

following ISO International Standards and as recognized by the EU pharmacopeia surface test. A titration method measures the pH of combined extract solutions from several containers and AAS analysis measures the alkalinity of individual containers.

### DIMENSIONAL AND COSMETIC INSPECTION

The dimensional and cosmetic inspections in the ISO 8 Clean Room are the final controls of the glass containers. Dedicated equipment with a double turret for inspecting the whole container without mechanical interference of the handling system is used (see Figure 7).

As shown in Table 3, the Critical cosmetic parameters are classified as per the PDA Lexicon defect classification manual while the dimensional measurements verify URS of the pharmaceutical customer.

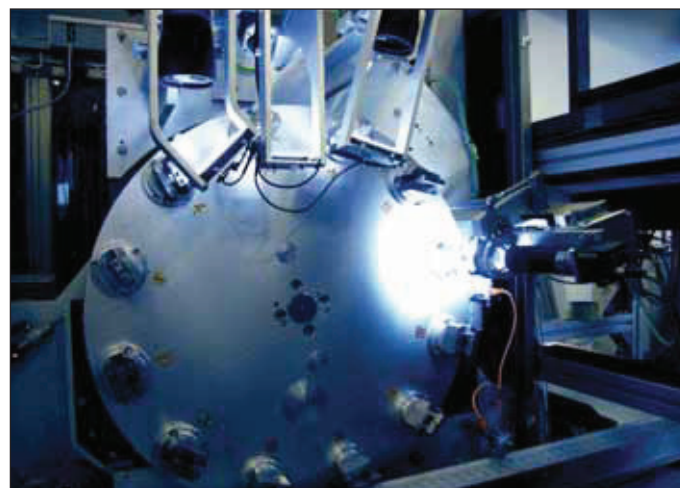
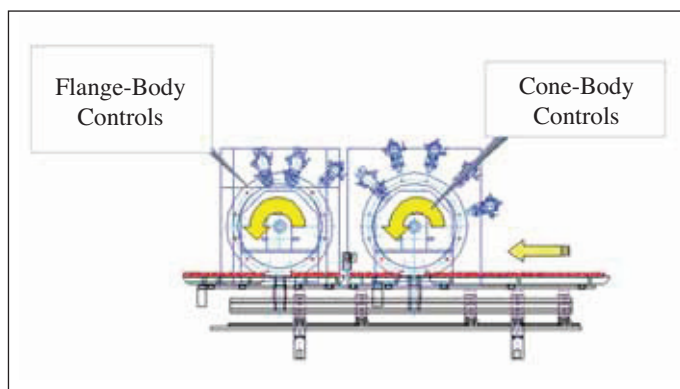
An extended number of parameters, other than those required by international standards, are currently used. The system has built-in redundancy since more than one camera covers the same area, and syringes must pass inspection to continue.

For selected critical cosmetic defects, a Japanese quality standard of 0.04 AQL is used, which is more stringent than international standards.

On request, optional controls can be added by using customer inspection algorithm in order to match the results of the customer inspection machines and reduce false rejects in its production lines.

### NEEDLE ASSEMBLY CONTROL

The needle assembly phase is critical and requires precise mechanical



**Figure 7: Double-turret equipment general scheme (left) and frontal photograph (right)**

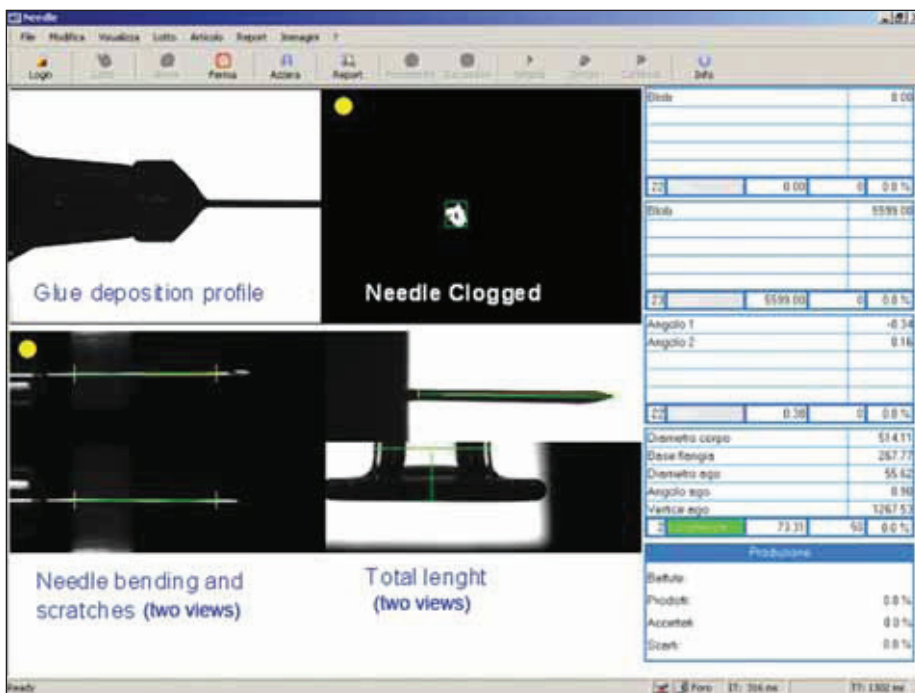


Figure 8: Polymerisation evolution in time measured by Near Infra-Red (NIR)

handling, exact glue dosing, curing-light control and gentle handling of the needle's micro-tube.

Spami has developed a dedicated machine for this assembly operation, integrating the most sophisticated assembly and inspecting technologies.

Glue distribution, and needle position and integrity, are controlled using vision systems and special optical layout directly on the assembly machine to give fast feedback to the system in case of anomalies (Figure 8).

Blowing tests and "pull-off" tests are also integrated for verifying needle functionality and mechanical resistance (Figure 9). The "pull-off" test is not well accepted by customers (even if required by regulations) because of the potential risk of damaging the needle during the operation. For this reason alternative methods such as optical can be used to measure glue polymerisation; in particular

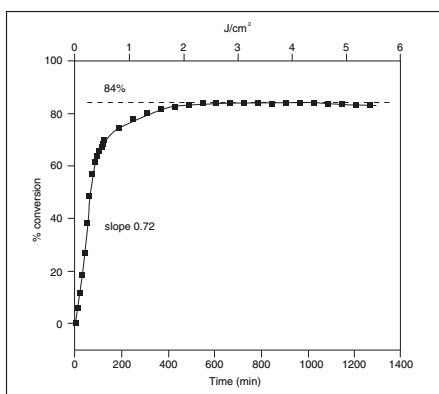


Figure 9: "Pull-off" test results graph

on the inner surface of the cone which could come in contact with drug.

### WFI WASHING, SILICONISATION, SHIELD ASSEMBLY AND NESTING

After needle assembly, the syringes are transferred in an ISO 7 clean room with an ISO 5 washing and siliconising machine integrated with a nester. For the sterile line, the equipment from a company with a good reputation in sterile machinery is used.

The line is equipped with an optical system for sprayed silicone distribution control and pressure control for blocked needle and needle shield integrity control.

Presence and pop-off of shield is checked with an optical laser system. Presence of glass fragments during unloading is detected with an optical barrier.

At the out-feed a Bausch & Stroebel nester collects the syringes and a vision system verifies the presence and the integrity of the syringes before sealing the tub.

Finally, the sealed tubs are sent for EtO sterilization.

### CONCLUSIONS

Requests for ever increasing quality pose new challenges to the processing and control of sterile containers. The synergy between the glass converting division and the engineering division is an important advantage in meeting these challenges.

## ABOUT STEVANATO GROUP

S.P.A.M.I. and Optrel comprise the Engineering Division of the Stevanato Group, which is among leading suppliers of glass primary packaging for the global pharmaceutical industry.

The Engineering Division is strongly linked with the Glass Division, consisting of Nuova Ompi, Alfamatic, Medical Glass and Ompi of America. These companies specialise in the design, manufacture, installation and after-sales support of high-speed precision machinery for the production and control of glass containers as well as vision inspection systems.

S.P.A.M.I. is the technological leader in the design and production of machinery for glass tubing converting for the production of vials, cartridges, syringes, ampoules and special devices.

Optrel has a long tradition in the inspection machine market for the pharmaceutical industry including parenteral drug, injectable and solid dosage inspection with automatic and semiautomatic equipment.

Following its acquisition by the Stevanato Group, Optrel has developed, based on the same field-proven technology, a range of inspection machines for empty glass articles: ampoules, vials and syringes. The range of defects covered matches the requirement from the PDA glass task force and comprise also metrological controls recorded in a SCADA-like interface for production control. The system is 21CFR11 compliant relating to recipes and batch recording.

Stevanato Group produces a full range of glass packaging including important traditional products such as vials and ampoules and also strong growth products such as cartridges for pen-injection systems and auto-injectors as well as prefillable syringes. Syringes are available in both bulk (stake needle & luer finish) as well as from the EZ-fill™ line.

EZ-fill™ offers clients an important new source for reliable, flexible supply of prefillable syringes packaged in convenient nested tub formats (washed, siliconized, sterile).