Overcoming most of the limitations still present nowadays on glass prefilled syringes is possible thanks to an innovative engineering approach, combining high-quality glass forming with pioneering features.

Glass syringes are the primary packaging of choice for drugs and vaccines in the US and European pharmaceutical markets. Quality requirements for primary packaging are steadily increasing following US FDA recommendations to reduce any risk of failures and to insure functional performance with the latest generations of delivery devices and safety devices.

Fulfilment of these new requirements is only possible by combining expertise on glass forming with a new designing and engineering approach for development of innovative process.

Stevanato Group, by combining the design capabilities of its Engineering Division with the long experience in the production of superior quality glass containers for pharmaceutical packaging, has designed and developed fully re-engineered glass syringe manufacturing equipment with implementation of highly efficient devices and innovative solutions. Application of these solutions to mass market products has led to the development of improved glass syringes that give a broad range of benefits for Pharma Companies and innovative features for the final users.

PREFILLED SYRINGE CHALLENGES

Prefilled syringes constitute one of the fastest growing markets in the drug delivery and packaging sectors, with estimated global production of 2.4 billion units in 2010.1 Several studies predict this growth to continue in the next years and the ready-to-use format is gaining more and more standard solutions, such as EZ-fill® in nest/tub configuration.2

The standard requirements for syringe manufacturing are well fixed by ISO 11040, and the 1ml long format has become the most common configuration for biotech products.

Nowadays quality expectations for syringes are growing at a rapid rate especially linked to safety and convenience for patients. Pharma company and regulatory agencies are pushing suppliers to reduce defects and at the same time to improve syringe performance in combination with drug delivery devices.

The growing demand in the market for safety systems and auto-injectors due to recent legislation and to the final user request is highlighting the critical aspect of interaction between glass syringes and metal and plastic components.

To analyse this aspect, the Stevanato Group division, Nuova Ompi, decided to put in place a study using two well-known safety system and auto-injectors suppliers.

Attaching devices or backstops can utilise the flange, often these devices are snapped onto finger flanges. Moreover self-injection systems such as spring-driven auto-injectors, which incorporate prefilled glass barrels, lead to high pressures and forces on the primary packaging (see Figure 1). Often the internal configuration is adapted to the proper syringe formation.

Incoporating improved technical features in glass prefilled syringe manufacturing for pharmaceutical use

Whilst the standard 1ml prefilled glass syringe is now well accepted by the industry with billions being manufactured each year, small problems still crop up with the design, especially in the context of combining the prefilled syringe with add-on devices such as auto-injectors and safety features. In this article, Mr Paolo Golfetto, R&D Manager of Stevanato Group’s Glass Division, focuses closely on some of these issues and describes how, with expertise and excellent design capabilities, they can be overcome.
Thus, we determined the complete settings of the relevant critical design of the primary packaging where there is a gap between the nominal and the optimal values (Figure 2).

The Stevanato Group consists of the Glass Division that manufactures glass containers from tubular glass, with Nuova Ompi being the largest part, and the Engineering Division, which designs and builds machines for the production and quality control of containers from glass tubing. The Engineering Division consists of the companies S.P.A.M.I. and Optrel. Thanks to the synergistic combination of expertise of the Glass and Engineering Divisions, Stevanato Group has the complete converting process covered. Syringe assembly machinery is optimised with innovative proprietary solutions to achieve the finest quality production.

**PROCESS**

Manufacturing glass syringe barrels can be described in the briefest terms as: placing in a vertical position the glass tubing; cutting Type I borosilicate glass cane to the desired length; heating both ends and forming the cone and flange; annealing; inserting a staked needle if required; washing; and siliconising.

The first critical step is the barrel-forming process. At Nuova Ompi this is performed by the latest generation of machines from S.P.A.M.I. that are designed to continuously monitor the glass temperatures during the cone and flange forming process. In addition, flow meters are used to keep the gas mixture of the burners under control. This precise temperature control, together with the components being held and moved by specialised grippers and high precision servo motors, combine to produce barrels with tight dimensional tolerances and reduced critical defects. Cone-tip forming and flange forming are performed reaching an accurate overall length thanks to recalibration action (see Figure 3).

To reduce circular runout we introduced a new generation of holding chucks, key tools of an autocentering system obtaining a very high centricity and a high degree of precision.

After forming, the barrels undergo 100% dimensional inspection by the Novis camera system, which is an internal development of S.P.A.M.I. with special attention being given to the critical area of syringe cone (see Figure 4).

Due to the stress that could be placed onto the flanges by safety systems and auto-injectors, as mentioned earlier, we performed a study on the flange mechanical resistance with a mathematical analysis study of the variables that lead to reduced performance. The results, which are depicted in Figure 5, suggest that the use of a reduced radius round flange could have the best mechanical resistance.

New inspection technology developed by Optrel controls the geometry according to the new requirements checking especially for com-
pability with the latest generation of safety devices and auto-injectors:

- orthogonal deviation (flange robustness, syringe handling and assembling operations).
- window fit (based on customer specs).
- bending (flange geometry).
- body deformation (design compliance).

The barrels then enter the lehr tunnel for the clean annealing phase, an important process that removes the internal strains developed in the glass during the forming process. Special technological applications allow a strong reduction in particle contamination. Temperature monitors are placed at multiple points in the tunnel to control the thermal cycle accurately and ensure reproducible results.

Following the lehr, additional cosmetic inspections are performed in a cleanroom prior to the next steps in the process. All manufacturing phases are glass-to-glass contact free thanks state-of-the-art handling systems in order to avoid any possible critical and cosmetic defects generated by the process.

The last area investigated by the Nuova Ompi R&D team has been the one identified as “Extractables”. It has become increasingly relevant in the last five years and relates to potential interactions between sensitive molecules (especially biotech formulations) and the primary packaging. Three main concerns evaluated are:

- Tungsten residuals.
- Needle assembly (adhesive).
- Silicone quantity and distribution.

Tungsten is introduced into the syringe during the forming process, from the pin used to create the internal channel on the barrel tip. This material is used because of the good combination between resistance to high temperatures and mechanical properties. The sudden change of temperature in the pin is responsible for two sources of contamination:

- Part of the Tungsten vaporises at high temperature and deposits in the funnel area as it reaches the “cold” glass.
- Part of the Tungsten oxidises at 800-900 °C, this oxide reacts at about 1200 °C with Sodium Oxide (Na₂O) that emerges on the surface from the glass structure forming Sodium Tungstate (Na₂WO₄). It has been demonstrated that high temperature causes the migration of substances to the glass surface, and some biotech molecules can interact forming undesirable protein aggregations.3,4

Ompi established a new way of processing the cone-tip forming, dramatically reducing the level of tungsten residuals through optimised control of key process parameters.

Nowadays, there are three different families of syringes:

1. Standard Process: syringes produced with Tungsten tools, extractable Tungsten level is low and compatible with most of the drugs / proteins currently in development.
2. Low Tungsten Process: syringes produced with Tungsten tools and optimised processes, extractable Tungsten level is very low and compatible with very sensitive drugs / proteins.
• Low extractable silicone profile (low silicone.
• Gliding performances (high silicone oil quantity).

Consequently the risk of protein-silicone aggregation and sprayed droplet size.

The full automation of our prefilled syringe production lines provides several parameters that can be fine tuned in order to set the silicone oil deposition profile. Starting from these parameters we conducted a DOE (Design of Experiment) study focused on determining the different families of syringes based on varying the process parameters.

One important aspect to reduce the interaction between biopharmaceuticals and silicone is the dimension of silicone droplets applied on the glass surface.

Thanks to the research conducted we were able to identify several potential silicone profiles with a new silicone atomisation based on reducing the overall dimension of silicone droplets. A key phase in the process was setting the air pressure and the air activation to have a better atomisation and smaller silicone droplets.

Through this reduced droplet size we achieved a significant reduction in quantity of silicone oil used and an optimised surface coating without jeopardising the gliding force performance expected.

Tests have been conducted using a ZebraSci Instrument system in order to verify distribution profiles and droplets size results. The reduction of sub-visible particles in prefilled syringes manufactured by Ompi has been registered at a customer’s site, confirming as hypothesised at the beginning of the study, the existing direct relationship between the optimisation of distribution and droplet size (see Figure 6).

CONCLUSIONS

Only integrating expertise on glass forming with a new design and engineering approach for the development of an innovative process allows us to overcome most of the limitations still present on glass prefilled syringes.

Stevanato Group, by combining the design capabilities of its Engineering Division with the long experience in the production of superior quality glass containers for pharmaceutical packaging, designs and develops fully re-engineered glass syringes manufacturing equipment with implementation of highly efficient devices and innovative solutions.

This uniqueness allows us to achieve relevant developments of improved glass syringes that give a broad range of benefits for pharma companies and innovative features for the final user.

ABOUT STEVANATO GROUP

Stevanato Group, Nuova Ompi Glass Division, produces glass tubing containers for pharmaceutical use. Standard production from neutral glass includes vials-cartridges-syringes (bulk and sterile) and ampoules. Optrel, Engineering Division makes machines for semi-automatic inspection of ampoules-vials-bottles and other containers for liquids, powders/freeze-dried products.

The company produces more than two billion glass containers per year for pharmaceutical use, generating sales designating 87% for export. Nuova Ompi supplies EZ-fill™ clean, sterile and ready to fill. Nowadays this concept is offering the market the advantages of the EZ-fill™ syringes concept for other major container types, including vials and cartridges. This allows clients to continue the trend of delegating services to partner suppliers while improving operational efficiency. The most recent phase in Stevanato Group’s expansion is the construction of a new manufacturing facility for glass containers at a site near Monterrey, Mexico.

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Award Benchmarking Criteria:

- Unique Features/Functionality
- Quality/Complexity
- Customization
- Matched to Target Markets Needs
- Brand Perception of the Uniqueness of the Product

A Best-in-Class Company/Partner.

Synchronized Solutions, Synchronized Value Chain.