



EZ-FILL™:

OFFERING A NEW CHOICE IN GLASS PRE-FILLABLE SYRINGES

Prefilled glass syringes have shown strong gains in sales in the last few years and the annual increase is predicted to continue. In this article, Dr Michael Eakins, Principal Consultant of Eakins & Associates, describes how Nuova Ompi has planned and executed a new production facility for glass prefillable syringes presented in a tub format by utilising internal synergies within the Stevanato Group together with partnering with leading equipment suppliers and consultants from the pharmaceutical industry.

Global pharmaceutical sales continue to show steady growth with the total world market being estimated at US\$643 billion in 2006, an increase of 7.0% over 2005.¹ The market share for injectable drugs, representing about 24% of the route of drug administration, is outpacing the total market growth by increasing at approximately 10% annually.²

There are a number of compelling reasons cited for this observed increase. Firstly, for example, both the number of products in

steps for the patient and therefore the risk of dosing errors. This procedural simplification equally applies to health care workers too.

For the pharmaceutical company there are the benefits of a reduced overfill in a prefilled syringe compared with a vial (especially when the drug is very expensive to produce) and that the correct therapeutic dose is ready to administer. Furthermore, for the pharmaceutical industry there is competitive pressure within a therapeutic area and also lifecycle management to protect the branded product when it loses its exclusivity.

For 2006, the sales of pre-filled syringes were \$33 billion (22.5% of the total injectables market) and showed an 18% rise over 2005. The total number of units sold worldwide is over 1.2 billion with Europe still leading the US with 48.5% of the total versus 32.6% in the US.²

Given the view that these drivers will not only continue but also increase in the future, it is confidently predicted that the prefilled syringe market will continue to grow and outperform other container systems for parenteral drugs with numbers expected to top 2.4 billion syringes by 2010.³

Unfortunately this success has led to a problem. In my experience working with pharmaceutical companies, there has been a change in the last two years in the way companies are looking at the introduction of prefilled syringes for their products. Until recently, the usual sequence was to launch the product in a glass

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development and marketed products from the biotechnology industry has grown and are predicted to continue to increase further. The physical nature of these biotechnology-derived drugs means that they are administered by injection. Second, new treatments for diseases and chronic conditions have been developed especially in the areas anaemia, multiple sclerosis, oncology and rheumatoid arthritis. Thirdly, in the past, a healthcare worker or physician would administer the injection. Today an increasing number of drugs are being self-administered by the patient and the packaging of a drug in a pre-filled syringe as against a vial reduces the number of



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vial and then at a later stage introduce a glass prefilled syringe either as a replacement or as an optional container. With the continued success of the product, the third stage was to introduce a pen-injector or an auto-injector with the drug still housed in a glass container.

Now many companies have decided to launch their parenteral product in a prefilled syringe from the outset, rather than in a vial, which means that they will need a supply of prefilled syringes to conduct not only their initial compatibility and development studies but also their formal stability and Phase III clinical trials.

So what is the problem? In a word – supply. Pharmaceutical companies are finding it difficult to obtain the relatively small number of samples required for their development studies in a reasonable time with delivery timelines being quoted as 9-12 months in some cases. This is especially the case with companies that have not worked with prefillable syringes before and have no leverage of a current order. The prefillable syringe suppliers are struggling to keep up with the rising demand of products that are already on the market and there is no spare capacity.

It is therefore very opportune that Nuova Ompi has developed EZ-fill™ as a new source of prefillable syringes in a nested tub format. The development of this product has been achieved in a unique way as it has utilised a tripartite approach of combining the expertise and experience within the Stevanato Group together with leaders in the field of syringe assembly machinery (Bausch + Ströbel, among others) and consultants from pharmaceutical companies.

The Stevanato Group consists of the Glass Division that manufactures glass containers from tubing glass with Nuova Ompi being the largest part and the Engineering Division that designs and builds machines for the production and quality control of containers from tubing glass and consists of SPAMI and Optrel companies. The project to develop EZ-fill™ represented a synchronised effort between the Glass and Engineering Divisions to ensure that the Stevanato Group had complete control over the entire production process that combines glass technology with engineering experience (see figure 1).

In order to explain what this means in practical terms for manufacturing a prefillable glass syringe, we need to take an in-depth examination of the key steps in the process. A description of the manufacturing process for EZ-fill™ can be divided into the formation of the glass barrel, followed by the placement of the fully assembled barrel in the tub configuration. While the design and construction of prefilled syringes

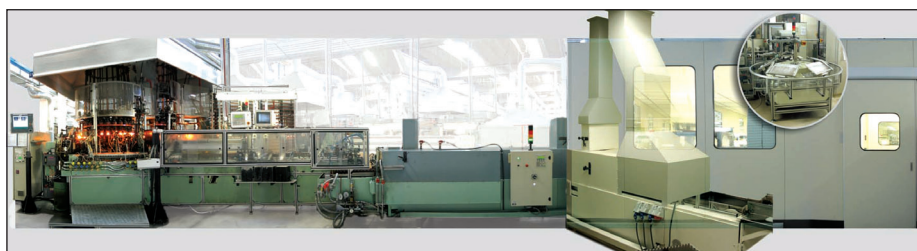


Figure 1: The S.P.A.M.I. barrel forming line leading to the controlled environment area.



Figure 2: Inspection of staked needle

has been described elsewhere⁴, a summary of the process for manufacturing glass barrels can be described as cutting Type I borosilicate glass cane to the desired length, heating both ends and forming the nozzle and finger grip, inserting as staked needle if required, annealing, washing and siliconising. This description, while correct, does not convey the complexity of the technology involved in order to produce a device consistently of the highest quality.

The first critical step is the barrel-forming process. At Nuova Ompi this is performed by the latest generation of machines from SPAMI that are designed to monitor the glass temperatures continuously during the nozzle and finger grip forming process and this information is fed back to the flow meters controlling the gas mixture of the burners. This precise temperature control together with the components being held and moved by specialized grippers and high precision servo motors combine to produce barrels with tight dimensional tolerances and reduced critical defects.

After forming, the barrels undergo 100% dimensional inspection by the Novis camera system, which is an internal development of SPAMI with special attention being given to the critical area of syringe cone. The barrels then enter the lehr tunnel for annealing at tempera-

tures of over 500°C, an important process that removes the internal strains developed in the glass during the forming process. 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 clean-room prior to the next steps in the process. Needle insertion for staked needle products can now be performed using customised high-speed assembly units operating in the cleanroom, which include 100% automated inspection for needle deformation, clogged needles and adhesive distribution.

The EZ-fill™ production area at Ompi is a new purpose-designed building that is dedicated to prefillable syringes. The design of the building was made with input from consultants from pharmaceutical companies to achieve the most advanced and efficient facility for producing devices so critical to the pharmaceutical industry. Areas of key importance were the air handling system, water for injection supply, layout of the clean rooms and the use of modular designs. The facility design allows for capacity expansion to respond to the needs of the market.

The barrels, already controlled and assembled with needle, enter this facility in a controlled and interlocked area to be loaded through a detraying



Figure 3: Tub format

machine in an overall environment classified at ISO level 7⁵ (equivalent to the superseded FED STD 209E Class 10,000) and progress into a series of modular chambers under laminar flow (see figure 2). The Bausch + Ströbel designed production line consists of a detraying machine, a washing / siliconisation / rubber closure assembly and then the tub nesting machine.

The barrels are washed with water for injection only (no recycled or purified water used) and dried with air filtered through a 0.22 micron sterilising filter.

The next step is the key process of siliconisation of the barrel and the needle (if present). Here Medical Grade silicone is applied to the internal surface of the barrel via a diving spray nozzle that is inserted for the full length of the barrel and applies silicone as the nozzle moves back down the barrel. The transparency of the glass is measured by sensors before and after the application of the silicone, checking each barrel to ensure that the correct amount of silicone has been applied. Non-siliconised or excessively siliconised barrels are automatically rejected.

The external needle surface can also be siliconised at this point. A needle shield, rigid needle shield or tip cap is then applied and the syringes moved to the nesting machine. Automatic inspection devices check for: the presence of the needle shield; clogged needles; silicone presence; pierced shields; total length; shields or caps having popped-off; and breakages. General and cosmetic inspection on the package is 100% guaranteed during a production run.

The final steps place the nested syringe barrels into polystyrene tubs, seal with a Tyvek sheet, package in Tyvek/plastic steribags and case-pack allowing for sterilisation with ethylene oxide. Equal attention is given to the cleanliness of the packaging components as to the production of the syringe barrel itself. The tub, nest, Tyvek liner and Tyvek/plastic steribag are all produced under ISO level 7 conditions (see figure 3).

A Validation Master Plan has been followed to qualify the utilities, machines and instruments and to validate the processing steps and the cleaning and sterilisation operations. Externally, annual audits are conducted with suppliers. Strict compliance is maintained with European and US GMP requirements and a Type III Drug Master File is maintained with the FDA. Nuova Ompi has been ISO 9001 certified since 1994 and Nuova Ompi achieved the accreditation to Chinese SFD in 2003. It achieved also conformance with ISO 14001 environmental management systems

In summary, EZ-fill™ is now available in a tub format in 0.5 ml, 1.0 ml and 1.0 ml long sizes with a staked needle, and customers have the choice of formulations from Helvoet Pharma, Stelmi and West Pharmaceutical Services for the needle shield formulation. EZ-fill™ is also available in 1.0 ml and 2.25 ml sizes with a luer tip and a choice of formulations from Stelmi and Helvoet for the tip cap. Additional presentations are under development (see figure 4).



Figure 4: Selection of syringes

EZ-fill™ AVAILABLE FORMATS		RNS 1/2"		NS 1/2"		NS 5/8"		TC (Ribbed)	
		Rigid Needle Shield		Needle Shield		Needle Shield		Tip Cap (Ribbed)	
		Closure Supplier							
SYRINGE CONFIGURATION		STELMI	HELVOET	STELMI	WEST	WEST	HELVOET	STELMI	
	0.5 ml ∅ 8.85 mm Needle 1/2" 27G - 29G	⚙️	⚙️	⚙️	⚙️				
	1.0 ml Long ∅ 8.15 mm Needle 1/2" 27G - 29G	⚙️	⚙️	⚙️	⚙️				
	1.0 ml standard - 2.25 ml ∅ 10.85 mm Needle up to 5/8" 23G-29G	⚙️	⚙️	⚙️	⚙️	⚙️			
	1.0 ml - 2.25 ml ∅ 10.85 mm Luer tip						⚙️	⚙️	

Figure 5: Summary of available formats

CONCLUSION

The planning and execution of the manufacture of EZ-fill™ has been achieved by harnessing the synergy within the Stevanato Group of long-term experience in forming glass containers of the highest quality using the latest machinery for forming and inspecting syringe barrels to provide a synchronised solution. Equally important is the establishment of a partnership with key suppliers and consultants from the pharmaceutical industry to design and build a new manufacturing facility to meet the growing needs of the pharmaceutical industry. EZ-fill™ offers the industry a new choice for glass prefillable syringes.

ABOUT NUOVA OMPI:

Nuova Ompi is the glass-tubing converter in Italy and among the top leaders in its market.

The company, with its sister companies of the Glass Division, Alfamatic (located near Rome, Italy) and Medical Glass (located in Bratislava, Slovakia) produces with its team of 1,050 employees more than more than 1.7 billion glass containers per year for pharmaceutical use, generating sales of approximately €145 million (US\$230 million), designating 70% for export. The standard production from neutral glass tubing includes: syringes with and without needle; screw neck pilfer-proof blow back and pill vials; dental cartridges; and pen cartridges and ampoules.

Nuova Ompi has started to supply EZ-fill™ syringes clean, sterile and ready to fill. The next development of this concept will offer the market the advantages of the EZ-fill™ 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 50,000 m² site in Mexico, near Monterrey. Initiated in late 2007, the initial phase will include 6,500 m² of production space that will be enlarged, starting from 2011, reaching 11,500 m² with an overall investment of €37 million. This new production site is designed to support over 500 million high quality containers serving the production of the growing requirements in the Americas zone and the world.

ABOUT THE AUTHOR

Dr. Michael N. Eakins is Founder and Principal Consultant of Eakins & Associates based in New Jersey, USA with over 25 years of experience in pharmaceutical research and development. Michael provides advice on non-clinical drug development and parenteral packaging, especially pre-filled syringes and anti-counterfeiting technologies and lectures on these topics worldwide. He holds a B.Sc. Hons in Physiology and Zoology and a Ph.D. in Physiology from London University, UK and has written or contributed to 51 articles and holds 8 US Patents. He is Vice Chair of the USP Packaging and Storage Expert Committee for 2005-2010 cycle.

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