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THE CONTAINER OF CHOICE FOR TODAY'S INJECTABLES



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Front cover image “Inspection of staked needle” reproduced with kind permission from Nuova Ompi (www.stevanogroup.com)

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INTRODUCTION

THE RISE OF PREFILLED SYRINGES FROM NICHE PRODUCT TO PRIMARY CONTAINER OF CHOICE: A SHORT HISTORY

Demographics in developed countries suggest that aging societies will see an increased usage of pharmaceuticals. Many of the innovative products will be large molecules like monoclonal antibodies, proteins and peptides which, for the foreseeable future, will all need to be delivered via the parenteral route.

Prefilled syringes are now the primary container of choice for most parenteral drug delivery systems. This is due to a number of factors – chief amongst them the greater medication safety and increased convenience from using a prefilled device. Alternatives, like a vial and syringe combination, require several procedures in preparation for the entire injection of the drug.

Today the global market for prefilled syringes comprises more than 2.2 billion syringes; over half are produced as sterile versions, ready to be filled without further activities prior to filling. The rest are supplied as so-called bulk syringes, where washing, siliconisation and assembly with rubber parts have to be performed close to filling.

The origins of the prefilled syringe's rise as the preferred container were in the extremely successful market introduction of syringes as the drug delivery unit for heparins by Sanofi and Rhône Poulenc-Rorer (both now Sanofi-Aventis) in Europe in the early 1980s.

Prior to this, prefilled syringes were seen as relatively insignificant niche market products. The following years saw demand for prefilled syringes explode, and they were soon used in all major therapeutic classes for injectable drug formulations.

The breakthrough was achieved mainly by the clear advantages prefilled syringes have over traditional vials and ampoules, as the use of a prefilled syringe often involves nothing more than removing the syringe from the package and performing the injection. Together with the low overfill required for prefilled syringes compared to a classical vial, new markets in the biotech area were explored by the prefilled syringe. Over the last few years the

main market for prefilled syringes opened up from Europe and spreading towards the US and Asia; both of the latter two up until recently being typical vial-based drug container markets.

During the 1990s and early 2000s the prefilled syringe had become the primary drug delivery container. However, new challenges were raised, including broadening their field of application to biotechnology and new safety regulations.

A number of other changes and new or different requirements have impacted on the prefilled syringe market over the past few years. We have seen a steady increase in the technical requirements on the (to-date) usually glass-based delivery container platform.

Break resistance and tighter tolerances for finger flanges and glass cone dimensions have changed the quality requirements for syringes. In addition more complex formulations and protein-based active substances challenged the common syringe production technology to increase process control for key production steps and implement substantial improvements in production technology.

SOLUTIONS & ALTERNATIVES FOR SILICONE & TUNGSTEN

Siliconisation of the glass barrel is one of the key process steps, as silicone is the lubricant required to allow movement of the rubber plunger through the syringe forcing the drug out of the container to finalise the injection. Protein molecules can interact with silicone and therefore the amount of silicone sprayed into the barrel has to be controlled. A balance must be struck in order to generate reasonable gliding characteristics while retaining product stability.

A number of syringe system solutions have been developed either to reduce the silicone amount significantly or to eliminate it. Low silicone systems can be achieved either by baking the silicone after application or by using a reactive silicone system applied as liquid and then being

polymerised.

Baking the silicone – which requires heating the siliconised syringe at a specific temperature for an appropriate time – results in substantial stabilisation of silicone-sensitive drug formulations, as presented during the November 2007 PDA conference on prefilled syringes and injection devices in Berlin.

But it is not only the amount of silicone sprayed into the barrel which can create issues with drug stability. The distribution of the silicone inside the syringe should be homogeneous and uniform to generate a smooth sliding profile for the plunger stopper. This is of particular importance when syringes are combined with auto-injection devices and the administration of the drug is not done by manual injection controlled by a human hand.

Another point to be considered is the known tungsten sensitivity of some protein molecules. Manufacturers have developed several ways to reduce or eliminate tungsten as a product contact material. For glass syringes, manufacturers have introduced alternative materials to replace tungsten as heat resistant material in key glass forming process steps. Such technology is now standard and available to stabilise sensitive proteins.

Tungsten residuals together with silicone issues can be removed by using new innovative primary containers made from cyclo-olefin copolymer (COC) or cyclo-olefin polymer (COP).

One manufacturer has developed such a system which is free of silicone due to full fluoropolymer film lamination of the syringe plunger stopper. The fluoropolymer is sufficiently lubricious that the barrel does not need to be lubricated. Another approach to eliminate for example siliconisation is the use of chemical vapour deposition or plasma technology to generate non-silicone lubricant films on the barrel or piston, or on both.

Together with these new technologies and multiple accessories around the syringe, a real universe of drug

delivery components are available, which can be combined to form customised and therapeutic class-focused innovative drug delivery systems.

As an interesting aside, alternative drug delivery routes such as nasal, intradermal or even needle free are being introduced or close to market introduction, yielding individually patient convenient medication systems with a syringe-based primary container for the drug formulation.



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CONVERGENCE OF INJECTORS WITH PREFILLED SYRINGES

Returning to prefilled systems in needle-based applications, perhaps one of the most overt developments, most noticeable to the patients and medical professionals who use prefilled syringes, has been the combination of prefilled syringe with safety accessories and injection devices. This has transformed the prefilled syringe from a humble and relatively simple injection device into a true advanced drug delivery system.

Historically we witnessed the emergence of pen devices for the delivery of insulin and human growth hormones. Those therapies typically required injection daily or even several injections daily, and at variable doses. Consequently the devices were able to provide multiple doses from a convenient primary container like a cartridge. A strong focus was on delivering the correct described dose and innovations included digital devices, dose-correction features, larger cartridges, higher doses and smaller dosage increments, to name but a few.

Frequent injection devices were initially reusable, and the users were able to perform up to several hundred annual injections after receiving proper training.

The first pen was launched for insulin by Novo Nordisk in 1985. It took longer before the prefilled syringe achieved its current status of the primary container of choice for single-use, fixed-dose auto-injectors.

The prefilled syringe is a different primary container for devices. It is typically a fixed dose and can be up to 1 ml for subcutaneous delivery. This means that the plunger stopper needs to travel all the way through to the shoulder/end of the syringe. Many new therapies for indications such as rheumatoid arthritis, psoriasis, multiple sclerosis, anaemia and Crohn's disease are fixed doses, given less frequently than every day.

The very first auto-injectors were used with disposable (not prefilled) syringes. Early models were manufactured by Owen Mumford. This concept was then adapted for prefilled syringes. As they were reusable, there were many steps and they did not prevent accidental needle stick injury after they had been used.

With the new indications a different patient type emerged – some with dexterity issues – most of them demanded as the number one feature ease-of-use,

and consequently as few user steps as possible. Other requested features were automatic needle insertion and dose delivery while the needle should not be visible before, during and after the injection, and the needle be locked away after the injection was finalized.

The injection experience could be described best as having just three steps:

- 1 Remove the cap
- 2 Place device on the injection site (and release interlock)
- 3 Press the triggering mechanism

More human factor studies have been conducted and the outcome is visible as it created a wide array of device options: No firing button (i.e. Ypsomed's Silberhorn); new and different shapes (i.e. Bang & Olufsen Medicom's Leva®), tamper evidence (i.e. BD's Physioject™) or numerical cues (i.e. Owen Mumford's SnapDragon)

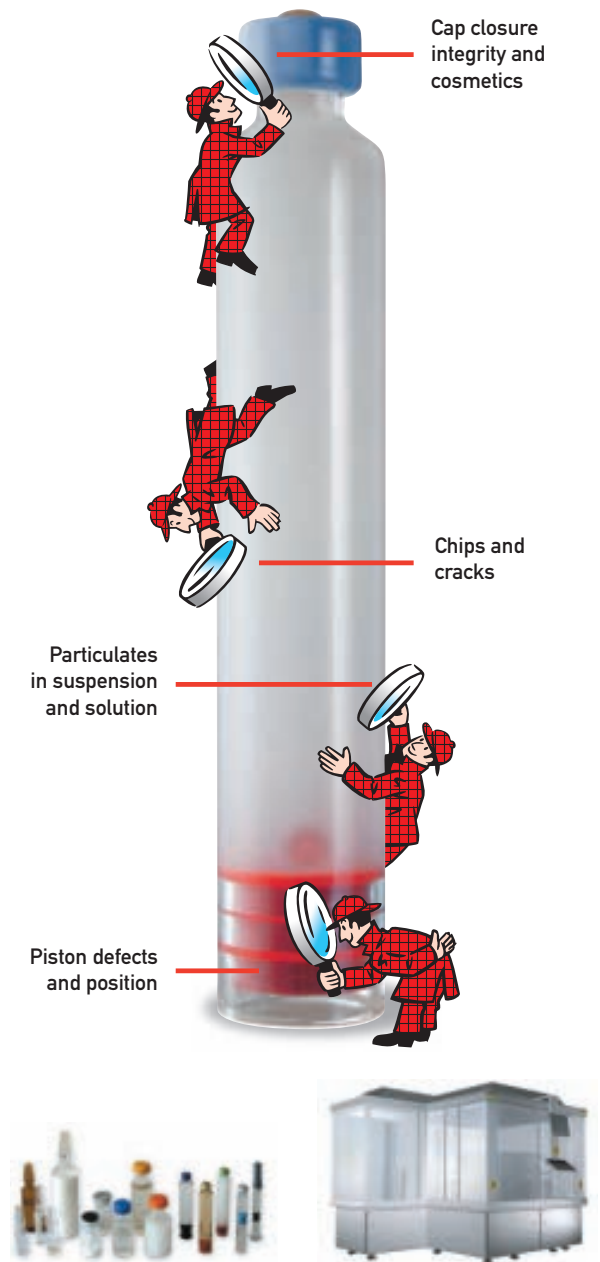
The marriage of disposable auto-injector and prefilled syringe also has its challenges:

- 1 Combination products are now evaluated like a drug by regulatory authorities
- 2 Project often includes three partners (pharmaceutical company; device maker; prefilled syringe supplier)
- 3 A larger investment is required as assembly of syringe and device is necessary; furthermore higher capacity tools and moulding machines may be required for high volumes
- 4 Management of robust large-scale manufacturing, infrastructure, production flow and device/syringe inventories
- 5 Tighter specifications for prefilled syringe dimensions as delivery of whole dose needs to be guaranteed

Examples for the above exhibiting reduced user requirements are Amgen's SureClick™ device for Enbrel® and Aranesp® as well as Abbott's Humira® Pen.

In the years to come the market will see more drugs being launched with the aforementioned disposable auto-injector platforms. New needs for innovation may be driven by high viscosity drugs and volumes higher than 1 ml that need to be delivered via the subcutaneous route. Examples for the former are The Medical House's ASI and Antares Pharma's Vibex™.

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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 prefilled 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

THERE HAS BEEN A CHANGE IN THE LAST TWO YEARS IN THE WAY PHARMA COMPANIES ARE LOOKING AT THE INTRODUCTION OF PREFILLED SYRINGES FOR THEIR PRODUCTS.

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 prefilled syringes before and have no leverage of a current order. The prefilled 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 prefilled 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 prefilled 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 silicising. 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 prefilled 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 / silicisation / 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 silicisation 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-silicised or excessively silicised barrels are automatically rejected.

The external needle surface can also be silicised 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 112"	NS 112"	NS 5/8"	TC (Ribbed)			
		Rigid Needle Shield	Needle Shield	Needle Shield	Tip Cap (Ribbed)			
		Closure Supplier						
		STELMI	HELVOET	STELMI	WEST	WEST	HELVOET	STELMI
	0.5 ml Ø 4.85 mm Needle 112" 270 - 290	☉	☉	☉	☉			
	1.0 ml Long Ø 5.15 mm Needle 112" 270 - 290	☉	☉	☉	☉			
	1.0 ml Standard - 225 ml Ø 10.85 mm Needle up to 5/8" 290 - 290	☉	☉	☉	☉			
	1.0 ml - 2.25 ml Ø 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 prefilled 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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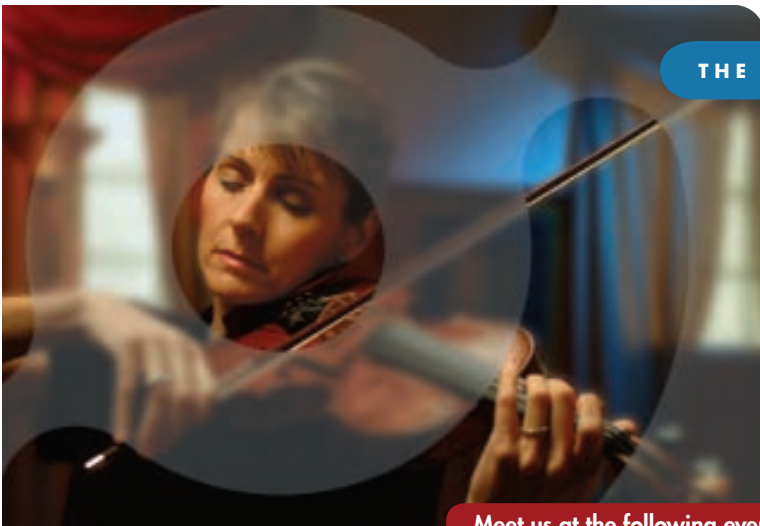
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STELMI RIGID NEEDLE SHIELD: THE SUCCESSFUL CONCEPT WITH THE ANTI POP-OFF PATENTED DESIGN

Over many years, Stelmi has gained a high level of expertise in the field of elastomeric components for prefilled syringes. In this article Stelmi outlines the design and functional characteristics of its rigid needle shield

Developed at the end of the 1990s, the rigid needle shield is the mechanical assembly of a soft needle shield in a polypropylene cover. It thus combines the sealing properties of rubber with the rigidity of polypropylene.

personnel providing care. These advantages can all be gathered into four groups:

- It is primarily a closure system; it assures the integrity of the packaging.
- Its patented design makes it possible to

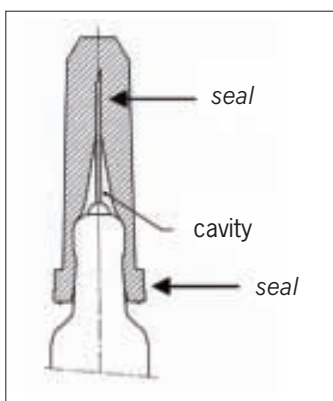


Figure 1: Diagram of rigid needle shield showing assured seal

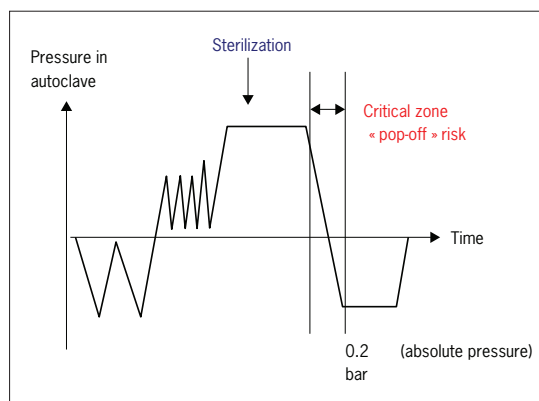


Figure 2: Typical sterilisation cycle in an autoclave

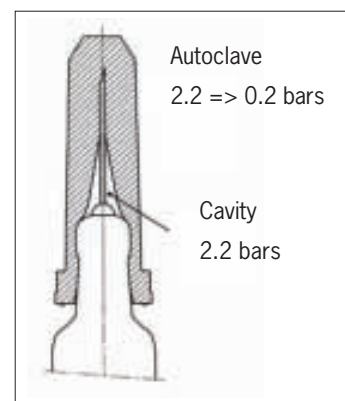


Figure 3: Schematic showing pressures in the autoclave and inside the cavity during autoclaving

The rigid needle shield is one of the most complex elements to manufacture of all elastomer closure systems. This is explained first of all by its small diameter form and its large depth. Then, a balance must be struck between the two elements it is comprised of (a rubber needle shield and a polypropylene shell) one being rigid and the other flexible for the requirements of utilisation. Assembly of the Stelmi rigid needle shield is done in a way which makes it possible to obtain substantial solidarity between the two elements and a pleasing aesthetic appearance.

The rigid needle shield has a number of advantages beginning with the production of the injectable product and up to the final use by the

personnel providing care. These advantages can all be gathered into four groups:

- It protects the needle.
- It provides safety to the personnel providing care.

THE ASSURED INTEGRITY OF PACKAGING

A harmonized formulation

The needle shield must quite obviously be inert vis-à-vis the medicine and must maintain sterility over the entire period of storage. Although the potential contact surface may be very minimal between the medicine and the nee-

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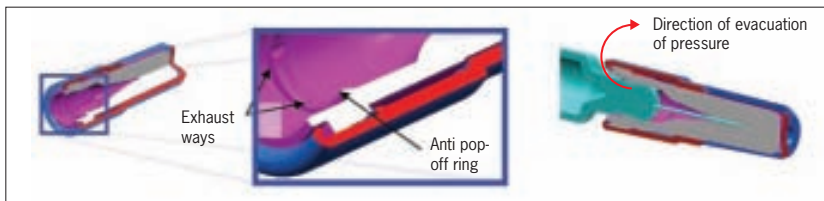


Figure 4: Diagram showing the patented design of the needle shield with exhaust ways

dle shield, the needle shield must nevertheless be made of a harmonised formulation. This is why the Stelmi rigid needle shield is comprised of a flexible formula 4800GS needle shield based on synthetic polyisoprene (latex free and non – cytotoxic), especially studied for this utilisation.

Indeed, during the development of the 4800GS formulation, the following parameters were carefully addressed in order to ensure the best combination of properties:

- High packaging integrity.
- Optimised mechanical properties for resistance to coring by the sharp edge of the needle.
- Excellent physical properties for stability on the syringe during steam sterilisation.
- High gas permeability for short sterilisation cycles both with steam and ethylene oxide.
- Optimised biological properties according to USP <87>, USP <88> biological reactivity tests.
- High output on automatic lines.
- Compliance with 3.2.9 paragraph of the European Pharmacopoeia for rubber closures.
- Resistance to aging during sterilisation and storage.

Regarding the resistance to ozone: the ozone quantity met during the process of preparing and filling the syringes is very low and the exposure time is very short. The syringe is then packaged in a blister which is in a carton box, protected from light and ozone. A syringe equipped with a needle shield made with 4800GS can be kept in a blister for five years without any observed cracking.

All these advantages make the formulation 4800GS the standard for needle shields on the market.

Assured seal

The seal is assured at two points (see figure 1):

- At the top of the needle shield, at the point where the needle is implanted in the rubber.
- At the bottom of the needle shield by the contact of the rubber of the flexible needle shield with the glass of the syringe barrel.

A FACILITATED PRODUCTION PROCESS

Improvement of machinability

First of all, due to its rigidity, the rigid needle shield improves machinability to the extent where it provides better gripping by the machine. It is

initially pre-positioned on the syringe and then secondly fully assembled on the syringe, thus increasing production efficiency. The needle is then implanted in the rubber during this second step.

Shortening of sterilisation cycles: an optimised design

- A design that enables sterilisation

A needle shield must adapt to the production of medicinal product in prefilled syringes and must allow sterilisation. The high gas permeability of formulation 4800GS combined with the windows of the rigid shell allow efficient sterilisation either by steam or ethylene oxide.

- An anti pop-off design

Positioning of the rigid needle shield is much more stable during and after the sterilisation cycle compared with that of a standard needle shield. Figure 2 shows a typical sterilisation cycle.

The main risk of pop-off occurs after the sterilisation step, when a vacuum is applied to the autoclave in order to dry the syringe.

In the present example, the abrupt drop in pressure from 2.2 bars to 0.2 bars in the autoclave causes the relative pressure to be greater in the cavity (see figure 3). Therefore the rubber formulation combined with the design of the part prevents the rigid needle shield from coming off of the syringe.

The Stelmi rigid needle shield design is the patented design that provides mechanical stability at the time of autoclaving (see figure 4).

- The anti pop-off ring prevents slipping and makes possible a better hold of the needle shield on the syringe.
- The four exhaust ways allow the overpressure to escape and thus play the role of a valve.

PROTECTION OF THE NEEDLE FOR PAINLESS INJECTION

The rigid needle shield allows manipulation of the syringe without risking damage to the needle during production or during any handling and it keeps the needle intact over the entire storage period.

By virtue of its very elastic characteristics, it prevents the needle from generating rubber particles by coring and prevents any deformation of the needle. The elastomer is non-abrasive vis-à-vis the needle bevel and thus does not risk damaging it.

The table below (figure 5) shows results from a test performed on 30,000 needles. These needles were initially checked in order to guarantee their quality prior to starting the test. The numbers of damaged needles were then compared after their assembly with the rigid needle shield using a standard formulation and the Stelmi needle shields made with the 4800GS formulation. **The Stelmi rigid needle shield makes it possible to obtain almost ten times fewer distortions.**

It should be noted that performance depends on the quality of assembly and that painless injection relies on the quality of the siliconisation of the needle.

Figure 6 (on page 16) illustrates the difference of puncture effort between non-siliconised and siliconised 27G needles when measured on a polymer membrane simulating human skin.

Moreover, the same measurements performed with the same syringes after assembly with the rigid needle shield and sterilisation confirm that the piercing force is not modified, showing evidence that :

- the rubber material does not affect the sharpness of the tip of the needle,
- the rubber material does not remove the silicone oil which lubricates the needle.

Functional properties

Figure 7 (on page 16) provides the evolution of the pull-off forces of the needle shield at different stages. We have seen that the rigid needle shield is firmly attached to the syringe at the most critical times in the production process.

	Distortion of the needle bevel	
	Standard formulation	4800GS Formulation
Barbed tip	7	1
Twisted tip	235	25
Syringes quantity	15000	15000

Figure 5: Results of test comparing needle damage with standard formulation and 4800GS needle shield formulation

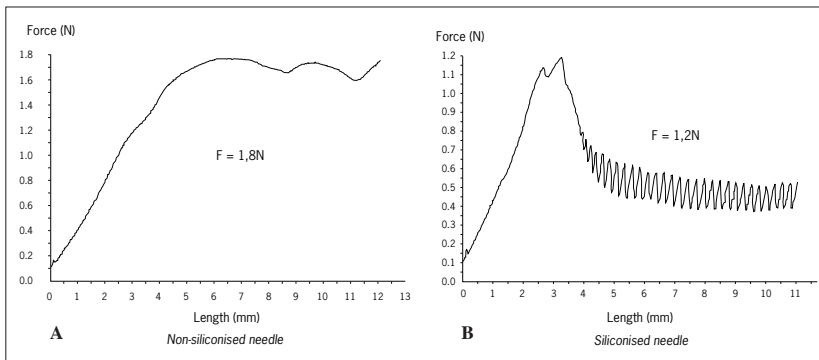


Figure 6: Comparison of puncture effort through polymer membrane using (A) a non siliconised needle and (B) a siliconised needle

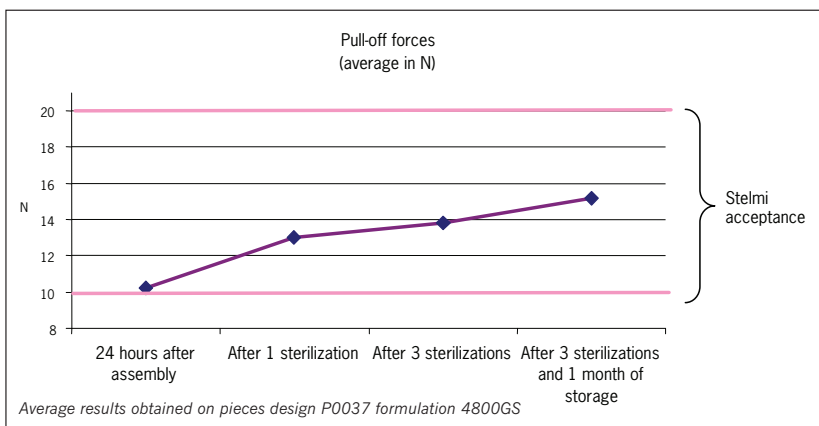


Figure 7: Needle shield pull-off forces following assembly, sterilisation cycles and storage

Uncapping of the needle, however, is still easy for the final user even after three cycles of sterilisation and a month of storage.

The question could also be asked as to the risk of separation of the two components

(rigid and flexible) of the rigid needle shield. Accordingly, the following test was conducted: a defect was intentionally created in gluing the flexible component to the syringe; then an extraction of the plastic shell was done

and the forces necessary for separating the two components were recorded. Figure 8 pro-

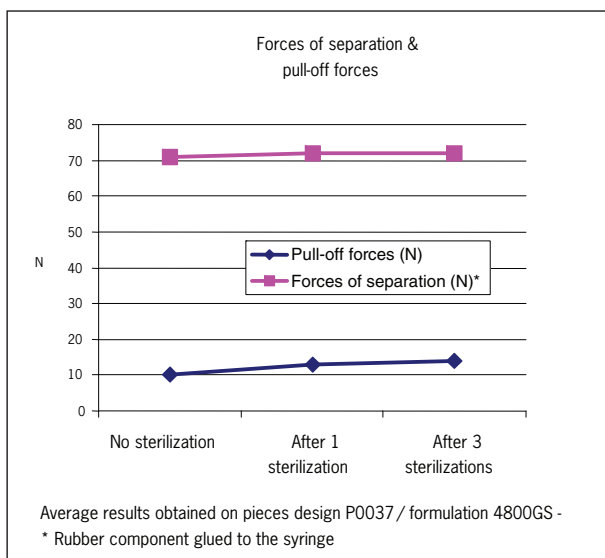


Figure 8: Forces of separation for the two components (rigid and flexible) of the needle shield. (Pull-off forces also shown for comparison.)

vides the measurements recorded, from which it can be confirmed that a force seven times greater than the removal force is required for separating the two elements even after three cycles of sterilisation.

FORMULATION TPE: A NEW OPTION

The rigid needle shield has originally been developed with synthetic thermoset rubber as the soft part of the rigid needle shield. An other option of Stelmi rigid needle shield is also available in a new formulation made of ThermoPlastic Elastomer (TPE).

CONCLUSION:

The Stelmi rigid needle shield combines the sealing properties of rubber or thermoplastic elastomer with the rigidity of polypropylene. It has advantages in the production process by improving the machinability and in reducing the sterilisation time by a substantial permeability of the rubber and by reduction of the risk of pop-off. Its design also provides the advantage of allowing uncapping of the needle that is easier and safer for the user, while protecting the needle. It ensures needle's tip integrity and does not remove silicone oil from the needle, thus allowing painless injection. Furthermore, the absence of coring avoids obstruction of the needle by rubber fragments.

The Stelmi rigid needle shield is available in three sizes (see figure 9) : 1/2 inch (ref. P0037) and 5/8 inch (ref. P0038) and 1 inch (ref. P0046).

Stelmi is a registered trademark of Stelmi S.A. in various countries.

Stelmi's rigid needle shield is a registered patented design.

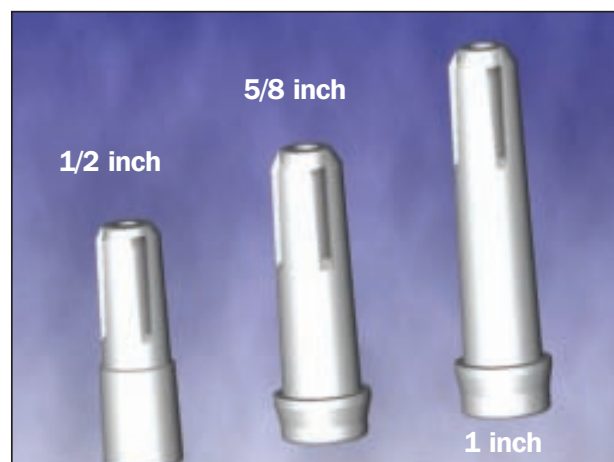


Figure 9: The Stelmi rigid needle shield is available in three sizes

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CURRENT CONSIDERATIONS AND FUTURE DIRECTIONS FOR E-BEAM STERILISATION IN THE PREFILLED SYRINGES MARKET: AN OVERVIEW

By Guy Furness

INTRODUCTION

Prior to filling, prefillable syringes are presented in Tyvec® (lightweight polyethylene) bagged tubs, each containing 100 (or 160) pre-sterilised nested syringes. The sterilisation level of the filling line along which the tubs pass increases stepwise until it reaches Class A (Class 100) where the syringes are exposed in order to be filled and sealed.

The current role of electron beam (e-beam) irradiation in the prefilled syringe production process is, in essence, to sterilise the external surface of the tubs as they move into the Class A filling isolator from the Class D (Class 100,000) area which precedes it. Specifically, the e-beam must irradiate the external surface of the tub with a dose of at least 25kGy. It must do this while delivering little or no energy to the inside of the tub as this would cause unwanted effects: the formation of ozone and nitrogen oxide gas inside the tub; and discolouration of the type I borosilicate glass traditionally used to make syringe barrels.

BRIEF HISTORY

It was relatively recently, in 2000, that the first e-beam tunnel for this purpose was conceived when Linac Technologies was asked to develop its existing e-beam systems for syringe tub sterilisation by a large pharmaceutical company client.

"E-beams had been used since the 1960s for irradiating food and for the sterilisation of medical devices [under ISO 11137]," explains Linac's Managing Director, Philippe Fontcuberta, "but that was for core sterilisation. Surface sterilisation is more difficult to validate."

To fit inside the pharmaceutical plant's clean syringe filling facility and deliver the correct dose, Linac built an original "miniature" surface sterilisation unit, the SterStar, for its client comprising three low energy (200 keV) accelerators positioned at 120° in an e-beam tunnel to pharmaceutical GMP standards. Its design ensured the correct dose distribution at all points on the product's surface, maintained by a control and monitoring unit controlling electron energy, beam current and exposure time. By 2002, their machine had been validated with no contamination having been found on treated surfaces on any occasion.

In 2004, isolator company Getinge La Calhene purchased Linac Technologies in order to acquire its e-beam technology and know-how. By this time a total of four machines had been manufactured. "Three were installed for pharma clients and all three are still operating to this day," Fontcuberta notes. "Today a total of 18 machines have been manufactured by Linac Technologies and five by other companies."

ADVANTAGES OF E-BEAM

Before e-beam technology stepped in, methods for sterile tub transfer included successive debagging and chemical sterilisation. Successive

"THE E-BEAM IS NOW ACCEPTED AS THE DE FACTO STANDARD FOR TRANSFERRING TUBS INTO THE FILLING AREA"

debagging involves removing the outer bag as the tub moves from a Grade E to a Grade C environment, and then removing the inner bag as the tub moves into the Grade A filling area. For chemical sterilisation, either a "spray and wipe" system (with alcohol-based disinfectant as each bag is removed) is used, or a vaporised hydrogen peroxide (VHP) chamber, which sterilises batches of tubs prior to entering the filling isolator.

Among the disadvantages of these methods are that they were: highly operator dependent; difficult to validate; and usually batch processes rather than in-line processes. Even in-line H₂O₂ sterilisation is hard pushed to keep up with the six-tubs-per-minute regular speed of the filling line. Furthermore, H₂O₂ being a chemical treatment left chemical residues on the tubs.

In contrast, e-beam sterilisation has a number of clear advantages, including:

- It is a physical treatment (like heat), therefore leaves no residues
- Unlike heat, it is a cool treatment and so there are no morphological effects.
- It is an in-line process

- Very precisely tuneable.
- Highly effective (consistent log 7 reduction in contaminants)
- Easily validated
- Can comfortably work at 8-10 tubs per minute, easily keeping up with the filling line's pace.

"The e-beam is now accepted as the *de facto* standard for transferring tubs into the filling area," states Scott Ross, Product Manager at Advanced Electron Beams (AEB). "Every new filling line uses e-beam and some companies with older lines that don't have e-beam are retro-fitting it."

He gives the example of a pharma company in Europe which has two filling lines in the same building, one being an older filling line without e-beam and one being a new line with e-beam. The company is to upgrade the old filling line with e-beam technology. Set alongside the old filling line, the new line offers a reduction in risk and allows the company to run the isolator for longer between VHP cycles.

CONSIDERING DIFFERENT SUPPLIERS

It would not be so useful here to discuss the general factors - factors that anyone must consider when sourcing any high-value (more than \$1 million) piece of equipment (such as relative costs, supplier track record, reputation, or geographic location of prospective suppliers etc). Neither is it useful within this article to conduct a detailed differential analysis of e-beam technology suppliers, since each end user has individual criteria.

However, there are a few broad points - yet specific to the topic of e-beam tunnels - that are usefully raised here, based on brief discussions with Linac and AEB as examples.

The business models of these two companies differ. Linac, as mentioned above, is a subsidiary of Getinge La Calhene. The latter specialises in supplying isolator and transfer systems to the pharmaceutical industry and manipulator and transfer systems to the nuclear industry. Linac not only manufactures the e-beam emitters themselves, but also supplies complete e-beam tunnels and provides the associated maintenance and servicing. It can claim to be the only company specialising in purely pharmaceutical applications of e-beam technology. It has the longest experience

in this field and it designed and developed the first e-beam tunnel for syringe tub sterile transfer.

AEB specialises in the development and manufacture of the e-beam emitter devices. Its strength is its e-beam emitter technology, and it supplies these emitters to companies experienced in developing equipment for, and working closely with, the pharmaceutical industry - companies such as Metall + Plastic and Skan. These companies incorporate AEB's emitters into their own e-beam tunnels which they supply to, and maintain and service for, their existing pharmaceutical company clients.

The emitters from AEB and Linac are also different. Linac's emitters work on a scanning basis whereby a pencil beam of electrons, steered by a magnet, rapidly scans over the surface it is treating, like the cathode ray of traditional television sets. "This gives the capability to have fine adjustment of the dose on complex surfaces such as the surfaces of the tubs," says Fontcuberta. Linac's emitters incorporate an electrostatic (ionic) vacuum pump.

AEB's emitters are fixed beams, more akin to a flashlight beam. AEB says that a small number of moving parts leads to fewer variables in the system. Its emitters do not require continual vacuum pumping but are sealed like light bulbs meaning that they are smaller and they can be installed on a "plug-and-play" basis. Maintenance

is rapid - it takes 20 minutes to change an AEB emitter and little training is needed.

Linac's emitters can also be installed on a "plug-and-play" basis needing little training.

NEW DEVELOPMENTS

Linac's first machines were installed in 2002 and in 2007 it began work on a new design. Importantly, there has been no modification to the emitter or treatment area as no improvement was required and efficiency was proven. The modifications, some requested by customers and others made in anticipation of forthcoming FDA regulation include: a smaller footprint; lighter-weight; and an all-on-one level, in-line conveyor. Also, vertical laminar air flow has been installed in order to achieve Class A after sterilisation. Finally, a new fixed lead shielding design (i.e. with no moving or mobile parts) has been implemented.

Another development from Linac is in-line terminal sterilisation of filled syringes. One machine is to be installed in May this year and another is under construction. The tunnel is in-line with the filler and works at a rate of 300 units per minute.

Looking further ahead to new applications of e-beam technology within the sphere of the pre-

filled syringe industry, two interesting avenues are opening up.

Noting that the cost of an e-beam tunnel is well over \$1 million, with a significant additional cost of validation to consider, AEB's Scott Ross explains possible additional uses of the tunnel. "The process that is validated is the sterilisation of the outside of the standard tubs. Once you have validated the e-beam process and you have validated the tub, it makes no difference to the e-beam what is inside the tub," he reasons. "Why not therefore use this process for tubs containing other things?"

Ross terms this a "universal tub concept", which significantly increases utility for the end user. "It allows you to introduce materials into the isolator," he says. Examples of items that routinely require introduction into the isolator include environmental monitoring plates and plunger stoppers. These are currently dumped into a hopper and introduced through a port. Tubs could also be used to transfer unscheduled material, such as tools, into the isolator quickly and efficiently, he adds.

The second avenue within prefilled syringes that e-beam technology is likely to begin travelling along in the years ahead is dependent on another major change occurring in the sector; the change from traditional glass to cyclo-olefin copolymer (COC) and cyclo-olefin polymer (COP) syringes.

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“COC and COP can be exposed to e-beam without discolouration,” says Philippe Fontcuberta, “opening the possibility of sterilising empty syringes [not just the surface of their tubs] just prior to filling.” This fundamental change, which would have “huge implications”

“IN THE MEDIUM TO LONGER TERM WE WILL SEE E-BEAM STERILISATION APPLIED TO ITS CURRENT FUNCTION IN MORE EFFICIENT WAYS, SUCH AS IN-LINE STERILISATION OF SYRINGES DIRECTLY”

for the syringe filling process, will begin to take place in two to three years, he believes.

Currently two separate sterilisation processes take place. After manufacture, syringe barrels are ethylene oxide (EtO) sterilised prior to packing into tubs and bagging. Then, after being shipped to a different site, the external surfaces of the tubs are sterilised by e-beam prior to transfer into the filling isolator. With polymer

syringes a new approach would eliminate the need for the first sterilisation step.

“In-line sterilisation of polymer syringes represents true process compression,” Ross agrees. Lead times that are currently measured in weeks would be reduced to minutes.

“Another nice thing that in-line sterilisation does for you is for example in dealing with stoppers,” he adds. “They are currently loaded into the isolator through hoppers after which they require straightening and orientation. With in-line sterilisation you can do all this in a Grade D environment just prior to sterilisation.” This speeds up the process and reduces the amount of large equipment inside the isolator, meaning that smaller isolators can be used. Upfront costs and operating costs are reduced.

Although in-line sterilisation is still a few years ahead for prefilled syringes, it is already in place in the food and beverage industry. For example, Procomac Spa (Italy) e-beam sterilises bottle caps for drinks in-line at a rate of 500 per minute prior to bottle filling in its aseptic beverage filling operation.

CONCLUSION

In a relatively short time, the e-beam has become firmly established as the gold standard for tub transfer into the filling area. There is little room for improvement in the core function of the beam emitters themselves, since they are already proving consistently 100% effective. However in the near term we will see companies enhancing tunnel design for smaller, less costly machines that are easier to service and maintain.

To date, the application of e-beam technology in syringe filling is mainly in transferring syringe tubs into the Class A area. However, this highly effective, precise, totally reproducible, traceable and readily validated technology seems very well suited for the world of prefilled syringes which is, out of necessity, most stringently and closely regulated. There is significant potential to leverage the technology further. Thus, in the medium-to-longer term it seems that we will see e-beam sterilisation applied to its current function in more efficient ways, such as in-line sterilisation of syringes directly (rather than of syringe-containing tubs). We shall also likely see e-beam technology further applied to other functions within the prefilled syringe production process, and beyond.



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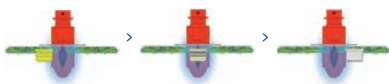


E-Beam Tunnel

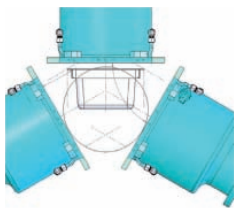
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Hyaluron Contract Manufacturing (HCM) is a leading provider of process scale-up development and aseptic filling services, including lyophilization services, from preclinical through commercial phase production. Core competencies include: process engineering and scale-up; aseptic filling of syringes, vials and custom containers; as well as stability optimization services.

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HCM accommodates newly established to large-scale commercial pharmaceutical and biotechnology companies by operating three state-of-the-art fill lines, producing lot size ranges from 100 to 150,000 syringe/75,000 vial units per day.

HCM has introduced the industry to its patented, innovative process for filling pre-filled syringes. This process, known as Bubble-free filling®, eliminates the headspace inside a pre-filled syringe offering several advantages.

Studies have shown that Bubble-free filling inhibits stopper movement under reduced atmospheric pressure, such as during airline shipping and high altitude ground transportation. There is also evidence to suggest that Bubble-free filling enhances the stability of oxygen sensitive compounds where dissolved oxygen may negatively impact solution stability. Proteins once thought too unstable for all but a lyophilized presentation, can now be offered in liquid form due to the elimination or reduction of protein aggregation that results from the air-to-liquid interface.



HCM's clients enjoy the benefits of multiple container/closure and filling options...traditional filling or bubble-free filling of syringes, and liquid or lyophilized vial options.

The article entitled, "A better fill for pre-filled syringes: applications & advantages of bubble-free filling for today's parenteral products", by Dr Shawn Kinney, HCM's President, which appeared in ONdrugDelivery's Prefilled Syringes issue 2007, is available for download from via the following link: www.ondrugdelivery.com/publications/hyaluron2007.pdf.

SERVICES AND SUPPORT OFFERED

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- Bubble-free filling®
- Traditional filling

Vial Filling:

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- Liquid filling
- Lyophilization
- Class 100 capping

Custom Containers:

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- Screw-top bottles

Additional Services and Support Include:

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- Disposable manufacturing technology
- Homogenization
- GMP analytical lab to support manufacturing
- Redundant systems for product production security assurance
- Product labeling and packaging
- Sterility programs
- Controlled storage



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THE NEXT GENERATION OF READY-TO-USE PREFILLABLE SYRINGES: FIRST IN SILICONE-FREE SOLUTIONS

For high-value injectable drugs, plastic refillable syringe systems represent a compelling, cost-effective delivery solution rooted in simplicity, accuracy, durability, functionality, flexibility and quality. Here, Bernard Lahendro, Vice-President, Daikyo Crystal Zenith® Technologies, West provides more detail.

With their ability to provide convenient, pre-mixed, sterile, fixed dosages, prefillable syringes are increasingly the delivery device of choice. Prefillable syringes are often considered for vaccines and biotechnology drugs used to treat diseases and chronic conditions such as multiple sclerosis, infertility, osteoporosis, hepatitis, rheumatoid arthritis, cancer, anaemia and haemophilia.

Many drugs in today's pipeline are targets for the prefillable syringe form, as segments of the market are moving toward home health care and doctor office/outpatient administered care. For existing drugs, pharmaceutical companies are using prefillable syringes in combination with other medical devices as a potential differentiator in crowded therapeutic categories.

THE CHALLENGES FOR CURRENT SYRINGE SYSTEMS

To date, most prefillable syringes have used borosilicate glass barrels, rubber pistons and nozzle caps, and silicone lubricants. Glass barrels, however, are not without disadvantages and may not have the properties appropriate for certain drug products.

Glass syringes require the application of silicone oil to the barrel to improve piston release and travel forces. Silicone application can be inconsistent, which leads to variability in functional properties. The silicone oil in glass syringe barrels can transfer to the drug product, a cause of protein aggregation and a possible source of immunogenicity risk and product returns.

Glass can generate particles in the drug product, which can cause rejects. Glass syringes can break. Broken glass causes manufacturing delays, safety

concerns, costly over-runs and product returns. Users and health care professionals are vulnerable to the risk of shards and exposure to drugs.

PLASTIC SYRINGES: SIGNIFICANT ADVANTAGES

Although not yet reaching the adoption level of glass syringes, plastic syringe systems continue to gain strong acceptance from pharmaceutical makers because of recent improvements in their design, composition and manufacture. Plastic syringes, which first came onto the market in the early 1990s, were historically made from polypropylene, which does not have the clarity of glass.

Aiming to address unmet market needs, plastics makers developed a new class of thermo elastic polymers: cyclic olefin polymers that are as clear as glass but are lighter and less prone to breakage. These resins are also more resistant than polypropylene to water transmission, which lengthens the shelf life of the drugs they contain. One of the most popular is a cyclic polyolefin (COP) called Daikyo Crystal Zenith (CZ). Crystal Zenith provides an impressive array of physical and chemical properties that are attractive to drug makers:

- High heat resistance: the material is autoclavable;
- Excellent low-temperature characteristics, including tolerance of freeze drying and liquid-nitrogen exposures;
- Excellent drainability: CZ offers a non-wettable surface with low surface energy and a contact angle of 80°, compared to 7° for glass;
- High break-resistance;
- High transparency;



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Figure 1: West has introduced the Daikyo Crystal Zenith® RU syringe system, the market's first silicone-oil-free, ready-to-use prefillable syringe system that can mitigate the risks associated with glass syringes.

- Low extractables: there are virtually no metal extractables from CZ;
- Solvent resistance;
- Wide pH range, from 2 to 12; and
- Easy, safe, environmentally friendly disposal: the syringes can be incinerated with virtually no residual ash;

Prefillable syringe manufacturers have redoubled their efforts to minimise silicone to facilitate piston function in these designs. With CZ syringes (see figure 1), for example, the manufacturer uses a proprietary fluoropolymer film on syringe components to provide excellent piston release and travel force without the use of silicone and its attendant concerns about leachables and extractables from elastomeric components. The film is moulded to the surface of the piston and inside surface of the nozzle cap and provides an effective barrier against organic and inorganic contaminants.

These fluorocarbon films minimise interactions between the drug and the piston and maintain the piston's seal integrity. The film reduces adsorption and absorption of the drug product, an important benefit for maintaining the full strength and shelf life of most drugs. In addition, the low surface energy of the film provides lubricity without the need for silicone oil, eliminating one chief source of particulate contamination.

Further, as pharmaceutical companies incorporate end-of-line vision systems in their manufactur-

ing process, they are discovering that the silicone oil used in traditional syringes creates a significant increase in the number of in-line rejects.

RISK MITIGATION THROUGH READY-TO-USE PREFILLABLE SYRINGE SYSTEMS

Daikyo Crystal Zenith® RU (Ready-to-use prefillable syringe systems) provide pharmaceutical and biopharmaceutical manufacturers with a solution that can help mitigate the risk of bringing high-value drugs to market. Because the systems are delivered sterile and ready to use, the manufacturer can eliminate some of the preparation steps from its process, mitigating compliance risks. The syringe supplier sterilizes the components and assembles the nozzle caps to the syringe barrels and provides the documentation required by regulators. The system is delivered in packaging that is appropriate for introducing the syringe barrels and pistons directly into aseptic and barrier isolator filling lines (see figure 2).

A SOLUTION FOR AUTO-INJECTORS

The trend toward home health care and the associated desire for competitive medical device differentiation has created a significant opportunity for the adoption of auto-injectors, single-use devices that simplify drug administration. With an auto-

injector, the patient typically does not see the needle throughout the administration process. Interest in auto-injectors is expected to grow in the near term as pharmaceutical companies further explore how to differentiate drug device delivery products.

Auto-injectors contain a prefilled syringe with a staked needle or, in some cases, a prefilled cartridge. The use of traditional syringes inside auto injectors, coupled with more viscous pharmaceutical preparations, has created a new series of challenges for manufacturers, such as the variability of piston release force. Variability can be attributed to dimensional tolerances coupled with silicone dissipation over time. This variability could result in a force that breaks the glass within the auto injector.

Crystal Zenith syringe systems mitigate this problem through their break-resistant properties. The material reduces the amount of piston release force required and, because silicone oil is not required, travel force variation due to silicone oil dissipation is limited.

EXTRACTABLES AND LEACHABLES: THE CONTAMINANT CHALLENGE

Glass can also introduce extractable and leachable contaminants into the drug solution.

An extractable is a chemical that can be released from a container or syringe component that can potentially contaminate the dosage form. Under certain solvent, temperatures and time conditions,

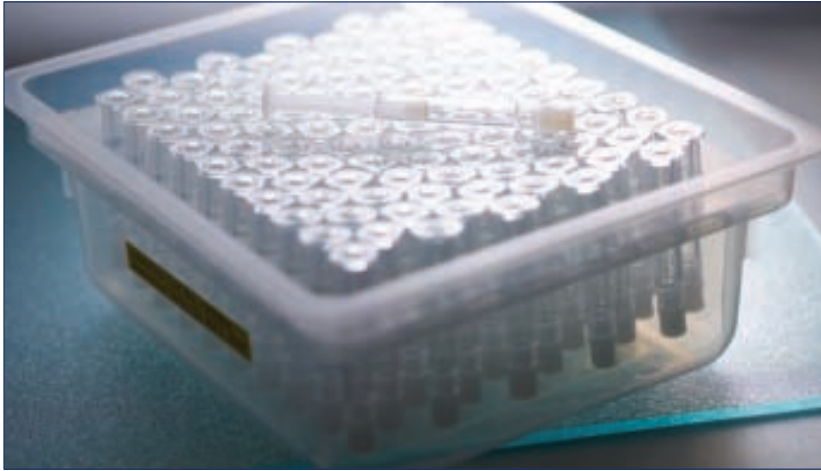


Figure 2: Daikyo and West worked together to develop a packaging system that is appropriate for introducing the pistons and syringe barrels directly into aseptic and barrier isolator filling lines.

extractables may be caused by an interaction within the prefilled container system. Similarly, a leachable is a chemical that migrates from packaging or other components into the dosage form under normal conditions of use or during stability studies.

Unlike a vial, in a prefilled syringe, the drug and diluent may be in constant contact with the primary container closure system components (including, for instance, the piston and nozzle cap) for months or years. With the increasing prevalence of protein- and peptide-based drugs that can bind to the surface of glass surfaces and be more susceptible to degradation from silicone oils, prefilled syringes present design and manufacturing challenges. When selecting a delivery system, the pharmaceutical company must consider the materials used to manufacture the components, the surface treatments applied to those components, processing aids, the dosage form's active ingredients and excipients, sterilisation processes, storage conditions and other factors.

To meet the need for lubricity, syringe manufacturers use silicone to coat the elastomer components and glass barrels and have more recently started to bake silicone layers onto glass barrels. This is an effort to limit the amount of free silicone that may interact with the drug product. However, pharmaceutical manufacturers have found that, too often, the result has been unacceptable levels of extractable, aggregated contaminants. While there have been no studies showing a measurable loss of efficacy or undesirable side effects from aggregation, it presents market challenges. Patients often are reluctant to proceed with injections of a product that looks less than pristine (particles may be as large as 50 microns). This can lead to wasted products and clinical compliance issues.

Pharmaceutical makers have responded to this challenge adding surfactants (polysorbate)

that increase cost, introduce chemical-interaction uncertainties, and run the risk of denaturing the proteins. These detergents can potentially spawn peroxide at time zero or within six to twelve months, as accelerated conditions frequently used to test pharmaceutical products can often exacerbate the aggregation phenomenon.

Drug product can also degrade when exposed to the tungsten residuals, the leftover traces of metal that remain after the glass-forming processes. During barrel manufacturing, heat-resistant tungsten pins are used to form the glass syringe luer cone. Many biopharmaceutical makers are finding that tungsten extractables can cause aggregation in their protein formulations. They are unable to use glass syringes where tungsten tools were used in the fabrication of the glass because the process leaves a small amount of tungsten that reacts with the drug product.

Shipping can exacerbate the tendency for aggregation of the drug product. Air-bubble-free syringe filling, as used in prefilled syringes, can potentially reduce or eliminate the aggregate attributed to agitation.

THE POPULARITY OF PREFILLABLE SYRINGES

The broadening acceptance of prefilled syringes is not surprising because of the range of compelling benefits, including: *simplicity, suitability for home use, a reduction in wasted product, and dosing precision.* Prefillables are convenient and help ease the administration process. Patients do not have to worry about transferring a drug from a vial to a syringe and therefore do not have to worry about leaving a small percentage of the dose behind. For at-home patients who suffer from diseases and conditions with significant dexterity and vision challenges, this is a significant benefit.

Prefilled syringes are efficient in clinics and doctors' offices for vaccine administration. Prefillables provide greater patient safety by reducing the potential for inadvertent needlestick injuries and exposure to toxic products that can occur while drawing medication from vials.

Prefillables, with their pre-measured dosage, can reduce dosing errors and increase patient compliance. Unlike vials that typically overfill (by as much as 20-30%) to account for potential waste, a prefilled syringe can virtually eliminate the manufacturer's need to overfill. This is particularly important where manufacturing and product costs are high and bulk manufacturing capacity is limited.

CONCLUSION

Ultra high-quality plastic syringe systems provide a compelling alternative to glass syringe systems. Through simplified usage, support for new classes of biopharmaceutical products, reduced waste, break-resistance, dosage precision and the virtual elimination of extractables and leachables, plastic prefilled syringes present attractive benefits that are gaining increased attention from manufacturers seeking new answers to today's and tomorrow's drug-delivery and administration challenges. The introduction of ready-to-use systems provides pharmaceutical and biopharmaceutical manufacturers with a prefilled syringe solution that can help mitigate the risks of bringing high-value drug products to market.

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Daikyo Crystal Zenith is developed by Daikyo and licensed to West Pharmaceutical Services, Inc.

IDEAL USES FOR PREFILLABLE PLASTIC SYRINGES

- For cytotoxic or classified drugs where breakage concerns are higher;
- For rheumatoid arthritis or multiple sclerosis patients with dexterity issues who must self-administer their medications;
- For high-cost drugs where overfill, spoilage or supply chain waste are concerns;
- For biological entities where adsorption, leachables, extractables and silicone interactions are factors.

Market-Proven Prefillable Syringe Technologies



West is your total solutions provider,
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Pistons, Needle Shields and Tip Caps

- Patented barrier films and coatings
- Westar® ready-to-sterilize and ready-to-use processing
- Minimize risk of drug/component interaction

Prefillable Syringe Systems

- Unique Daikyo Crystal Zenith® material
- Silicone-oil-free system
- Significant reduction in protein aggregation

Safety and Administration Systems

- Safe reconstitution, transfer and mixing
- Easy-to-use, needleless systems
- Compatible with current vials, syringes, IV sets

West Analytical Services

- Extractables/leachables testing
- Comprehensive functional testing for systems
- Total program management



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UNDERSTANDING THE COMPLEXITIES INVOLVED IN MANUFACTURING AND MEETING CUSTOMERS' EXPECTATIONS IN DELIVERING PREFILLABLE SYRINGES

As the demand of prefillable syringes increases, pharmaceutical and biotech companies are looking out for good, reliable and stable manufactures for these syringes. With market growth set to continue, Sewa Medicals sees itself as a partner for pharmaceutical & biotech companies worldwide. With doctors and nurses preferring prefilled syringes as a mode of administration vis-à-vis the vial and disposable syringe, the product presentation of most drugs is changing from the traditional vials / ampoules to a prefilled syringe. Mr Harsh Shandilya, President, Pharmaceutical Systems, at Sewa Medicals explains how the Tyfill™ prefilled syringe system offers complete flexibility for the customer.

THE PREFILL CONCEPT

Prefilled syringes have traditionally been made of a glass body formed from USP type 1 borosilicate glass, elastomeric plunger and plastic rod. The drug is packed in the glass body and is covered on both sides by elastomers. A plunger rod is fitted behind for the drug to be administered. Hence the Prefilled syringe concept is termed as a primary drug container used for liquid drug administration. The definite advantages of using the system are :

- Low contamination risk
- Measured accurate dosage
- Easier Product Identification
- Speed in emergencies
- Shorter preparation time
- Pharmaceutical product differentiation
- Improved product and Company image
- Convenient to medical staff
- Boost to sales and marketing efforts

THE TYFILL™ PREFILLABLE SYRINGE SYSTEM

The Tyfill™ prefillable syringe range demanded by today's customers ranges from 0.5ml to 20ml for small volume parenterals. The types offered include LT syringes (Luer Tip i.e. Luer cone), LTLL syringes (Luer Tip Luer Lock i.e. Luer lock adaptor) and FN syringes (Fixed needle i.e. Staked needle).

Tyfill™ Luer tip syringes are preferred when the drug is simple and aqueous, and the choice of needle to pick for administration is kept with the doctor. Tyfill™ Luer lock syringes are chosen when a secure connection is required with the needle for administration. Tyfill™ Fixed Needle is ideal when the drug determines the application. For example, subcutaneous (SC) injections are generally administered with 26 G and 27 G needles. Hence an SC drug offered with a pre-filled needle is extremely advantageous.

The elastomer is also a critical part in the entire syringe system. The Tyfill™ Luer Tip & Tyfill™ Luer Tip Luer Lock syringes are offered with a variety of tip caps in various sizes and formulations, including the latest latex-free products. The Tyfill™ Fixed Needle syringe is offered with both a regular needle shield as well as a rigid needle shield.

A variety of plungers have been validated by us. They are available in various formulations, including latex-free, Teflon-coated and higher pH-resistance formulations. Such are available from West Pharmaceutical Services, Stelmi and Helvoet Pharma. We offer the customer a variety of formulations from all three suppliers to choose from.

Customers are given a choice of material of construction of the plunger rods (polypropylene, polystyrene and polycarbonate, for example) depending on the mode of sterilisation the protocol of the drug demands. All materials comply with US, European and Japanese Pharmacopoeias.



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Figure 1: Tyfill™ syringe with enhanced finger grip

COMPLEXITY IN THE SYRINGE SYSTEM

Both designing and manufacturing prefilled syringes are complex processes. As a prefilled syringe manufacturer, Sewa Medicals integrates a combination of seven broad key capabilities.

1. Glass tube engineering
2. Multiple component handling at a single time
3. Surface treatments
4. Pick & Place
5. Clean room movement control
6. Polymer moulding
7. Needle bonding

Mastering these technologies ensures superior production of syringes.

The complexity of the design can be explained when we ask, "What is the task of the prefilled syringe?" It may be suitably answered that the task is three-fold:

1. It must functionally perform smoothly and in an adequate manner as desired, at the time of administration.
2. It must protect the drug from contaminations and impurities
3. Safety of the patient & doctors/nurses needs to be ensured

To ensure that the tasks are fulfilled over the period of the shelf-life of the drug, at Sewa we do the following:



Figure 2: A selection of Tyfill™ syringes

1. Functional performance can be measured by the break-loose force and gliding force. These are one of the most commonly faced issues that can be present during the tenure of the drug being packed in the syringe system. Adequate siliconisation and the in-house developed method of applying the silicone, ensures the performance of the Tyfill™ syringes. A finger grip (backstop) will ensure further easy handling of the Tyfill™ syringe system while administering the dose. Figure 1 shows a design with an enhanced finger grip.
2. Impurities and contaminations are prevented by having suitably tight tolerance on components. Two areas from where contamination can enter are the contact point where the drug, plunger and glass unite. The internal diameter of the barrel and the outer diameter of the plunger stopper need to be just right in order for the drug not to leak, at the same time, not allow any impurities inside the barrel. The second area where the contamination can occur is at the tip cap. The precise fitment of the cap on the tip ensures integrity of the Tyfill™ syringe system. These can be determined by performing the leak test and dye test.
3. Safety of patients and medical professionals is a paramount requirement. Thinner needles with innovative bevels ensure a smooth and painless administration to the patient. The rigid needle shield guarantees safety of the needle inside and safer handling to the doctors/nurses thus avoiding needle-stick injuries.

To ensure this, we manufacture Tyfill™ syringes to the most stringent international regulations & standards.

CUSTOMER EXPECTATIONS

At Sewa we believe that meeting customers' expectations is the foremost priority for us as a prefilled syringe manufacturer. The factors on which we understand pharma & biotech companies assess a supplier are:

1. Range offered, flexibility
2. Consistent quality manufacturing capability
3. Components offered
4. Regulatory & technical support
5. Timely deliveries

1. Range offered, flexibility presented

Customers demand a complete range of prefilled syringes with the entire range of components. We manufacture the entire range from 0.5-20 ml Tyfill™ Glass Prefillable syringes. A selection of our syringes is pictured in figure 2. Double cham-



Figure 3: Coloured syringes



Figure 4: Comparison of siliconisation methods. Sewa's in-house method used on syringe (A) and standard spray method used on syringe (B).

ber syringes are also a part of our standard range. Dental and insulin cartages are also formed and have dedicated lines for customers. 50ml Glass Prefillable syringes can also be supplied on specific enquiries. Our flexibility is evident, for example, when we can customise syringes for customers through the use of different printing matters and colour (see figure 3 on page 29).

We feel, our strength is that even though we provide large lots of syringes to leading pharma companies, we also provide and serve smaller lots for start-up operations. This is purely a part of our commitment to a total customer service program.

2. Consistent quality manufacturing capability

Customers want to have the satisfaction that all their syringe components are being treated in the same manner. At Sewa we ensure that our customers are satisfied. Strict control on tolerances is made for all outgoing materials at each and every station. We ensure that the glass is formed in a controlled environment. We offer a number of choices in printing on the Tyfill™ Glass Syringe including our in-house developed ink and ceramic printing, which are approved. Needle bonding is performed in a complete controlled environment and each needle is checked for blocks and hook formulation. Tyfill™ Syringes are washed and cleaned with WFI to avoid any antibody remains.

Siliconisation is done by a method developed in house to ensure silicone is applied uniformly throughout the glass barrel. This is shown in figure 4, where syringe A has been siliconised using our in-house siliconisation and syringe B has been siliconised by a standard spraying method.

The controlled environment consists of clean rooms with HEPA filters. Treatments take place under Class 10,000 conditions. Component assembly and tub packing are done in Class 100 conditions under laminar air flow.

Sterilisation is done in house. All materials are kept in quarantine and tested for break-loose and gliding forces, and sterilisation as per SAL (sterility assurance level) 10^6 specifications. We have a complete equipped in-house quality control lab which is capable of providing customers' tests and reports as per the various guidelines laid down by respective international bodies.

3. Components offered

All plastic components like luer locks, plunger rods, barrel nests, plunger stopper nests and tubs are made in house in a controlled environment to GMP, to maintain a strict control on quality. All processes are validated periodically to ensure consistency of quality material output. All our processes comply with GMP for manufacturing primary packaging material. Batch records of each manufacturing process are stored in a unified manner. Based on the quality records gathered by the quality control department, they are in a unique position to authorise each batch released and issue a certificate of analysis. With this we meet the highest international quality standards. With unified standard and specifications, we offer our customers a world class product.

4. Regulatory & Technical Support

We empower our customer with all the data they need to use our product and have it registered with the appropriate regulatory authority, be it the FDA, EMEA or another regulator. Our "technical dossier" informs our customers on primary container information such as details of component specifications, and material of construction. It also covers topics related to quality, safety & effectiveness of the Tyfill™ syringes.

Our Drug Master File (DMF) contains information about our manufacturing processes, material and suppliers. The contents of our file are based on the format laid down by the FDA guidelines. The Drug master file is the tool which allows regulatory authorities to approve ANDA/NDA applicants to distribute their products into the specific markets with our Tyfill™ syringe.

5. Deliveries

Pharmaceutical companies today demand perfection when it comes to performing as per

the laid down agreement. We have achieved this every time, bringing back our customers to work with us again and again. We work with our customers as a team, and understand the importance of this vital packaging material.

EXPERTISE

Our expertise has been in glass tube engineering since the 1960s. We have not only mastered the technology of glass forming, but also make our machines for forming. This expertise helps us when we have to immediately increase capacities, as the base technology for any prefillable syringe manufacturing supplier is producing the glass syringe barrels. We also have skills in plastic moulding and handling various polymers such as polypropylene, polycarbonate and polystyrene. Managing multiple activities in controlled environment has also been mastered by Sewa Medicals.

Our expertise also includes complete flexibility when it comes to choosing a syringe system in terms of design, siliconisation, cosmetics quality, accessories and packing.

THE FUTURE

We have developed a number of innovative components for the prefilled syringe, for which patent applications are pending. By 2009, in addition to glass, we plan to begin working with the high-end polymers used for manufacturing prefilled syringes in order to offer our customers a wider variety to choose from. These we realise have greater potential in the higher volumes of syringe systems, from 10-100ml. We are also developing a new type of controlled mechanism for delivering viscous solutions.

ABOUT SEWA MEDICALS LTD

Sewa Medicals Limited is professionally run family business of the Shandilya family. The group has a history spanning more than 128 years, having started trading in 1880. In the 1960s India had an import stop on all foreign goods, including a number of medical products such as glass syringes. We collaborated with a Japanese company and the technology for manufacturing glass syringe was transferred to India from Japan. From this foundation, we became the largest manufacturer of glass syringes & LOR (Loss of Resistance) syringes in India. In 1994 we saw the prefillable syringe as the next dimension in the glass syringes market, and have been supplying, Tyfill™ prefillable syringes since 1995. With around 100 pharmaceutical companies using our glass syringes, we feel we have a competitive world-class product to offer the pharmaceutical industry worldwide.




Prefill Syringes



Simple Action

Using our Tyfill™ – ready to use syringes, you can expect Talior made viable solutions along with complete support. You can be sure of complete stability of your product in our syringe system.

We assure you our assistance through the path of choosing the Tyfill™ Pharma systems,

-  Offering you the right components
-  Partnering with your machine supplier
-  Work with regulatory experts

Processed in Clean Room controlled environment, we offer you a complete syringe system solution from a single destination.

Glass Prefillable Syringe System is offered in 0.5 ml, 1ml long, 1ml Standard, 1.5 ml, 2 ml, 2.25 ml, 3 ml & 5 ml ; in luer tip, luer lock & fixed needle formats. Available in Sterile Tub pack / Bulk pack Non-Sterile Rondo Tray / Bulk pack.

We look forward to working with you.

We also welcome your enquiries for Large volume syringes, Customised syringes and Special syringes.

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NEW TECHNOLOGIES FOR THE PROCESSING OF SYRINGE NESTS

In this article, Klaus Ullherr, Product Manager at Robert Bosch GmbH Packaging Technology, Business Unit Pharma, considers factors and recent developments in processing syringe nests.

A NEW DIRECTION: FROM BULK TO NESTED

Prefilled syringes are a rising trend for packaging liquid parenterals. Self-administered medications, biotech products, and the marketing opportunities afforded in the pharmaceutical sector are all key drivers in the development of this technology.

In the past, syringes were cleaned, siliconised and sterilised before being filled – so-called “bulk syringes.” In the current market environment, pre-sterilised syringes are increasingly the standard. The majority of contemporary processing lines process pre-sterilised syringes almost exclusively as the primary packaging. These syringes come in syringe nests, have the appropriate tip / closure installed, and have already been cleaned and sterilised by the packaging material vendor.

The evolution from bulk syringes to pre-sterilised, nested syringe format is natural step. A strong technological basis in the bulk format leads logically to the pre-sterilised, nested format. For example, the technology for filling and closing (direct plunger insertion and closing in a vacuum environment) as well as syringe handling and transportation is comparable between the two approaches.

INNOVATION IN FILLING AND CLOSING OF THE SYRINGE

The special requirements in filling and closing of the syringe are production rates and flexibility, precision and protection.

Currently 36,000 syringes / hour performance is available for 10 position filling machines. During the insertion of plungers, via seating / placing tubes, the air gap between the seating tube outside and the syringe body is only 0.3 mm, and potentially less depending on the tolerances. The precise transport system positions the syringes such that no additional centring device is necessary, which ensures protection. The fill-

ing of biotech products via disposable filling systems is a rising trend which must be integrated into the machine in place of, or in addition to, pump systems or Time-Pressure Filling systems.

Because of the delivery of syringes in separated nests, many systems feature a typically brief process interruption after the filling and closing of one nest and prior to continuing with the next nest. However, systems can be designed to use a syringe transport system in conjunction with a handling unit such that filling and closing can be performed continuously, resulting in better filling performance and more reliable feeding of the plungers.

For example, figure 1 shows Bosch's FXS 5100 filling and stoppering station, which offers continuous filling and stoppering without any interruption during the change of the nest.

From a pharmaceutical point of view, the syringe needs to be closed as soon as possible after filling, thereby minimising the risk of contamination. This can be accomplished by using a syringe transport system with a perpendicular horizontal offset motion to compensate the offset of the syringe rows. Taking this approach it is possible to fill a row of syringes, move them one position forward, and immediately close them. Obviously, the processes prior to filling are also of enormous importance. The syringes need to be transported to the filling machine while maintaining sterility, and without particulate contamination. Fully automated solutions for the opening of the bags and the opening of the tubs are now standard. The protection and anti-contamination requirements must also be ensured during the tub bag process.

INNOVATION IN TUB OPENING

Production rates can be up to 6 tubs / min, regardless of the nest configuration. The tub bag has the primary task of protecting the tub during the infeed loading process. It should



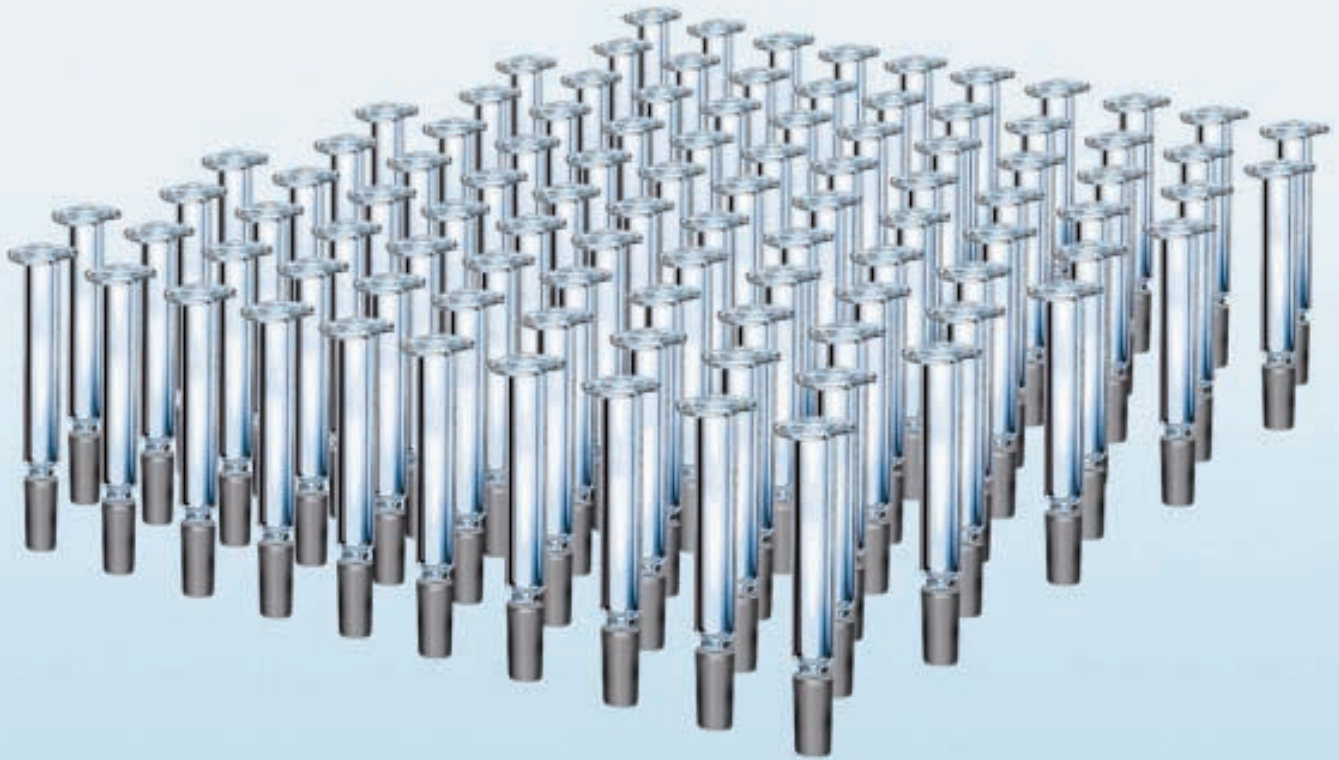
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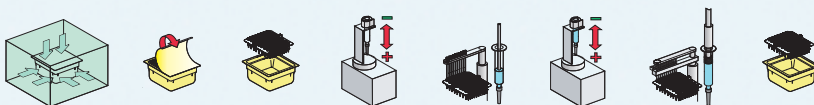


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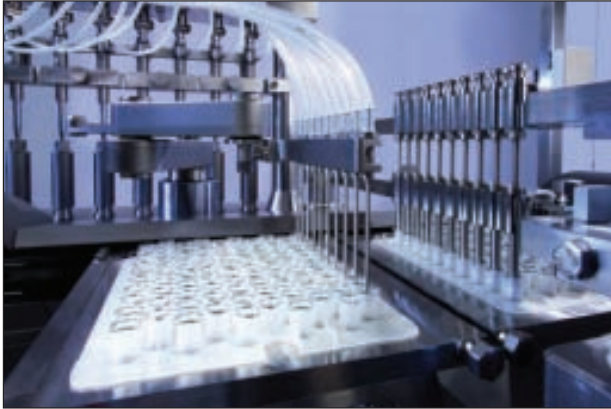


Figure 1: Filling and stoppering station FXS 5100. Provides continuous filling and stoppering without any interruption during the change of the nest.

remain around the tub as long as possible and removed "at the last moment". With the automatic bag opener (ABO), the bag will remain on the tub until the tub reaches the transfer gate, and at this point the bag is opened and the tub is transferred directly into the next clean room area. The separating process of the bag and the tub must be a very reliable function. This is a difficult task due to the bag design. Blockages could happen easily and would have to be fixed via manual intervention. Additionally it must be ensured that the outer surface of the bag, under no circumstances, touches the tub or nest; potentially contaminating the syringes.

When opening the bag, the risk of particle contamination is not as great as when opening the tub. However, it is still recommended that this risk should be kept to a minimum. To provide for this, the operations should take place under laminar flow (LF) airflow and a special blade for the cutting open of the plastic bag is provided. The design also includes a stretching of the bag opening and an optimised cutting

motion to make the concept function perfectly.

Additionally, the cutting blade has been designed for easy replacement. The disposal of the bag is made easier by ensuring that the bag remains in one piece.

To ensure the performance of the line, tub opening also requires 6 tubs / min.

Figure 2 shows Bosch's fully automated tub opening equipment.

At this point in the process, the avoidance of particulate contamination is of particular importance due to the removal of the protective Tyvek foils and the direct exposure of the syringes to the surrounding area. A gripper motion with a very sharp "tearing angle" (Tyvek surface to tub flange) in conjunction with a heating of the glue area, will provide the best results. Contact heating is preferred to radiant heating, because the heat can be applied selectively. It is also important to prove the opening function without heating the glue area, as a heat source in the LF airstream is undesirable. This tends to increase the amount of particles generated, but levels



Figure 2: Fully automatic tub opening (ATO). Smooth and low particle opening process.

remain below safe opening principles when vacuum grippers are used.

AUTOMATED SOLUTIONS

A very reliable and repeatable function is of high importance. An automatic solution is desired because it minimises manual intervention. A particular challenge is the removal of the outer foil cover. This foil was not designed for automated removal and the primary difficulty is the reliable gripping of the foil corner, because the exact location of the foil varies for each tub. One solution to this is to cut one corner of the tub, but not cut free, with a heated knife, creating an easily removable flap which can then be gripped by the mechanical gripper and torn free, taking the Tyvek foil with it.

Two views of a high performance syringe line are shown in figure 3, with fully automatic bag opening (ABO), fully automatic tub opening (ATO) and filling machine FXS 5100 with integrated In-Process-Checkweigh.



Figure 3: Two views of a high performance syringe line with fully automatic bag opening (ABO), fully automatic tub opening (ATO) and filling machine FXS 5100 with integrated In-Process-Checkweigh.

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GERRESHEIMER: NEW MARKET INSIGHT INTO PREFILLED SYRINGES AND CLOSURE SYSTEMS:

PRIMARY DATA FROM PATIENTS, NURSES, PHYSICIANS AND INDUSTRY EXPERTS

In this special commentary piece, Dr Arno Fries, Head of Sales USA Syringes for Gerresheimer Bünde GmbH, Germany, presents an analysis of how, from their respective viewpoints, end users evaluate drug delivery systems, with a particular emphasis on prefilled syringes.

Declining productivity in pharmaceutical research and rising costs are shifting attention towards life-cycle management of established product portfolios. Drug delivery systems play a pivotal role in strategies aimed at differentiation from competition. The success of drug delivery systems in the marketplace is ultimately decided by the end users. Either professional staff (physicians, clinicians and nurses) or patients are the final decision makers depending on the nature of the drug therapy (figure 1). Preference for drugs is primarily based on efficacy and safety.

Prefilled syringes are among the fastest-growing classes of drug delivery systems. An increasing number of parenteral drugs and biologics in late-stage clinical trials are expected to support this trend. But what are the important needs of end users with respect to

prefilled syringes? To what extent can syringes be further improved? How can prefilled syringes and closure systems be utilised to gain a competitive edge in the market? Extensive marketing research is desirable in order to answer these questions.

OBJECTIVES

The goal of this research was to gain better insight into the prefilled syringe market. Our studies were aimed at industry experts on prefilled syringes in (bio)pharmaceutical companies, and physicians, clinicians, physicians' assistants (PAs) and nurses as end users of syringes.

METHODOLOGY

From September 2006 to April 2007, an independent contract research institute collected pri-

mary data on the requirements for prefilled syringes and components such as needle shields, tip-caps, plunger rods and new accessories. The field research was conducted in two phases in order to address experts in the industry and syringe users separately. Data on syringe requirements were gathered by asking open-ended questions without pre-set answers in order to allow for unbiased responses. After completion of the interviews, data analysis was accomplished with statistical methods by the contract research institute.

For the study with industry experts on prefilled syringes, 30 participants were recruited worldwide with a split into major pharmaceutical market regions. Interviewees were mainly (50%) in the age group from 41-50 years with 30% aged 30-40 years and 17% aged 51-60 years. Professional experience of the syringe experts ranged from 5-10 years (33%) to 21-33 years (13%) with most participants (50%) between these groups (11-20 years). A majority (67%) of the interviewees exerted major influence and 13% had minor influence on decision making for prefilled syringes and components. Decision makers accounted for 17% of the interviewees in the survey. Interviews were carried out by phone using a standardised questionnaire which was finalised in the pre-test stage of the study (figure 2).

Market research with end users of prefilled syringes was conducted with 110 clinicians, physi-

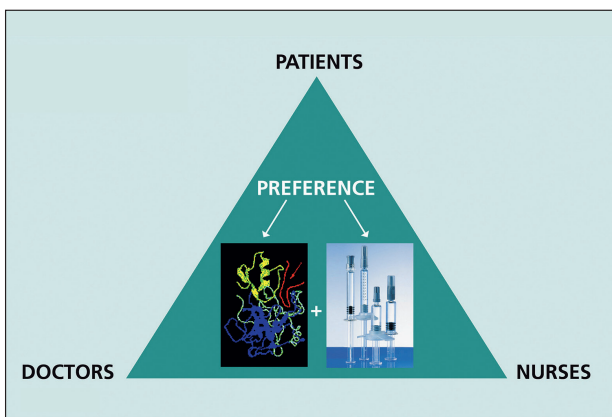


Figure 1: Ultimate users of prefilled syringes



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icians, nurses, physicians' assistants and patients. All end users included in the survey had experience with prefilled syringes. The recruited specialists were from Internal Medicine (33%), General Medicine (30%), Paediatrics (22%), Orthopaedics (8%), Ophthalmology (5%), Neurology (1%) and Surgery (1%). The patient population had medical indications in the field of General Medicine (54%), Internal Medicine (41%) and Orthopaedics (5%). As part of the interview process, sample syringes and components were provided for hands-on testing. The interviews were carried out face-to-face with the professionals in hospitals and doctors' practices in Germany and with patients in a research studio of the contract institute. Interviews followed a standardised questionnaire which was finalised in the pre-test stage of the study (figure 3).

RESULTS

This research produced a large quantity of primary data on market requirements regarding prefilled syringe systems. Selected findings from the study with industry experts in international (bio)pharmaceutical companies are shown in figures 4-6. These results cover decision-making processes for the selection of prefilled syringe systems in the industry. Requirements for further product improvement are also outlined from the perspective of the experts.

Key results from research with the ultimate users of prefilled syringes are summarised in figures 7-13. The demand of end users for optimisation of prefilled syringes, closure systems and other components is highlighted.

The most frequent requirements are analysed by subgroups of the end user population in separate graphs (figures 8, 9, 11 and 12).

All data are consolidated and grouped (professional staff and patients) in figure 13 for further analysis. Additional primary data from this research are on file and available from the author on request.



- Contract research by an independent institute January - April 2007
- Research with n = 30 industry experts for pre-filled syringes worldwide
- Phone interviews of the experts based on a standardized questionnaire
- Participants from R&D, Purchasing, Packaging Development, Marketing, QA, RA and other departments
- Industry experts from Europe (40%), USA (40%) and Asia (20%)

Figure 2: Methodology summary I



- Contract research by an independent institute September - December 2006
- Research with n = 110 ultimate users from a broad range of medical fields
- Face-to-face interviews of the end users in hospitals and doctors' practices based on a standardized questionnaire
- Hands-on testing of pre-filled syringes and closure systems by the end users
- End user subgroups include physicians, clinicians, nurses, PAs and patients

Figure 3: Methodology summary II

CONCLUSIONS

The universe of prefilled syringes consists of proven drug delivery systems with numerous advantages for (bio)pharmaceutical processing and the end users. However, industry requirements and customer preference in the (bio)pharmaceutical market are changing, so permanent monitoring is necessary.

This research provides market intelligence regarding decision

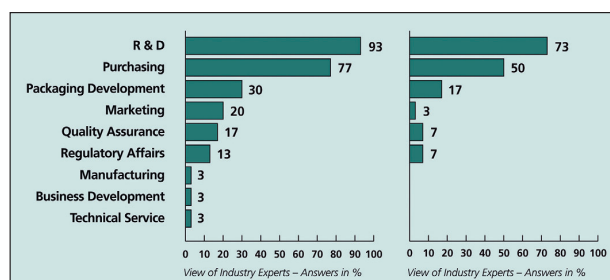


Figure 4: Industry departments involved in the decision making process for PFS selection

Figure 5: Industry departments responsible for the final decision for PFS selection

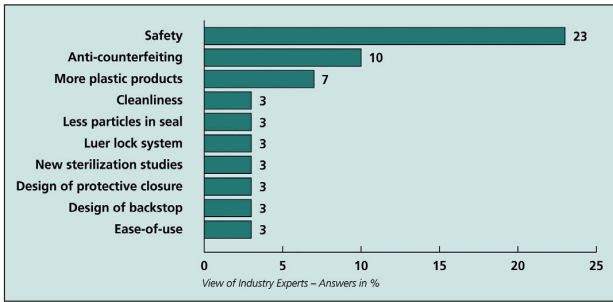


Figure 6: Industry expert answers to “What can be improved for PFS?”

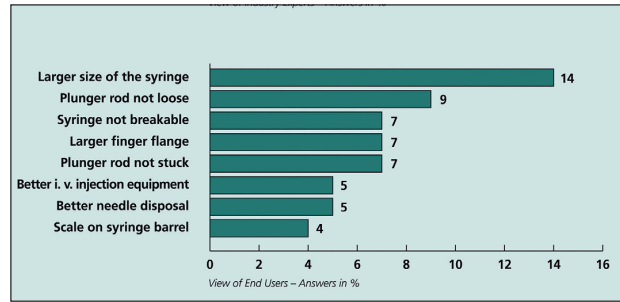


Figure 7: End user answers to “What can be improved for PFS?”

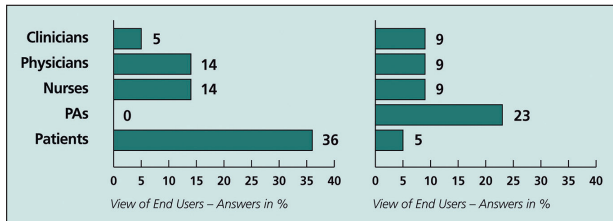


Figure 8: Breakdown of which end users wish for larger size PFS

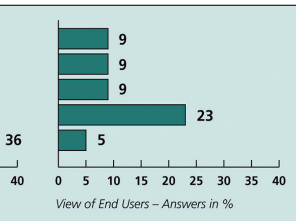


Figure 9: Breakdown of which end users wish for plunger rods which are not loose

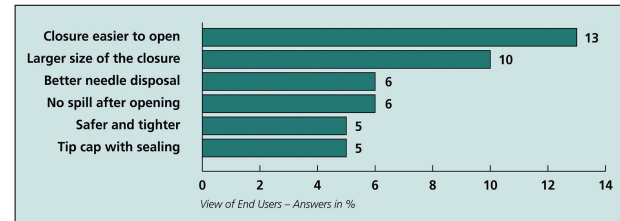


Figure 10: End user answers to “Rubber closures: what can be improved?”

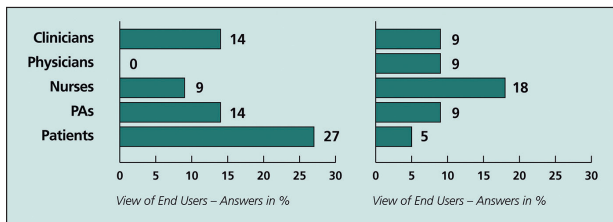


Figure 11: Breakdown of which end users wish for closures that are easier to open

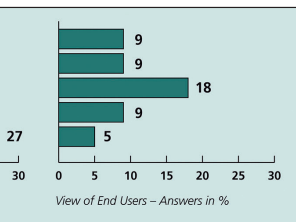


Figure 12: Breakdown of which end users wish for larger closures

making for prefilled syringes. Data on requirements of the industry and from the perspective of end users are highlighted. The methodology of an independent research institute

which used open-ended questions assured unbiased answers. Decision making on prefilled syringes in the (bio)pharmaceutical industry is a cross-functional process

driven by R&D (93%), purchasing (77%), packaging development (30%) and marketing (20%). Final decision making is shared between R&D (73%), purchasing (50%) and packaging development (17%) departments. Improved safety (23%) emerges as the outstanding requirement from the view of industry experts, followed by anti-counterfeiting (10%).

End users demand larger sizes of syringes (14%), larger closure systems (10%) and larger finger flanges (7%). This outcome is most pronounced among patients (36% for larger syringes) and nurses (18% for larger closures).

requirements and ease-of-use are also a major focus of the ultimate users and encompass closure opening (13%) and functionalities of plunger rods (16%).

Among the user subgroups, easy-to-open closures are most actively (27%) sought by patients, and physicians’ assistants have the highest need (23%) for better plunger rod functionality. With respect to closures, systems for safe opening without spills (6%) are demanded along with safer and more effectively sealed products (5%) and tip-caps with sealings (5%). Work process improvements together with safety aspects are mirrored in requests for unbreakable syringes, better iv injection equipment, improved needle disposal and scales on syringe barrels.

Market intelligence from this research deepens the understanding of prefilled syringe systems. It reflects the wealth of opportunities which prefilled syringes offer (bio)pharmaceutical companies to differentiate product portfolios and outpace the competition.

Continuous adaptation of prefilled syringes and their components to current market needs will sustain the fast growth of these drug delivery systems and underpin their dominance in the marketplace.

End User Group	Requirement
Medical Staff	<ul style="list-style-type: none"> • Larger size of syringe, finger flange and closure • Scale on the syringe • Closure easier to open • Plunger rod functionality • Better needle disposal
Patients	<ul style="list-style-type: none"> • Larger size of the syringe • Syringe not breakable • Closure easier to open • No spill after opening • Closure safer and tighter

Figure 13: Summary wish lists of medical staff and patients

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