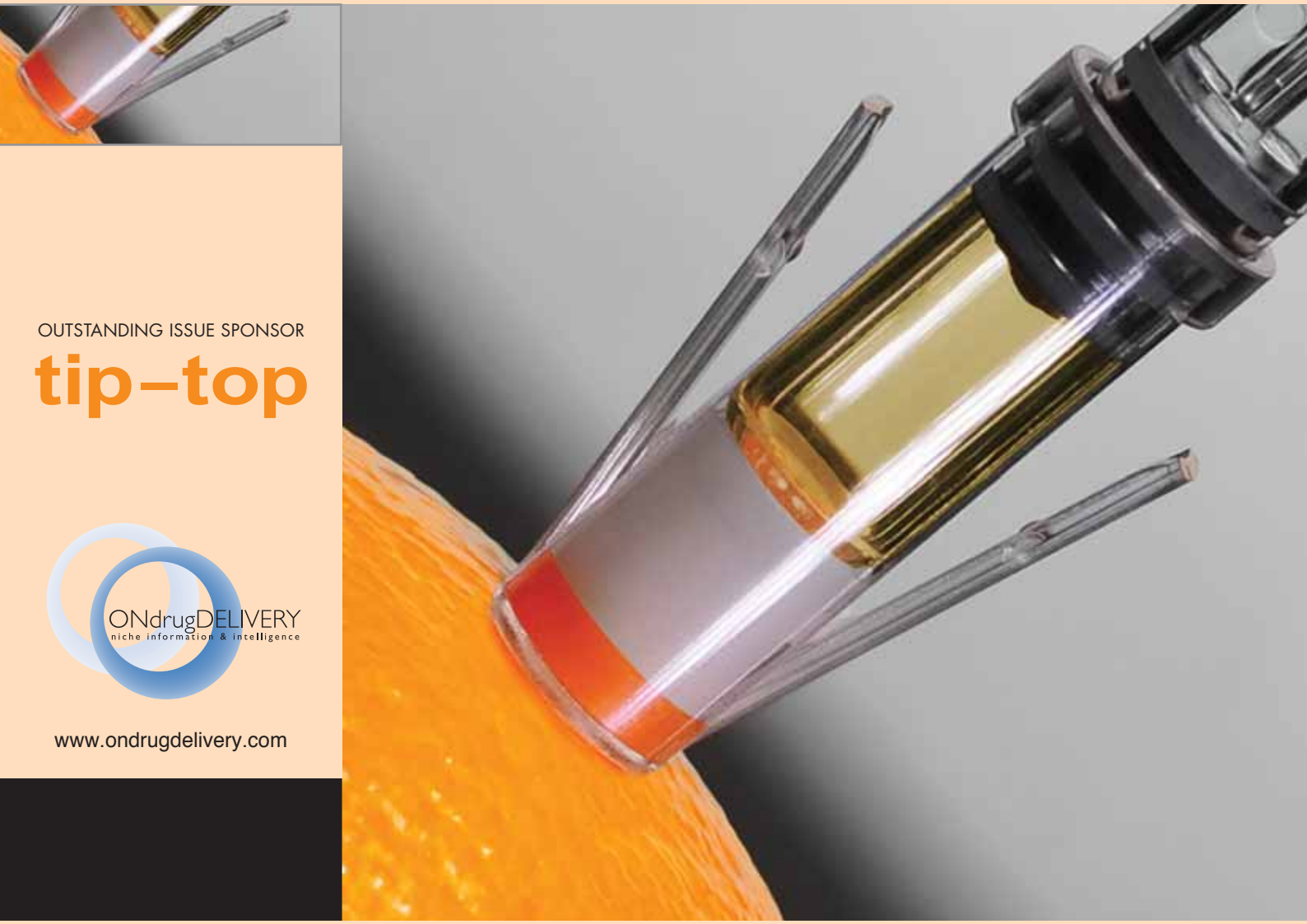
# PREFILLED SYRINGES:
## INNOVATION & INTEGRATION TOWARDS OPTIMUM SAFETY



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**"Prefilled Syringes: Innovation & Integration Towards Optimum Safety"**

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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**PRODUCTION/DESIGN:**
Mark Frost
www.frostmark.co.uk

"Prefilled Syringes: Innovation & Integration Towards Optimum Safety" is published by Frederick Furness Publishing.



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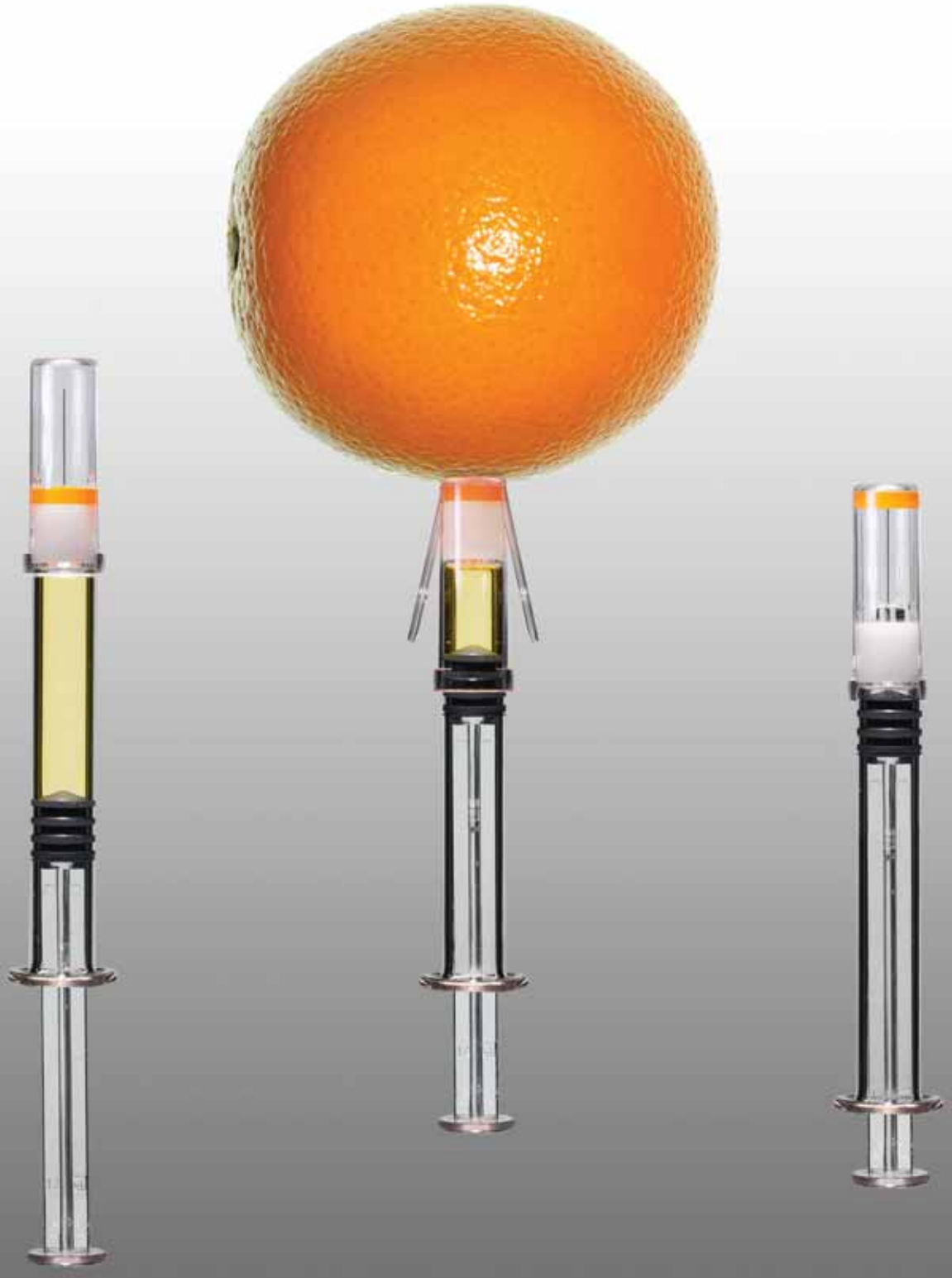

# integrated needlestick protection for ready-to-fill syringes

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# TRULY PASSIVE INTEGRATED NEEDLESTICK PROTECTION FOR PREFILLED SYRINGES

**Having carefully observed trends in the parenteral drug delivery sector for almost two decades, tip-top has distilled and miniaturised passive needle shield design down to its very essence. Here, tip-top's Managing Director, Barry Liversidge, introduces mini-Max, an ultra-simple, very low-cost, fully integrated needle shield, compatible with, and non-disruptive to, existing prefilled syringe manufacturing, sterilisation, filling and packaging infrastructure. It requires no modification to the primary drug container. Its functionality is truly passive and it is the first such device to provide full needle shielding pre- and post-injection. minim, its sister product, is a second-generation passive safety needle, based on the same technology.**

## THE TREND TOWARDS SAFER SHIELDING NEEDLES

Over the past decade, the market has accelerated its respone to the growing demand for safer needles by developing a variety of safety needle systems and devices. Significantly, the trend (shown in Figure 1) clearly shows that this endeavour is addressing the need for fully-passive shielding needles that activate automatically, and without any user intervention.

The concept of safely shielding needles is well understood and accepted throughout the medical world. However, some existing safety-engineered devices for prefilled syringes provide only limited needlestick protection, despite the high costs associated with this type of secondary packaging. Other concerns relate to the bulk and waste generated by these 'clip-on' accessories.

## INTEGRATED NEEDLESTICK PROTECTION

These three industry buzzwords – *integrated needlestick protection* – relate to **ready-to-fill** syringes of the type supplied to industry in standard nest and tub formats, which are manufactured with an integral needlestick protection capability.

When this type of syringe leaves a fill-finish packaging line, needlestick protection is already integrated into the total drug product offering, without the need for a secondary packaging process to 'add-on' a needlestick protection device. And of course avoiding the need to 'bundle' or add a separate standalone safety needle along with the prefilled syringe.

A fully integrated needlestick protection system is an extremely attractive concept, espe-

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**Figure 1: The trend towards safer passive needle shielding.**

**Figure 2: A viable industry-standard safety needle system by simply replacing the ordinary needle cover on a ready-to-fill glass syringe.**

cially when the system can integrate into existing ready-to-fill syringe formats without the need for radical changes to the primary drug container or any changes or modifications to the internal syringe components.

## THE READY-TO-FILL STAKED NEEDLE SYRINGE OF THE FUTURE

The ideal prefilled syringe of the future will be low cost and have integrated needlestick protection 'built-into' the syringe. *In our opinion, clearly this must be achieved without causing any disruption to the primary drug container*.

A viable industry-standard safety needle system for ready-to-fill syringes that can be implemented by simply replacing the ordinary needle cover on a ready-to-fill glass syringe, with a mini-Max fully passive needle shield (see Figure 2).

mini-Max only requires a few extra plastic components to deliver fully-passive integrated needlestick protection to a standard ready-to-fill syringe (see Figure 3), and mini-Max is less than one quarter of the size and weight of other needle shielding devices, and importantly, there is no need for a metal spring of any kind. These factors reduce cost of materials, transport, and storage and greatly simplify the assembly process

"A VIABLE INDUSTRY-STANDARD SAFETY NEEDLE SYSTEM CAN BE CREATED BY SIMPLY REPLACING THE ORDINARY NEEDLE COVER ON A READY-TO-FILL GLASS SYRINGE, WITH A MINI-MAX FULLY PASSIVE NEEDLE SHIELD."

Hopper feeds and vibratory bowls on assembly line machines can be much smaller in size and there is no requirement for components to be glued or welded together. Mould tool manufacturing costs are lower and the density of cavities per mould/bolster can be higher.

Mini-Max can generate significant production cost savings. For example, when compared with the typical 'clip-on', secondary-packaged safety device in use today, the production of 100 million mini-Max units would use 500 tonnes less polymer. That's 500 tonnes less plastic to be purchased, shipped, warehoused, process moulded, stored, assembled and transported.

One of the most important points to highlight about mini-Max is that is has been specifically developed to be totally non-disruptive to the hard-fought status quo of the prefilled syringe as the established universal industry standard.

Firstly, its design maintains the integrity of the standard prefilled syringe as the primary drug container. No internal components of the prefilled syringe are modified. Even the standard plunger rod remains unchanged. Secondly, mini-Max complements the ready-to-fill syringe by integrating seamlessly into existing nest and tub drug filling and packaging lines (see Figure 4).

That latter point is key and warrants some further explanation, as follows. The mini-Max is fitted by the syringe manufacturer onto either 1ml Long or 1ml Standard syringes having either ½ or 5/8 inch needles, simply by replac-

**Figure 3: mini-Max only requires a few extra plastic components to deliver fully passive integrated needlestick protection to a standard ready-to-fill syringe**

**Figure 4: mini-Max integrates seamlessly into existing nest and tub drug filling and packaging lines**

**Figure 5: mini-Max is fitted by the syringe manufacturer onto either 1 ml Standard (left) or 1 ml Long (right) syringes having either ½ or ⅝ inch needles, simply by replacing the ordinary needle covers on the syringe.**

ing the ordinary needle covers on syringe, as shown in Figure 5. This provides integral needlestick protection for the standard prefilled syringe, removing any need for downstream secondary packaging machinery.

The size and shape of mini-Max mean that syringes with the device added are compatible with the standard ready-to-fill infrastructure and can be nested into standard tubs.

## USING MINI-MAX

From the point of view of the user, be they medical professional or patient, the key is the true fully-passive design. The user simply removes the cover, as normal, and administers the injection, as normal – the shield automatically covers the needle when the needle leaves the skin of the patient, and automatically locks securely to guard against needlestick injury. Figure 6 shows the mini-Max in action: before, during and after injection. (Note that in the middle "during" image the needle would normally of course be inserted into the patient's skin at this point. The needle is never exposed with mini-Max.)

"MINI-MAX HAS BEEN SPECIFICALLY DEVELOPED TO BE TOTALLY NON-DISRUPTIVE TO THE HARD-FOUGHT STATUS QUO OF THE PREFILLED SYRINGE AS THE ESTABLISHED UNIVERSAL INDUSTRY STANDARD."

When it comes to disposal, the small size of mini-Max means that it takes-up much less space in a sharps box compared with other safety devices, to ease medical waste disposal issues.

## CROSS-OVER DEVICE

From the user's point of view, another trend observed by tip-top and accounted for in the design of mini-Max is the increasing

need for parenteral drugs to be self-administered by patients. The design of mini-Max can provide patient-centric features, for example concealing the needle and helping easier adherence to proper aseptic injection techniques to enable patients to safely self-administer their medication.

Mini-Max is also the ideal Crossover Device – able to provide the mandatory safety required when used in a healthcare setting by medical professionals, but also equally 'at home' when used away from a hospital setting.

For patients requiring the additional functionality of an auto-injector, mini-Max presents no obstacle since it can be utilised into a spring-powered single-use or re-usable auto-injector that takes a standard prefilled syringe.

## SUMMARY

In summary, the mini-Max safety shield, and its sister product the minim safety needle (see boxed text), represent the distillation of needle safety to the optimum, by minimising cost, yet maximising protection.

For the user, tip-top's designs provide integrated pre- and post-injection safety that is truly fullypassive. For the industry, it provides the needle safety that the market, legislation and common sense increasingly demand, and as is the case with the mini-Max system, requires no disruption to the existing standard prefilled syringe production and filling infrastructure and, critically, with no modification or changes to the universally standard primary drug container of choice, the prefilled syringe.

tip-top holds more than 20 pending or granted patents covering many safety-engineered needle designs, including mini-Max and minim. The company has a strong independent source of funding and many years' of experience in the design of innovative engineered solutions, including more than two decades of experience in the design and production of plastic injection mould tools. Product development contracts with leading companies in the industry have been signed for previous devices, and interest in both mini-Max and minim from all quarters of the prefilled syringe industry has been very positive.

tip-top would welcome the opportunity to discuss the future development of its needle safety shielding devices, with interested parties. tip-top will be exhibiting at the upcoming PDA conference *Universe of Prefilled Syringes and Injection Devices*, in Las Vegas, NV, US, and at *Pharmapack* in Paris, France (February 23-24, 2011).

*minim and mini-Max are registered trademarks of tip-top.com Limited*

"A PASSIVE NEEDLE SHIELDING SYSTEM FOR READY-TO-FILL SYRINGES"

**Figure 6: mini-Max as it appears before, during and after injection.**

"DESIGNED AND DEVELOPED TO INTEGRATE INTO STANDARD NEST AND TUB FILL FINISH FORMATS WITHOUT CHANGING OR DISRUPTING THE DRUG CONTAINER"

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# ENGINEERING NEW SOLUTIONS FOR LIFECYCLE MANAGEMENT

**As high-end biotech products continue to enter the market, for use by patients and caregivers outside the clinical setting, issues are arising surrounding compatability of prefilled syringes with safety devices and auto-injectors. Here, Graham Reynolds, Vice-President, Marketing and Innovation, Pharmaceutical Delivery Systems, at West, describes how choosing a new material, Daikyo Crystal Zenith, not only addresses these issues, but brings with it various additional benefits.**

Growth in injectable therapies, driven by increased incidence of diseases such as diabetes and auto-immune and inflammatory diseases (including multiple sclerosis and rheumatoid arthritis), has resulted in the development and launch of an increasing number of new biologic drug products designed to treat these conditions. Most of these products require regular injectable delivery, often away from a clinical environment, by the patient or caregiver.

Evidence shows that there is continued growth in the number of biological products becoming available, and that most of these require delivery by injection. Alternative delivery routes continue to be evaluated. However, technology limitations and drug characteristics have led to injectable delivery still being considered as the preferred, if not the only, delivery route. An analysis of the top 20 biologics on the market by revenue demonstrates that most if not all of these products are delivered through injection. These trends are driving the need for prefillable syringe systems and other drug delivery devices and systems that can be used in either a clinical or home care setting.

Such home-based administration has spawned an increased need for combination drug delivery systems that are safe and convenient, and that help improve the preparation and injection processes, while ensuring the efficacy and compliance of the drug product .

> "AS PATIENTS AND CAREGIVERS BECOME INCREASINGLY INVOLVED IN DETERMINING THE BEST TREATMENT OPTION, BIOPHARMACEUTICAL AND PHARMACEUTICAL COMPANIES, WITH THE HELP OF DEVICE COMPANIES, ARE ADAPTING TO MEET THE NEEDS OF THE CONSUMER."

Among the earlier solutions for those with frequent injection needs were pen injectors and multi-dose cartridges. However, these products are limited to specific therapies such as diabetes and growth hormones, which often require weighed dosages or dose titration. While pen injectors are designed for frequent injections and for those who require variable dose capabilities, they are not ideal for chronic users of fixed-dose medications, including those suffering from dexterity issues.

Auto-injectors have been recognised as a convenient method for delivering drug products through an intuitive activation mechanism designed especially for patients who may have dexterity issues that impact their ability to inject a drug treatment effectively with a traditional syringe. As patients and caregivers

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**Figure 1: Daikyo Crystal Zenith® Luer Lock Syringe (top) and insert needle syringe (bottom).**

become increasingly involved in determining the best treatment option, biopharmaceutical and pharmaceutical companies, with the help of device companies, are adapting to meet the needs of the consumer.

Today's auto-injectors represent a compelling, easy-to-use delivery solution rooted in simplicity, accuracy, durability, flexibility and quality.

Auto-injector systems traditionally utilise 1 ml, long, glass prefilled syringes. These systems have been successful, but they have notable limitations, including:

- **Breakage** – Any glass product runs the risk of breakage during manufacture, storage and shipping. Additionally, glass syringes which were traditionally designed for manual injection create challenges for auto-injector manufacturers when these systems need to be designed to cope with the wide dimensional tolerances and inherent weaknesses of glass syringes. Incidents of glass breakage during activation of an auto-injector have led to US FDA concerns and recalls in specific cases.

- **Performance Issues** – Studies have shown that silicone oil, necessary to ensure lubricity and effective operation in glass syringe systems, can be distributed unevenly, leaving surface areas with insufficient lubrication. This will greatly increase the force required to operate the auto-injector and could lead to delivery of a partial dose to the patient if the piston should "stall" before it reaches the end of the syringe. Increasing the force necessary to eliminate this stall factor can create additional challenges due to extra force on weaker parts of the glass syringe, such as the flange area. In developing the ConfiDose® disposable auto-injector system, West can provide a system that overcomes many of the inherent challenges related to glass syringes by distributing the forces onto less fragile areas of the syringe, and safely providing a higher force that can allow for the delivery of high-viscosity products.

- **Interaction between the biologic and the syringe system –** Silicone oil and tungsten residues have been reported to induce protein aggregation in prefilled syringes, causing particle generation.

The solution to these issues can be found in creating a syringe system from novel materials, including cyclic olefin polymers. One such solution is the Daikyo Crystal Zenith® insert needle syringe system (see figure 1, bottom).

"THE CRYSTAL ZENITH 1 ML, LONG INSERT NEEDLE SYSTEM IS THE FIRST SYSTEM OF ITS KIND TO USE NO SILICONE OIL FOR SYRINGE FUNCTIONALITY AND REQUIRES NO ADHESIVE TO HOLD THE NEEDLE IN PLACE."

## THE NEED FOR PLASTIC SYRINGE SYSTEMS

In 2006, commercial lots of a drug product delivered by an auto-injector that contained a glass prefilled syringe were recalled in several European countries because of problems with slow or incomplete delivery of the drug. There was a similar occurrence in 2009 in the US, when an auto-injector batch was recalled due to high force-to-fire values.

Such issues with performance and quality have the potential to affect a company's bottom line significantly, not to mention patient safety and the effective application of the drug product. Failures of finished drug product (defects during manufacturing process and distribution), as well as internal failures in product development and production, can greatly increase manufacturing costs. Recalls based on breakage, aggregation or performance may require costly preventive actions and process improvement, and the overall response from the market to such problems can shake consumer confidence in the company and its product.

The Daikyo Crystal Zenith® 1 ml, long insert needle syringe system is a first-in-class solution to the issues faced by many manufacturers. Polymers like Crystal Zenith resin possess many advantageous properties, including glass-like transparency, which permits visual inspection of the manufactured components and of the parenteral products that are delivered to the end user. In addition, Crystal Zenith polymer is highly break resistant and forms an excellent moisture barrier.

Plastic prefilled syringes can eliminate the need for silicone oil and adhesive, depending on the quality attributes of the entire prefilled system, and do not use tungsten pins that are commonly used in forming glass syringe barrels. The Crystal Zenith 1 ml, long insert needle system is the first system of its kind to use no silicone oil for syringe functionality and requires no adhesive to hold the needle in place.

Instead, the system relies on lamination of the syringe piston with Flurotec® barrier film, which helps to lower protein adsorption and serves as a barrier to leachable substances. The fluorocarbon film provides an effective barrier against organic and inorganic leachables and extractables, and helps to maintain the strength and shelf-life of most dugs. When used in combination with B2-Coating, Flurotec coating provides lubricity without the need for silicone oil.

When used within an auto-injector, such as West's ConfiDose® auto-injector system, Crystal Zenith polymer's tight dimensional tolerance and consistency of syringe functionality can help to make an auto-injector's operation predictable – which makes it an easy-to-use, safe option for the patient, while mitigating risk associated with performance issues or breakage for manufacturers.

## A BREAKTHROUGH IN ENGINEERING EXCELLENCE

The Crystal Zenith insert needle syringe system is manufactured by West in conjunction with its partner, Daikyo Seiko Ltd, at a state-of-the-art delivery systems facility in Scottsdale, AZ, US. Because it is unique to the market, new processes were created to manufacture the system.

Since the insert needle is molded directly into the syringe, robotic handling is used to optimise quality and minimise biologic contamination. Once manufactured, the syringes are sent through a rigorous vision inspection that mitigates contamination and defect risk. This process helps to lower rejections on the pharmaceutical company's production line.

In addition, the needle is X-ray inspected to ensure proper positioning, which benefits the end-user by minimising pain upon injection, as well as ensuring sterility. Proper positioning also helps to assure effective drug delivery. The insert needle syringe system is produced in a ISO Class 7 clean room, and is then packaged in trays and sealed, prior to sterilisation.

West and Daikyo worked closely with fillers and machine vendors to develop the insert needle as a ready-to-fill solution that is compatible with existing fill lines. As such, manufacturers do not need to pre-treat the needle in any way – it is a fully-validated, sterilised system, designed to be compatible with their existing filling lines, or those that exist at leading contract fillers.

The combination of the unique Crystal Zenith material, engineering excellence, high quality manufacture and West's extensive knowledge of the needs of the pharmaceutical and biotech industries, driven by over 80 years' leadership in packaging and delivery systems for injectables, has led to an exciting new development, which may become the packaging solution of choice for all high-value biotech products.

"WEST AND DAIKYO WORKED CLOSELY WITH FILLERS AND MACHINE VENDORS TO DEVELOP THE INSERT NEEDLE AS A READY-TO-FILL SOLUTION THAT IS COMPATIBLE WITH EXISTING FILL LINES."

## A TESTED SOLUTION TO LIFECYCLE MANAGEMENT

The insert needle syringe system builds on West and Daikyo's portfolio of products made with Crystal Zenith resin. The material has been in production and in commercial use with marketed drugs in the US, Europe and Japan for many years. Customers can select Crystal Zenith materials with confidence that the material is market-approved.

In addition to the insert needle syringe system, customers can select from a variety of lifecycle containment solutions – thus keeping their product in the same material from discovery through commercialisation. Solutions include:

- Screw-top containers to store and transport drug products or drug substances
- Vials for serum and lyophilised drugs
- Luer lock syringes (shown in Figure 1, top)
- Cartridges for biopharmaceutical drug delivery applications
- Customised containers can be developed, specifically designed to interface with a delivery device

By using a Crystal Zenith resin product through the drug's lifecycle, a company can: offer superior protection in a silicone, tungsten and adhesive-free system; simplify regulatory filings; and avoid manufacturing delays caused by the need to continually test container closure systems.

As a one-source solution to production, West offers the technical expertise pharmaceutical companies need to develop a unique system for their drug product.

Materials like Crystal Zenith resin are the new standard for high-end biopharmaceuticals. Thanks to flexibility in design, such materials can be created to suit almost every need at any time during the lifecycle of a drug.

By choosing a single source for manufacturing, drug companies will not only mitigate risk and help to ensure patient safety, they will also receive the benefits of a partnership that will aid in the traditional areas of regulatory and compliance support, but also in the design and manufacture of unique systems that can differentiate products in a crowded market.

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SHL GROUP

Meet Molly
The ideal safety solution

# SIMPLE, COMPACT AND MAXIMUM SPEED TO MARKET: AN AUTO-INJECTOR THAT GETS THE JOB DONE

**In this article, Steven R. Kaufman, Marketing Director of SHL Group, describes how pharmaceutical and biotechnology companies can cope with the challenge of finding the right auto-injector for their drug, how to get their product to market more quickly and what to look for in a drug delivery device partner. To help discuss these points, Mr Kaufman highlights SHL's newest pre-configured auto-injector, Molly, which is now available for consideration.**

According to industry experts and several recent publications, over half of the world's top selling drugs will be biologics by the year 2015. As a result, the market for prefilled syringes, a more convenient injection alternative to traditional vials, has experienced significant growth over the past decade. However, the range of drug delivery solutions required continues to widen as the need for improved safety and self-administered therapeutics is also steadily increasing.

To meet these industry-driven demands, biopharmaceutical companies began partnering with device manufacturers to develop another alternative – the auto-injector. An auto-injector generally consists of a prefilled syringe or cartridge inside a device with enough mechanical force to fully inject the desired drug within the specified delivery requirements.

"THE ULTRA-COMPACT DESIGN OF MOLLY MAKES IT PORTABLE BUT ALSO REDUCES THE NUMBER OF COMPONENTS FOR EACH DEVICE."

Not only does the auto-injector address patient dexterity concerns, but it can also offer various safety features, such as a hidden needle, that protect end-users administering the drug from known safety issues such as needle-stick injury. In addition, such devices simplify the injection process for end-users.

Biopharmaceutical companies are now more experienced and knowledgeable about auto-injectors, and clearly see the value of launching their drugs in auto-injectors. As a result, they are requesting devices at earlier stages during the drug development process and seek devices that can be used for not just one but multiple projects. Drug delivery device companies are quickly responding by offering competitive and innovative solutions that address patient needs, and the drug company's desire to maximise speed to market.

However, the nature of doing business for a drug company as compared with a drug delivery device company differs greatly and this itself can bring with it some new challenges, especially when it comes to choosing the right device and partner. These challenges can include understanding which device design is most suitable for the desired therapeutic drug, and what core competencies are available to support the drug company's business model.

Here is a common question biopharmaceutical companies may face when venturing into the auto-injector market.

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**Figure 1: SHL's latest pre-configured auto-injector: Molly.**

**Question:** What should drug companies do when they have an injectable biologic soon ready for the market and they want to use a drug delivery device such as an auto-injector to launch the drug in?

**Answer:** Two main areas drug companies should focus on at this point are: a robust auto-injector that fits the drug's injection requirements for the targeted patient group and how quickly the final device can be developed to maximise speed to market. Aside from meeting the contained drug's injection specifications (such as delivered dose, viscosity, type of primary container, injection time, needle length, etc), it is crucial the chosen auto-injector also addresses patient-oriented factors. These may include safety features such as a permanently hidden needle and needle shield. Usability traits such as simplified operations and intuitive design are also crucial to the end-user.

It is common for a drug company to invest heavily and spend up to 20 years in the research and development of a new drug whereas a device may be developed within a much shorter period, approximately 3-5 years. Thus, when choosing an auto-injector as the final delivery platform, it becomes vital not to let the device become the potential 'bottle-neck', as this may be the only period of time where the drug company can minimise further investment and maximise speed to market.

Carefully taking these factors into consideration, SHL has recently introduced our latest auto-injector and the answer to the question above: Molly (see Figure 1).

## WHO'S MOLLY?

Molly is a revolutionary new auto-injector solution that focuses on helping customers maximise speed to market while providing various enhanced device features. The ultra-compact design of Molly makes it easy for users to carry around but also reduces the number of components that need to be manufactured for each single device.

Molly also has benefits ranging from a permanently hidden needle to a locking needle shield and even provides users with a simplified two-step operation. In addition to its many design features, Molly is also more environmentally sensitive than anything we've produced before.

Traditionally, a fully customised auto-injector project has been considered a premium solution due to the many costs involved for developing a device and the investments required for tooling, assembly and testing equipment. Unfortunately though, not all drugs can command the price or quantity to offset these costs. Additionally, the development timeline has a greater potential to impact a product launch date. Companies need to consider carefully when deciding on how they wish to present their drugs to customers, whether it be vial, prefilled syringe, safety syringe or medical device. However, with Molly, SHL believes we can offer an auto-injector which is '*the ideal safety solution*'.

## A NEW BUSINESS MODEL: MAXIMISE YOUR SPEED TO MARKET

In order to minimise investment and maximise speed to market, we've made it extremely easy to launch an injectable drug with Molly. This auto-injector is SHL's first 'pre-configured' injection device as we've standardised it to eliminate the need for customers to invest in individual tooling, assembly or test equipment.

With Molly, all that's required to kick-off a project is a minimal start-up fee. In other words, Molly opens up a new door for many to join in the growing auto-injector trend with just minimal start-up fees and is especially helpful to companies that are under time pressure to get their product to market quickly.

"WE ELIMINATE THE NEED FOR CUSTOMERS TO INVEST IN TOOLING, ASSEMBLY OR TEST EQUIPMENT. ALL THAT'S REQUIRED TO KICK-OFF A PROJECT IS A MINIMAL START-UP FEE."

To get started, the interested biopharmaceutical company would provide us with suitable syringe samples and we will optimise the device spring to match the drug viscosity and timing requirements.

It is important to note that further customisation is available under a traditional development


**Figure 2: Customers of Molly can benefit from SHL's new business model, which includes final assembly, device labelling and product packaging services.**

program. However, by sticking to the pre-configured device, customers benefit from faster speed to market, true economies of scale and the resulting effect of keeping capital investments down.

Molly is also a perfect fit for SHL's new facility in Florida, US, under the name SHL Pharma, where this new device is already optimised for the final assembly, labelling and packaging services offered at the new plant (see Figure 2). This new facility is scheduled to be operational in Q1 of 2011.

## SIZE MATTERS

In consideration of industry demands and end-user needs, devices coming to market are becoming smaller whenever possible and often utilise the newest technology available. Molly is no exception. This device is ultra-compact and is not much larger than a PFS (see Figure 3). The appearance of the device itself is discrete, attractive and ergonomic. Patients will not be embarrassed to use Molly to take their medications, even in public.

## KEEPING IT SIMPLE

One of the goals for any device manufacturer should be to design a device that is intuitive for end-users. With the use of shield activation injection technology, auto-injectors like Molly only require two steps to inject their medication. Just uncap and inject (Figure 4). In fact, our research has shown that Molly is regarded as one of the simplest and most intuitive devices that SHL has developed.

## SAFE. GET THE POINT?

As a device that may be distributed to millions of patients who regularly self-administer their medications, safety features are crucial in every aspect. Molly utilises a protective needle shield that locks into place as soon as the device is removed from the injection site. This passive protection feature is designed to protect users from needle-stick injuries after the device has been activated. Needle phobia is also an issue, especially for first-time users of injectable medicines. With Molly the end-user will never see the needle exposed (see Figure 5).

## WHERE CAN I FIND MORE INFORMATION ABOUT MOLLY?

For more information, simply go to SHL's dedicated website for this new device: www.meetmolly.com. Alternatively, contact SHL's sales offices. To help our customers try Molly first hand, we have put together a limited number of Molly auto-injector kits for prospec-

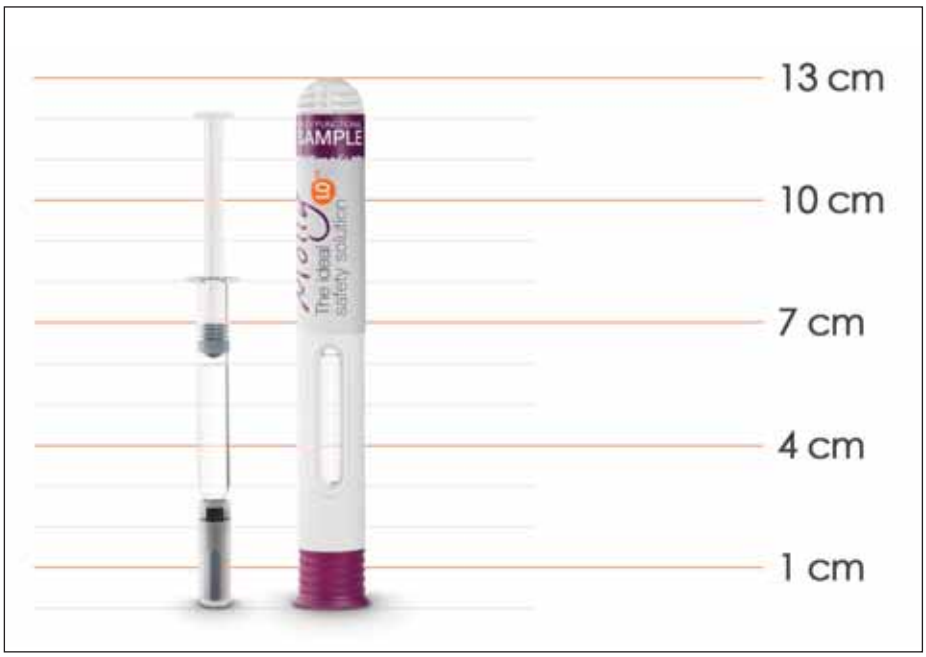


**Figure 3: Standing at just 13cm, Molly's size is comparable to that of a prefilled syringe.**


**Figure 4: With a simplified two-step operation, Molly is incredibly intuitive to administer.**


**Figure 5: The device features an automatic locking needle cover to protect users from needle stick injuries.**

tive clients (shown in Figure 6). These kits will be available at the upcoming PDA conference in Las Vegas, NV, US (October, 18-19, 2010) and the PDA Conference in Berlin, Germany (October 26-28, 2010).

With a growing number of auto-injectors on the market and soon coming to market, drug companies may, at first glance, find some that do meet the requirements discussed above. However, the actual development of the auto-injector device can easily become the bottleneck for the drug company if the chosen device manufacturer does not have the right core competencies.

## CHOOSING THE RIGHT PARTNER

When looking at the different players in the drug delivery device manufacturing field there are still only a few companies that have the required core competencies needed to design, develop and manufacture a suitable device. Clearly, finding a company that has the right balance of having an established track record and solid pipeline, experienced device professionals and the vital capabilities in-house can be a challenge.

## HAVING AN ESTABLISHED TRACK RECORD & SOLID PIPELINE

Drug delivery device companies that currently have devices on the market obviously have a distinct advantage. Most pharma companies are unwilling to be the 'guinea pig' and look to partners with experience going through the rigorous steps involved in taking a combination product to market. Whenever possible, working with established players is ideal.

Almost as important to pharma and biotech customers is finding a drug delivery company that has a range of devices already in development. A broad pipeline of devices gives customers a competitive edge by saving them development time and providing them with a variety of options to consider. Some of SHL's devices are shown in Figure 7.

Launching a robust auto-injector that can meet end-user's true needs is what drug companies hope to achieve. Devices like Molly have a proven concept and design – a unique starting point for most companies.

## DESIGN, DEVELOPMENT, MANUFACTURING, PROJECT MANAGEMENT & MORE

Look for drug delivery device partners with a strong team of professionals already in place. The challenge for most of these companies is establishing an integrated group of experts in their respective fields. For example, some companies may only offer design and development services, while others are only strong in manufacturing and project management. In-house regulatory expertise and proactive control of intellectual property are further examples of areas where only a few players have what it takes. The goal for companies developing injectable biologics is to find a device partner that has a diverse group of experienced professionals working for them and available to offer support when needed.


**Figure 6: A limited number of sample kits are available for prospective clients attending the October 2010 PDA conferences in Las Vegas, NV, US, and Berlin, Germany.**

**Figure 7: SHL has a proven track record of successful products as well as a strong pipeline of new devices.**

## KEY CAPABILITIES SHOULD BE IN-HOUSE

Looking at the complex processes and machinery needed to produce, assemble and test auto-injectors, one should take a closer look at what capabilities are controlled by the device partner. Understanding which capabilities or processes are outsourced and which are provided in-house is an essential point to understand. Certain established companies have taken control of their capabilities to ensure not only the quality of the finished product, but also that key timelines are met.

Aspects such as tooling, moulding, machining, automation, assembly, and metrology should ideally be maintained in-house. Some companies even make their own springs for their devices. Although providing such an extensive range of in-house capabilities can mean significant investment for drug delivery device companies, the controlled vertical integration of all the vital capabilities and processes benefit both device companies and drug companies.

## CONCLUSION

The growing need for a broad range of auto-injector solutions driven by industry demands is becoming quite a challenge, not only for the drug delivery device designers and manufacturers, but also for pharmaceutical and biotechnology companies. Customers will need more devices, but how many new devices will be available to these customers? Clearly, other companies will enter this growing market with their unique, or not so unique, drug delivery solutions, but only a few players currently have the experience needed to get the job done.

SHL has extensive experience with various biopharmaceutical companies, both large and specialty companies, combined with extensive in-house capabilities. This positions SHL as a preferred device manufacturer for many. With the introduction of Molly, SHL will further change today's auto-injector arena by providing our customers with a timely solution to one of their most vexing challenges – speed to market – while still meeting vital device design requirements.

Even with more than 25 new devices in the company's extensive pipeline today, SHL continues to innovate and expand the services provided to our customers. The introduction of new devices like Molly is a step in the right direction. And with Molly's unique business model, we will be able to help several companies fill their immediate needs for a simple, effective, and compact device that can get the desired drug to market faster than with a traditional development model.

## ABOUT SHL: THE COMPANY BEHIND MOLLY

SHL is the world's largest privately-owned designer, developer and manufacturer of advanced drug delivery devices. In particular, SHL is a recognised leader in the field of auto-injectors. After working with some of the biggest names in the pharma and biotech industry, senior management at SHL saw the need for a new approach that would help customers get these companies' drugs to market and give them immediate access to an amazingly compact and effective auto-injector.

While traditional development programmes are essential, and several are ongoing at SHL at this time, Molly is a fresh approach that is now being actively promoted globally.

What sets SHL apart from our competition is the sheer number of capabilities we have in-house. When initiating a project with SHL, you have a reliable partner that can perform in-house tool manufacture, moulding, component testing, assembly, automation equipment design and fabrication all under one roof. Our level of service means we bring these capabilities together in a way that nobody else can. This ultimately translates into superior products and unrivalled speed to market.

Visit www.meetmolly.com or www.shl-group.com to learn more today.

## ABOUT THE AUTHOR

Reporting directly to Swedish CEO Roger Samuelsson, Steven R Kaufman is SHL's Marketing Director, responsible for the global marketing & public relations strategy of SHL Group. He is also involved with joint-venture support and is active in business development. Mr Kaufman has extensive experience in Chinese & Western management cultures, having worked for more than 15 years in Taiwan and five years in North America. He has a BA (Hons) from the University of Western Ontario (UWO), Canada, received Canadian APMR (Accreditation of Pharmaceutical Manufacturers Representatives) certification, and completed his MBA coursework in Marketing & International Business at National Chengchi University (NCCU), Taiwan.


# Maximise
## your speed to market.

Molly is a brand new, ultra-compact autoinjector that requires minimum investment and offers maximum speed to market. To learn more about SHL's groundbreaking device, meet us at one of the PDA events below or visit our website: www.**meetmolly**.com

SCHOTT
glass made of ideas

# A NEW INNOVATIVE STAKED-NEEDLE SYRINGE FOR SENSITIVE DRUGS

**SCHOTT forma vitrum has developed a new syringe for improved drug stability and a gentle application under the brand name InJentle™. Here, Ms Carmen Heiter, Product Manager, Syringes, at SCHOTT, outlines the packaging requirements for sensitive drugs. She describes the drivers for the development of InJentle, how the syringe works and why it is both drug friendly and user friendly. Safety is guaranteed, among other things, by a new safety device that was developed with Safety Syringes, Inc.**

The global pharmaceutical market has seen a growing demand for prefillable syringes for years and this trend is expected to continue on a global level in the years to come. Ready-to fill syringes answer the growing demand for speed and ease-of-use, while minimising dosage errors. With the growing number of new and highly sensitive drugs in the development pipeline of pharmaceutical companies, syringes must meet ever more complex requirements.

**Figure 1: Injentle™, a completely unique packaging solution for sensitive drugs**

"ALTHOUGH THE SYRINGE INCLUDES MANY SPECIAL FEATURES, THE SYRINGE IS DELIVERED WITH STANDARD NESTS AND TUBS AND CAN BE FILLED ON STANDARD FILLING LINES, JUST LIKE STANDARD SYRINGES."

Injections generally produce better results and take effect more quickly than medications that are administered orally. There are also medications such as protein-based drugs, insulin and antibodies, that require parenteral administration due to the fact that, if they were to be taken orally, they would not be sufficiently reabsorbed by the bloodstream, or they would be broken down by enzymes in the digestive tract or destroyed by the hydrochloric acid inside the stomach.

A defined concentration can be set more easily in the blood with active ingredients administered in a parenteral manner than with orally administered medications, and so intravenous injections are becoming increasingly important, especially in emergency medicine. With the development of biomolecules and monoclonal antibodies, the pharmaceutical industry continues to develop more specific medications that are capable of combating diseases more effectively, yet are considerably more sensitive to contaminants.

To meet the requirements of such highly sensitive drugs SCHOTT has developed a completely unique packaging solution for the

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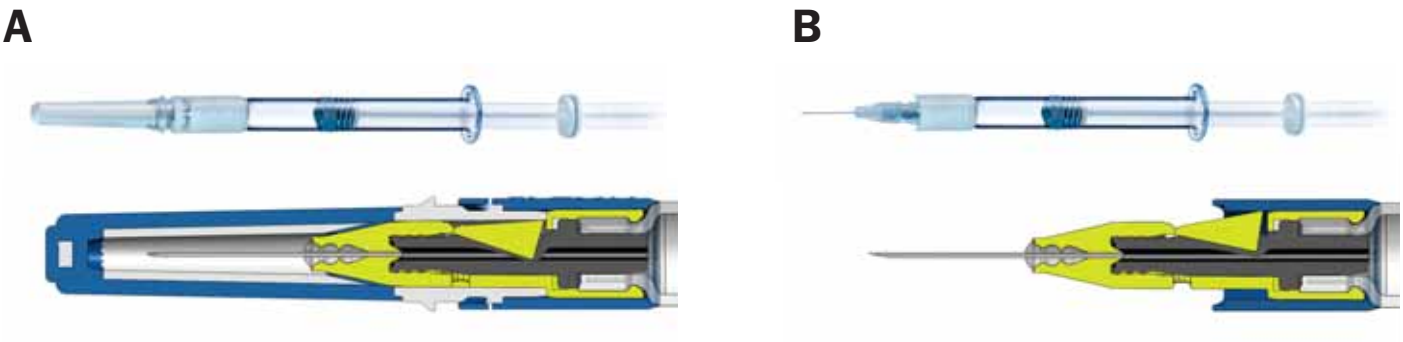



**Figure 2: a) When the needle-shield is on, the InJentle™ seal remains in the closed state, and b) when the cap is removed, the seal opens.**

pharmaceutical industry under the brand name InJentle™, in close co-operation with pharmacists and industry experts (see Figure 1).

Contamination of syringes with the heavy metal tungsten, or other foreign materials is only one important issue besides many others that are addressed by this packaging solution. Safety is another. Due to the fact that many biotechnology products are very difficult to manufacture and thus expensive to produce, issues such as patient safety and anticounterfeiting play a major role with respect to every development.

For instance, how can a physician or patient be sure that the syringe they are using has not already been used or that a syringe they have used will not be refilled and used again?

SCHOTT InJentle offers a number of novel features for the benefit of highly sensitive drugs, in particular. Its unique design offers improved drug stability, gentle application and also the flexibility to include further anti-counterfeiting features such as, for example, RFID (radio-frequency identification).

The drug does not come into contact with the needle during storage. This prevents sensitive drugs from interacting with the adhesive or the metal of the needle. The innovative seal design prevents the drug from flowing into the needle until the very moment that the syringe is opened, that is, when the needle shield is pulled off. A robust tamper-evident closure is integrated in the unique design of the syringe. As soon as the system is opened, this part will break and cannot be reconnected. This allows physicians or patients to determine easily whether or not a syringe has already been used.

SCHOTT InJentle offers a range of other advantages. For example, the special geometry of the glass barrel does not require any tungsten to be used during the glass forming process. As a result, the syringe is completely tungsten-free.

Tungsten has been found to be a leachable in glass prefilled syringes. Reports describe tungsten-based particulate matter that leached into and interacted with the protein drug product. Tungsten pins are typically used to keep the fluid pad open at the nozzle end of the syringe during the glass forming process. Residual tungsten can migrate into the drug product and cause the protein to form protein-tungsten aggregates. This phenomenon appears to occur with specific proteins. Production techniques that rely on another heavy metal than tungsten have been on the market for some time, however it is clearly preferred by pharmaceutical companies to completely eliminate this critical metal, of course.

The development of InJentle started in 2006. Following extensive market analysis, SCHOTT initially purchased an existing patent, but then decided to overhaul the entire approach so extensively that this ultimately led to an entirely new product solution with its own patent. For the intensive development work, SCHOTT relied on technical partnerships with various industry experts.

## INJENTLE SEAL DESIGN

How does the InJentle principle of the new seal design work? In the closed state, a small plastic arm presses against the rubber tube to seal the syringe (see Figure 2a). This means the container is closed by the arm. The part with the needle does not come into contact with the drug at all during the closed state. As soon as the needle shield is removed, the arm flexes out, removes the pressure and releases the seal (Figure 2b). The channel is now open and ready for the injection.

The unique design of SCHOTT InJentle means that the needle point is fully protected and does not touch the needle shield or any other material. This guarantees best needle lubrication and straight needles; hooks are avoided. The new syringe allows for the use of particularly thin needles of up to 32 gauge, which results in a reduction of pain for the patients during the injection.

No special training is required for healthcare personnel because SCHOTT InJentle is easy to handle and self-explanatory.

Although the syringe includes many special features, the syringe is delivered with standard nests and tubs and can be filled on standard filling lines, just like standard syringes.

The production process of InJentle is similar to that of standard syringes. The glass barrel is formed, washed and siliconised. The cap, needle holder, collar and bung are assembled in a sterile environment. Under laminar flow, the glass barrel and the sub-assembled plastic part are connected and then packed in the nest, tub and bag, as usual. Ethylene Oxide (EtO) sterilisation, batch release and shipment also take place in the same way as with other syringes from SCHOTT.

A production line is currently being built to manufacture the InJentle syringe, with mass production planned to start at the end of 2010 at the SCHOTT plant in Lebanon, Pennsylvania, US. Since October 2010, samples in 1ml long format have been available for functionality testing.

"THE DRUG DOES NOT COME INTO CONTACT WITH THE NEEDLE DURING STORAGE."

## NEEDLE-SAFETY MECHANISM

To meet the packaging requirements of sensitive drugs also in the future, the developers at SCHOTT haven't stopped here, but rather are

continuing to work systematically on making further improvements.

For example, a protective needle safety mechanism that shields the needle immediately after injection to protect healthcare professionals from accidental needlestick injuries has already been developed. The safety device was developed in co-operation with Safety Syringes Inc (SSI). SSI is the market leader in safety solutions for prefilled glass syringes and this product is a modified version of their UltraSafe® Passive product line that has been in use worldwide for some time. It has been a great success, having been combined with more than 25 medications.

Needlestick injuries represent a significant global problem. Each year, between 600,000 and one million accidents solely involving needlesticks are reported in the US. In Europe, as well, it is estimated that roughly a million accidents, which mainly pose a risk to medical personnel, occur each year.

Policymakers have already taken action in many countries. For instance, the US adopted the "Needlestick Prevention Act" in 2000, which requires that special safety devices be used with syringes. In Canada similar legislation was passed in 2008. According to a recent EU council directive (2010/32/EU), the EU member states must adopt more stringent sharps injury legislation, which includes needlestick prevention, by the year 2013.

"A PROTECTIVE NEEDLE SAFETY MECHANISM THAT SHIELDS THE NEEDLE IMMEDIATELY AFTER INJECTION TO PROTECT HEALTHCARE PROFESSIONALS FROM ACCIDENTAL NEEDLESTICK INJURIES HAS BEEN DEVELOPED IN CO-OPERATION WITH SAFETY SYRINGES INC."

The benefits that the UltraSafe Passive® Needle Guard brings to InJentle are clear. A wider plunger head, finger flanges and a rounded body design offer qualified personnel safe support, and no special procedures are necessary to put the syringes into operation.

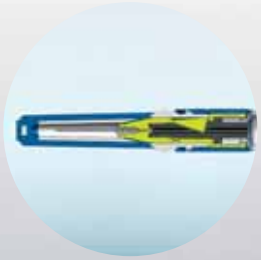
The safety feature is activated passively, shielding the needle automatically right after injection – a key requirement for effective needlestick protection, as a large portion of needlestick injuries happen when the bare needle is removed from the injection site. One-handed operation is possible, and no new injection technique is necessary. In addition, these syringes come pre-assembled in ready-to-use-packages.

SCHOTT will be presenting the new safety device complementing InJentle to industry experts and the broader public at CPhI (Paris, France, October 5-7, 2010) and at the PDA conference, *Universe of Prefilled Syringes and Injection Devices* (Las Vegas, NV, US, October 18-21, 2010).

# SCHOTT InJentle™
# Drug Friendly, Patient Friendly

## Prefillable staked needle syringe

- Tungsten-free
- No leachables from adhesives
- No contact between drug and needle
- Tamper-evident closure
- Gentle application
- Thin needle
- Easy handling



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glass made of ideas

# DELIVERING POWERFUL BRAND DIFFERENTIATION AND OPTIMISING PRODUCT LIFECYCLES

**In recent years, pharmaceutical companies have been turning increasingly to drug delivery devices to differentiate their products. The prefilled syringe has been a particularly valuable tool in this respect. However, today, true brand differentiation cannot be achieved with a prefilled syringe alone and so current differentiation approaches focus on safety and ease of use. Here, Alan Shortall, Chief Executive Officer, Unilife Corporation, describes how the Unifill® ready-to-fill syringe offers distinct advantages over ancillary safety devices and auto-injectors. Furthermore, Unifill can be integrated into existing fill-and-finish systems and, as a proprietary device, offers an attractive solution for pharma companies wishing to create genuine differentiation from competitor drugs supplied in a more common delivery format.**

The need for pharmaceutical manufacturers to optimise the lifecycle of their in-line and pipeline brands has never been more acute. Generic and biosimilar products are increasingly challenging the status quo of blockbuster drugs across a range of therapeutic sectors. In addition, government agencies are making the pathway for pipeline drugs seeking approval more onerous, with new potential blockbuster drugs being in short supply.

For mature drugs approaching the end of their exclusivity, the opportunity to protect or retain revenues in the face of generic or biosimilar competition holds particular appeal (see Figure 1).

Pharmaceutical companies increasingly recognise that the way in which a drug is presented and delivered can add significant value to a franchise. A distinct and innovative delivery device can provide many benefits to patient and healthcare facilities by improving the convenience, safety and functionality of drug administration. Such intuitive devices may also help extend the reach of a drug beyond healthcare facilities and into the hands of the patient to decrease overall medical costs.

For devices with superior features that truly deliver brand differentiation across crowded and fast-growing therapeutic classes, it can be the primary catalyst for building market share and adding recognisable value for a pharmaceutical company.

Prefilled syringes became established over the past two decades as an ideal vehicle for brand differentiation within a competitive therapeutic drug class. Compared with traditional vials, prefilled syringes are overwhelmingly preferred by healthcare workers and self-injecting patients due to their relative advantages in speed of preparation and delivery, reduced inventory, dose reliability and ease-of-use.

Today, however, the bar has been raised to a point where prefilled syringes are now considered to be the minimum prerequisite for the launch of an injectable drug product. More than 20 pharmaceutical companies actively use prefilled syringes across a dozen therapeutic drug classes (see Figure 2). There are approximately 65 injectable drugs and vaccines currently available in a prefilled syringe format, with combined annual sales of more than $50 billion.

Some drugs, such as the recently approved Prolia from Amgen, are launched in a prefilled syringe format. Others, such as Teva's Copaxone, have been upgraded with great success from a vial to a prefilled syringe midstream of their lifecycle.

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To secure true brand differentiation within competitive markets, pharmaceutical companies recognise that a basic prefilled syringe alone is no longer enough. In recent years, device differentiation has largely centered upon making prefilled syringes safer and easier to use.

The move towards prefilled syringes with safety features has been driven by laws within North America and Europe mandating the use of safety-engineered medical devices (SEMDs) that can protect healthcare workers from needlestick injury. To comply with these laws, many pharmaceutical companies will attach ancillary safety products onto a prefilled syringe after it has been filled with a measured dose, and prior to packaging. Various design approaches are available, as summarised in Figure 3.

However, the use of these relatively bulky ancillary products can increase packaging, transport and storage volumes by as much as 70%. Furthermore, their invasive appearance compared with an equivalent standard prefilled syringe may also exacerbate patient discomfort and increase medical waste disposal costs.

Pharmaceutical companies have also invested heavily in injectable devices that can improve the handling, portability and overall convenience of drug delivery – particularly by patients that self-administer prescription medication outside of healthcare facilities. For example, arthritis blockbuster Enbrel, co-marketed by Amgen and Pfizer, is available in either a prefilled syringe with wider flanges for improved operator handling, or in a disposable auto-injector.

Whilst an improvement over a normal prefilled syringe, auto-injectors and ancillary safety products have several limitations in their capacity to deliver brand differentiation or optimise drug lifecycles. Most are largely similar in terms of appearance and operator functionality (see Figure 4). They also require additional and often costly steps for attachment by either the pharmaceutical manufacturer or the operator. The antithrombotic and MS therapeutic classes offer prime examples of where drug products are competing against each other with almost identical device strategies that offer little in terms of brand differentiation.

Pharmaceutical companies are now increasingly seeking access to unique devices that can disrupt the status quo and shift consumer demand in their favour. In addition to at least seven drugs in prefilled format that are approaching the "patent cliff" and coming under threat from generic competition, it is expected that branded biologicals will soon face a similar situation now that a biosimilar approval pathway is available in Europe and is soon to be defined in the US. Finally, there are numerous pipeline products that will be launched into already crowded therapeutic markets over the coming decade.

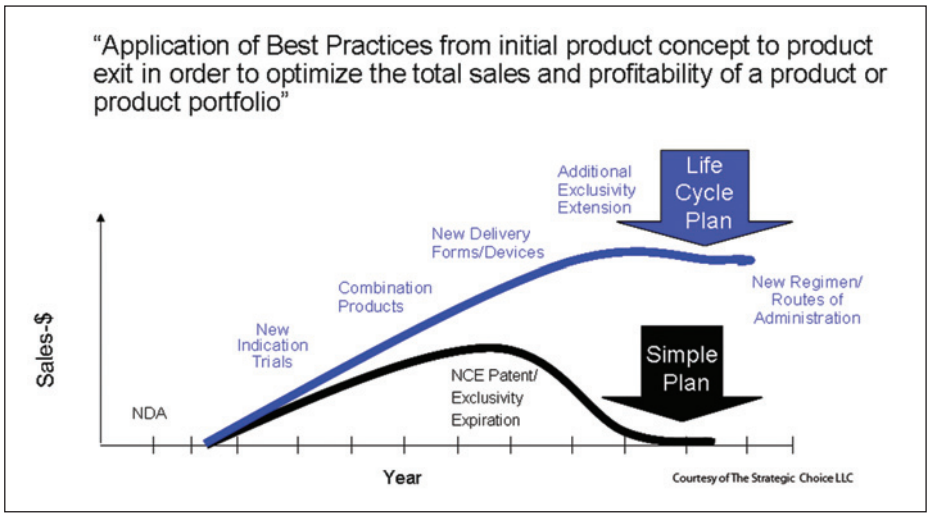


**Figure 1: Schematic showing sales resulting from successful lifecycle management strategies, compared with a simple plan without lifecycle management.**

Securing exclusive or preferred rights to a device within a target therapeutic class that can deliver unique claims, clinical benefits or other marketing advantages can create significant brand value and other barriers to competition.

Mathias Romacker, Principal Business Analyst at Amgen, wrote in the American Pharmaceutical Review in 2009: "As many drugs move into the mature age of their lifecycles, the presentation and delivery of a drug can play a major role as a differentiator for market success. The fewer other differentiators there are, the more important the role of injectable drug delivery may be. Consequently, in some therapeutic areas we see a lot of competitive activities focusing on devices rather than the drugs themselves."

Recent feedback from the US FDA to several citizens' petitions indicates that regulatory and IP barriers may also be achievable for unique drug-device combination products. Subject to the uniqueness of claims able to be proven and secured for the approved combination product, generic competition may be prevented altogether. Specifically, if a device provides "certain performance characteristics and critical design attributes" to the combination, competitor products might not be approvable by ANDA.[1] The generic would then have to pursue a 505(b)(2) application, involving additional expense and time to conduct clinical studies, ultimately resulting in a non-substitutable product. Although this response applies to an NDA/Non-biologic originator product, this may also apply to the biologic pathway, which is anticipated to parallel the ANDA process.

Sanofi-aventis has enjoyed significant success over the past decade utilising novel devices to build blockbusters, such as the insulin drugs Apidra and Lantus, with the SoloStar pen. Commenting on this success, Chris Viehbacher, CEO of sanofi-aventis said in the company's full-year results and outlook presentation, 2008: "I've certainly seen in my background, if you come up with a device that is differentiated and really means something to a patient, you will beat the competition."

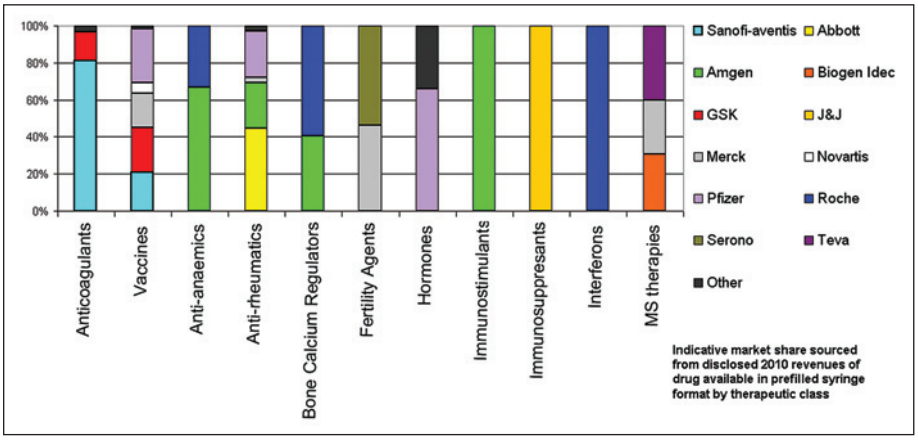


**Figure 2: Share of the prefilled syringe market by company and therapeutic category**

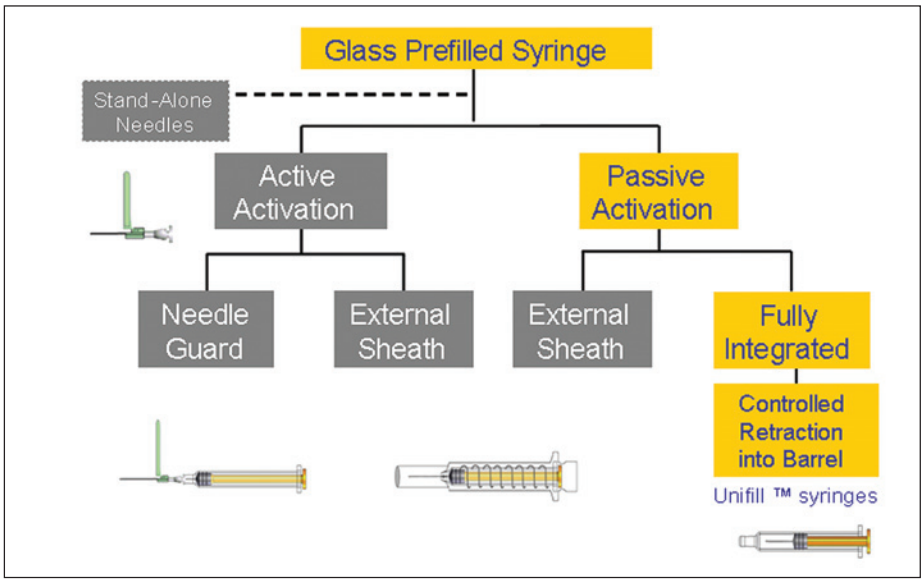


**Figure 3: Summary chart showing the different approaches to prefilled syringe needle safety**

Unilife entered into a collaborative relationship with sanofi-aventis in 2003 for the development of the Unifill ready-to-fill syringe – the world's first prefilled syringe with passive and fully integrated safety features. This leading global pharmaceutical company, and the largest consumer of prefilled syringes, has committed approximately $40 million for the commercialisation of the Unifill syringe, and the exclusive right to negotiate its purchase until June 2014 within antithrombotic agents, vaccines and four other confidential therapeutic sub-classes.

The Unifill syringe is a primary drug container with passive (automatic) safety features that are fully integrated within the glass barrel. It is supplied to pharmaceutical manufacturers as per standard handling processes, and designed for integration into the fill-finish systems used for normal ready-to-fill syringes.

The step of attachment of ancillary safety products after dose filling is eliminated. Furthermore, the Unifill syringe is similar in size to an equivalent prefilled syringe, and one-third smaller than those attached with an ancillary safety product, minimising packaging, transport and storage volumes.

As a primary container, all components within the fluid path utilise USP compliant materials and are sourced from established pharmaceutical suppliers. The handling and administration of the Unifill syringe is the same as injections undertaken with an equivalent prefilled syringe.

Upon the delivery of a full dose, a passive retraction mechanism is activated, whereupon operators may control the speed of needle withdrawal directly from the body into the barrel of the syringe virtually eliminating the risk of needlestick injury or aerosolisation (splatter). The plunger is then automatically disabled to prevent re-exposure, and to facilitate compact, convenient disposal.

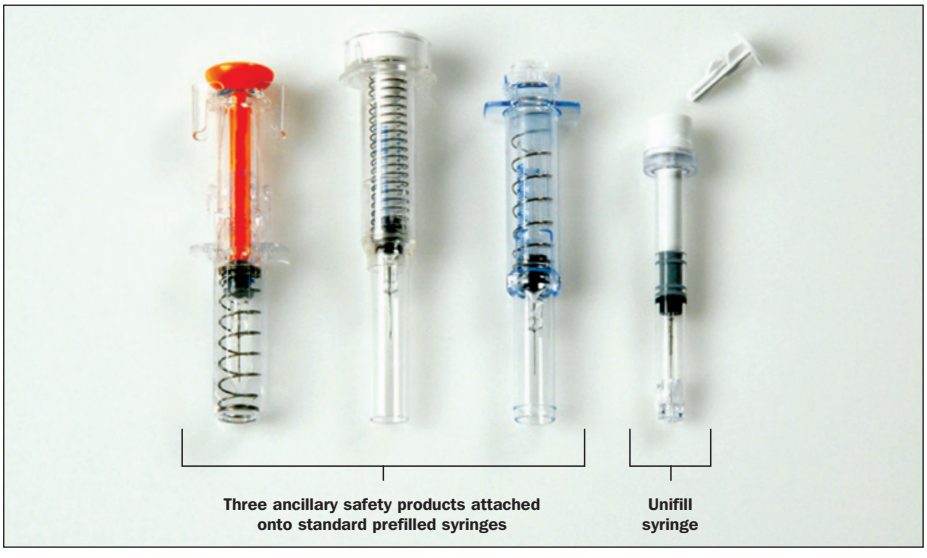


**Figure 4: Ancilliary safety devices, showing broadly similar design**

It is highly suitable for use either by healthcare workers or patients that self-administer prescription medication outside of healthcare facilities. Unilife recently conducted independent market evaluations with US-based healthcare workers comparing the Unifill syringe against two leading ancillary safety products that are attached onto currently marketed prefilled drugs. Healthcare workers preferred the Unifill syringe in all surveyed areas including safety, functionality, ease-of-use, performance and appearance. Indeed, 100% of healthcare workers preferred the Unifill syringe against the safety prefilled product most commonly used in US healthcare facilities.

The Unifill syringe is not a commodity product. It is a unique proprietary device that can only be sourced from Unilife. As such, the product can offer an elegant solution to pharmaceutical companies seeking to streamline their industrial processes and secure genuine brand differentiation against competing drugs supplied in a more common, traditional device format.

Given the unique, proprietary design of the Unifill syringe, it may offer pharmaceutical companies significant opportunities to enhance or extend product lifecycles and improve brand differentiation of drugs marketed in competitive therapeutic classes. It may also help companies to generate unique claims that reduce the likelihood of substitution by competitor products.

It is at the forefront of the new pharmaceutical trend focusing on the convergence of therapeutic drugs with delivery devices that are intuitive and market-differentiating.

Unilife is now in discussions with a number of pharmaceutical companies interested in the use of the Unifill syringe within therapeutic classes outside of those retained by the sanofi-aventis exclusivity agreement.

Commercial supply of the Unifill syringe is scheduled to commence next year, enabling pharmaceutical customers to begin stability testing for targeted drugs. The Unifill syringe will be manufactured at Unilife's new state-of-the-art headquarters in York, PA, US. Stage one of the 165,000 square foot (>15,000 square metre) facility will have the capacity to manufacture up to 400 million units per year.

## REFERENCE:

*1 King CP1: September 26, 2007, King CP2: January 29, 2009 and Dey CP3: December 2, 2009*

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Nuova Ompi
glass division

# INCORPORATING IMPROVED TECHNICAL FEATURES IN GLASS PREFILLABLE SYRINGE MANUFACTURING FOR PHARMACEUTICAL USE

**Whilst the standard 1ml prefilled glass syringe is now well accepted by the industry with billions being manufactured each year, small problems still crop up with the design, especially in the context of combining the prefilled syringe with add-on devices such as auto-injectors and safety features. In this article, Mr Paolo Golfetto, R&D Manager of Stevanato Group's Glass Division, focuses closely on some of these issues and describes how, with expertise and excellent design capabilities, they can be overcome.**

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

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

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

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

## PREFILLED SYRINGE CHALLENGES

Prefilled syringes constitute one of the fastest growing markets in the drug delivery and packaging sectors, with estimated global production of 2.4 billion units in 2010.[1] Several studies predict this growth to continue in the next years and the ready-to-use format is gaining more and more standard solutions, such us EZ-fill® in nest/tub configuration.[2]

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

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

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

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

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

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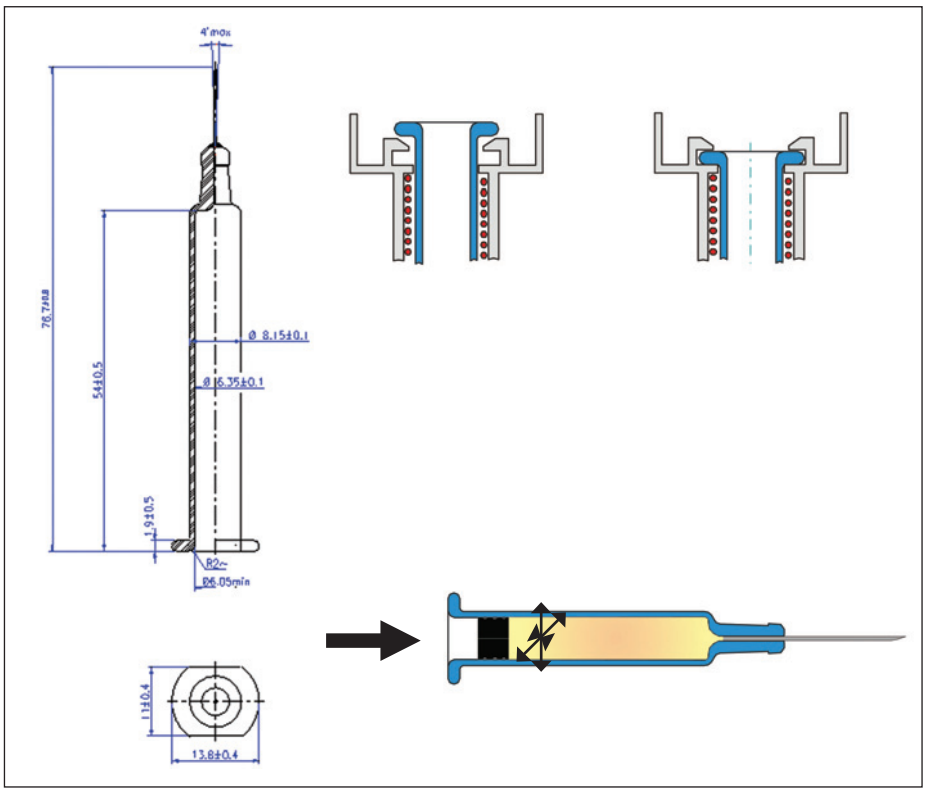


**Figure 1: ISO 11040 design and critical areas under stress by using auto-injectors or safety devices.**

Thus, we determined the complete settings of the relevant critical design of the primary packaging where there is a gap between the nominal and the optimal values (Figure 2).

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

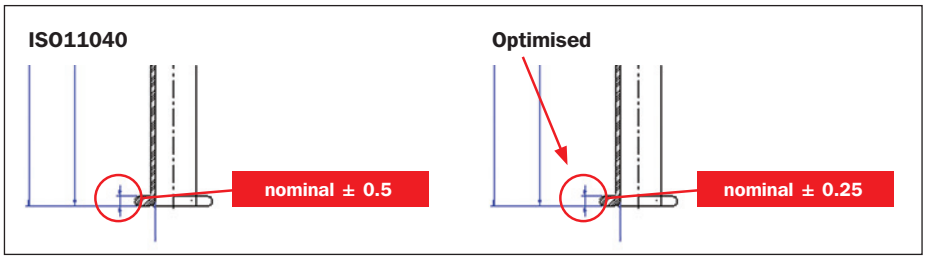



**Figure 2: Standard syringe design requirements and Ompi syringe improved tolerance.**

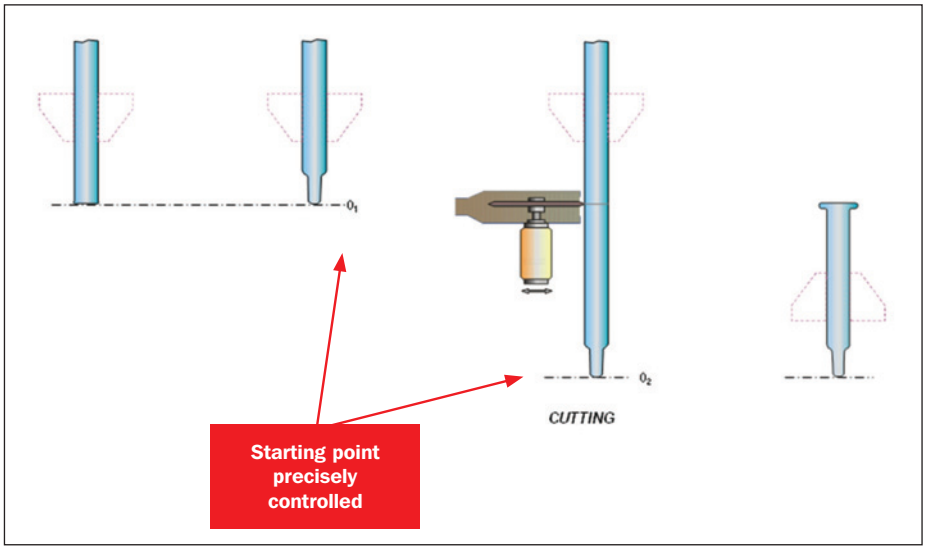



**Figure 3: Total length control technology applied to the glass syringe barrel**

## PROCESS

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

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

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

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

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

New inspection technology developed by Optrel controls the geometry according to the new requirements checking especially for com-

pability with the latest generation of safety devices and auto-injectors:

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

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

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

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

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

Tungsten is introduced into the syringe during the forming process, from the pin used to create the internal channel on the barrel tip. This

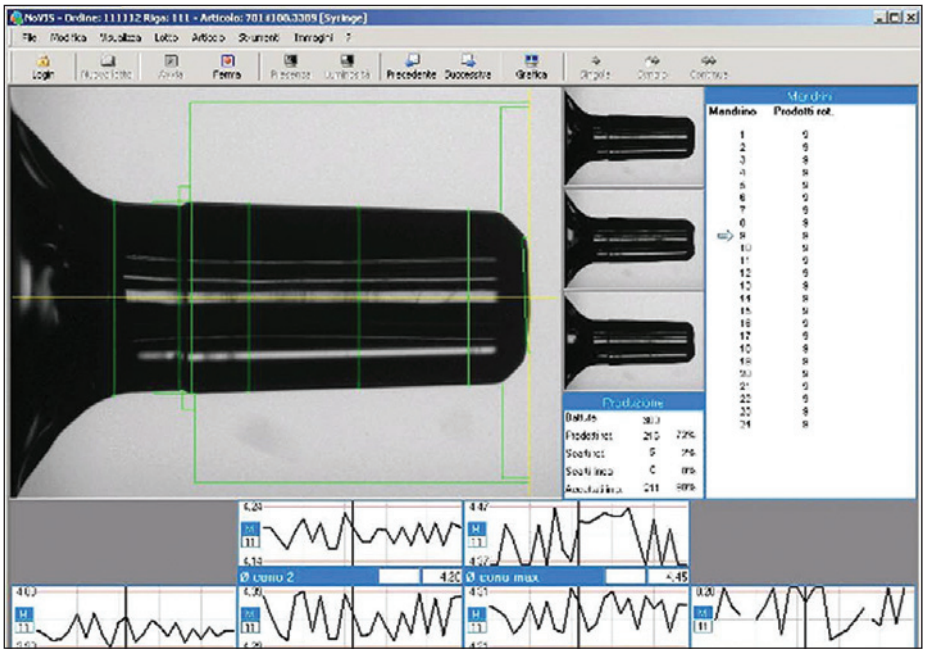


**Figure 4: 100% Camera controls performed inline by Novis technology and best results obtained thanks to new technology applied.**

material is used because of the good combination between resistance to high temperatures and mechanical properties. The sudden change of temperature in the pin is responsible for two sources of contamination:

- Part of the Tungsten vaporises at high temperature and deposits in the funnel area as it reaches the "cold" glass
- Part of the Tungsten oxidises at 800-900 °C, this oxide reacts at about 1200 °C with Sodium Oxide ($Na_2O$) that emerges on the surface from the glass structure forming Sodium Tungstate ($Na_2WO_4$). It has been demonstrated that high temperature causes the migration of substances to the glass surface, and some biotech molecules can interact forming undesirable protein aggregations.[3,4]

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

Nowadays, there are three different families of syringes:

1. Standard Process: syringes produced with Tungsten tools, extractable Tungsten level is low and compatible with most of the drugs / proteins currently in development.
2. Low Tungsten Process: syringes produced with Tungsten tools and optimised processes, extractable Tungsten level is very low and compatible with very sensitive drugs / proteins.

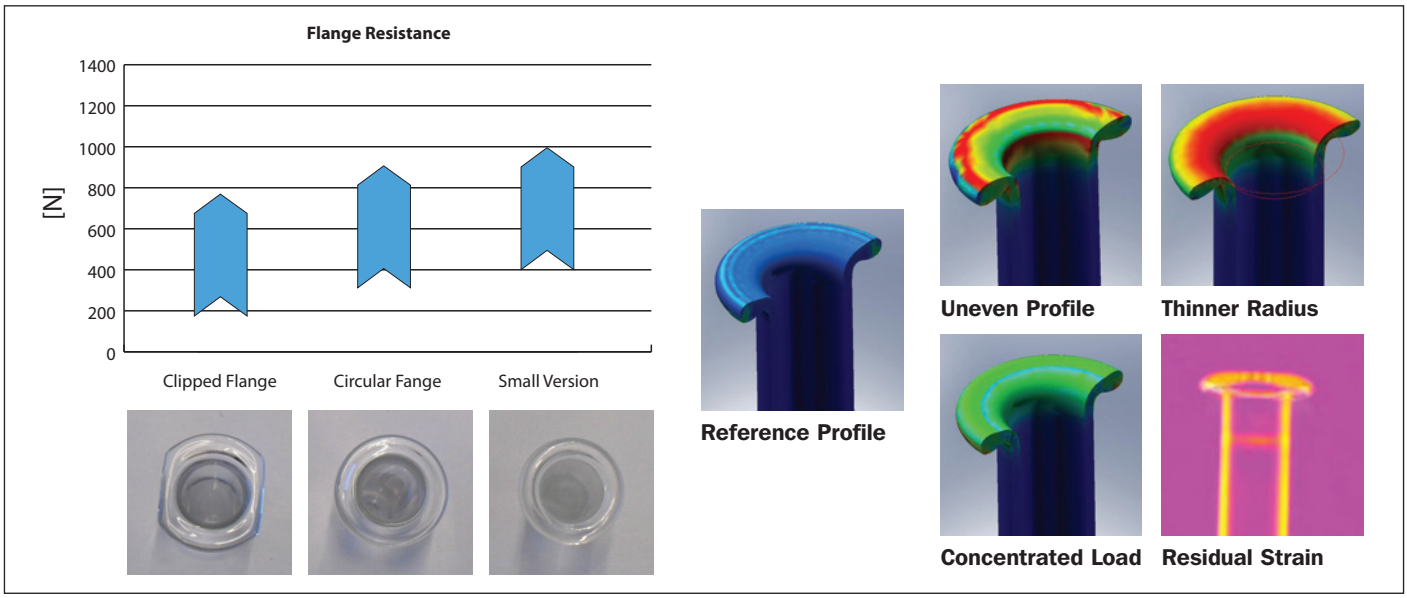
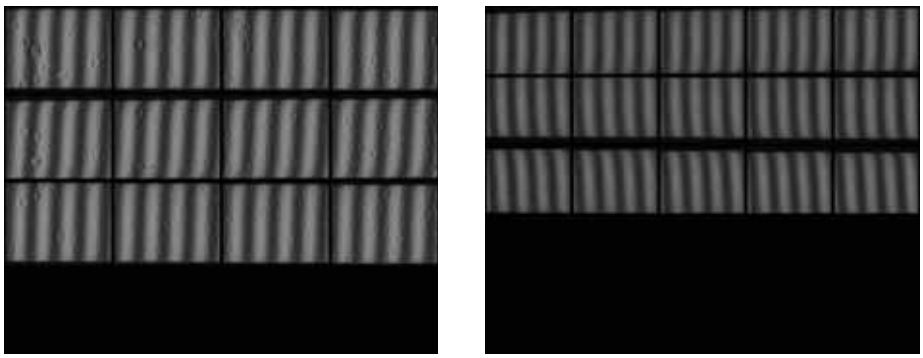



**Figure 5: Flange stress test results performed by R&D department in order to define flange resistance improvements.**



Previous silicone profile

New silicone distribution profile

**Figure 6: Distribution profiles with different droplet sizes (ZEBRA-SCI Images)**

3. Tungsten-free process: syringes produced with tools not containing Tungsten, no extractable Tungsten is present. The only critical issue is related to high cost of alternative tools

Needle insertion for staked-needle products can now be performed using customised high-speed assembly units operating in the clean room, which include 100% automated inspection for total height with needle, needle axially, needle tip deformation, clogged needles and adhesive distribution

Complete polymerisation of the glue is assured not only by checking the adhesion property of the adhesive but also having verified the cohesion property by introducing specific HPLC test to affirm the highest possible conversion rate. This important result has been obtained by validating an improved UV curing process including innovative UV irradiators and specific irradiation geometries.

Advances in drug formulation have allowed more biodrugs to be delivered in a liquid-stable form, reducing the requirement for lyophilisation. The liquid-stable form can then be packaged in a prefilled syringe, without passing through the lyo-vial phase, reducing time to market.

As more biomolecules are packaged in prefilled syringe systems, the issue of sensitivity to silicone becomes important, also linked to the nature of the Drug Product Vehicle, which may contain substances such as surfactants, which can increase the degree of silicone extraction from the glass surface.

This new trend is demanding enhanced biocompatibility, decreasing the quantity of silicone applied on the glass barrel, the distribution and the silicone droplets dimensions.

Decreasing the amount of silicone oil and new distribution patterns are direcly related to two aspects in conflict:

- Gliding performances (high silicone oil quantity).
- Low extractable silicone profile (low silicone oil quantity).

In order to understand the limits and potential improvements of the existing process based on diving nozzles, Ompi R&D decided to test:

- Syringe production with differentiated areas where silicone can be distributed.
- Evaluation of the correlation between silicone aggregation and sprayed droplet size.
- Several microscopic detection technologies, available on the market, in order to monitor the benefits potentially obtained on syringes.[5]

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

One important aspect to reduce the interaction between biodrugs and silicone and consequently the risk of protein-silicone aggregation is the dimension of silicone droplets applied on the glass surface.

Thanks to the research conducted we were able to identify several potential silicone profiles with a new silicone atomisation based on reducing the overall dimension of silicone droplets.

A key phase in the process was setting the air pressure and the air activation to have a better atomisation and smaller silicone droplets.

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

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

## CONCLUSIONS

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

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

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

## ABOUT STEVANATO GROUP

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

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

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# CHALLENGES AND KEY CONSIDERATIONS FOR THE STERILISATION OF PREFILLED SYRINGES

**As the prefilled syringes industry has grown and matured, so too have sterilisation techniques adapted to keep pace with innovation in syringe design and production process, and with new regulations. In this article, Jenni Hollinsworth, of Isotron (the Sterilisation Services division of Synergy Health), describes the various sterlisation options available, recent trends and developments, and the implications of current and forthcoming regulations.**

The parenteral drug industry has grown in recent years with the development of new treatments and formulations to treat a wide range of acute and chronic conditions. In tandem with this growth has been the increasing sophistication of the packaging, including prefilled syringes and disposable injection devices. The market has moved in this direction for a number of reasons, including ease of drug administration, additional security, lower contamination risk and ease of use for non-healthcare professionals. [1]

Prefilled syringes have actually been around for more than two decades. The European market for prefilled syringes is relatively more mature compared with the US market. However, the market for prefilled syringes has seen healthy growth as the pharmaceutical industry has grown and become more sophisticated. Amongst the major challenges for manufacturers, is the problem of interaction of prefilled syringes with the drug, which causes concerns regarding stability. Manufacturers need to eliminate the interaction between drugs, packaging and sterilisation technologies, and processing and quality assurance control are therefore vitally important. [2]

"THE RISK OF INFECTION FROM THE DEVICE PLUS THE CLEARLY DEFINED REQUIREMENT FOR TERMINAL STERILISATION OF DEVICES HAS MEANT THAT REGULATORY BODIES AND MANUFACTURERS ARE INCREASINGLY LOOKING FOR WAYS TO STERILISE THEIR COMBINATION DEVICES TERMINALLY."

With recent developments in advanced drug delivery systems, manufacturers and contract sterilisation providers are now required to work more closely together than ever before to find a satisfactory sterilisation option for these devices. A new generation of prefilled syringes offer a unique challenge to all parties as the regulatory environment requires that they conform to both pharmaceutical and medical device standards for sterility assurance. The contract sterilisation industry has been able in most cases to adapt its processes to handle current requirements through the use of microbiological control and new sterilisation techniques such as Electron Beam. However, going forward, regulatory changes are being looked at to make the process more adaptive.

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## CHALLENGES FOR DRUG DELIVERY SYSTEMS

Medical device manufacturers do not have the same challenges as their pharmaceutical counterparts, as devices are normally manufactured using plastics, metals or other materials that are easily adapted to terminal sterilisation. Sterility assurance is obviously still critical for this market and standards have been developed and unified over the last 30 years, which clearly outline how conformance to medical device sterilisation standards can be undertaken.

The latest version of ISO 11137: 2006, "*Sterilisation of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilisation process for medical devices*", defines the requirement to conform to a sterility assurance level (SAL) of $10^{-6}$ using irradiation as well as the microbiological tests required to achieve this.

The development of the drug delivery systems for complex diseases offers challenges to manufacturers about how to conform to both approaches. Whilst pharmaceutical manufacturers can follow either path, the risk of infection from the device plus the clearly defined requirement for terminal sterilisation of devices has meant that regulatory bodies and manufacturers are increasingly looking for ways to sterilise their combination devices terminally.

A number of approaches have been developed over the last 10 years by manufacturers and their sterilisation providers to find ways of sterilising the devices whilst not adversely affecting efficacy. These include:

- Electron Beam processing.
- Reduced irradiation dose (exposure) due to clean manufacturing.
- Temperature control and inert atmospheres.

## DIFFERENT STERILISATION OPTIONS

The pharmaceutical approach to understanding microbiological risk through Quality Risk Management (QRM), using ultra-clean and consistent processes has stood the test of time whilst avoiding the need for terminal sterilisation. This approach has developed largely due to the issues associated with using the main industrial sterilisation techniques of Gamma irradiation and Ethylene Oxide gas.

These high-energy processes involve free-radical production which has always caused problems with the efficacy of the drug. In the case of Ethylene Oxide, the addition of heat and steam and residual safety concerns has made this technique non-viable. However, terminal sterilisation using Gamma radiation has remained an option for pharmaceutical manufacturers and is used in some cases.

### Electron Beam Processing

Over the last 20 years, the developments of 10 MeV sterilisation beams (which are commercially viable and used by a large proportion of the medical device industry) have created new options for pharmaceutical manufacturers. Time is the main advantage of this technique as the sterilisation dose can be applied in a matter of minutes, as opposed to the hours needed for Gamma irradiatiom. This reduction in exposure time directly correlates to a reduction in free radical generation and the negative effects that this causes to drugs and medical plastics.

The use of Electron Beam for drug-eluting stents has been common for many years. In addition the use of shielding, thin product target areas (pizza box shapes) and orientation of products to the beam have allowed maximum doses to be controlled to relatively low levels of around 40 kGy.

### Reduction in Irradiation Dose

Historically, contract irradiation plants have processed medical devices at dose ranges in the region of 25-40 kGy in line with medical device requirements set out by the industry and the Association for the Advancement of Medical Instrumentation (AAMI) (www.aami.org) in the 1970s.

The development of ISO 11137 over the last 15 years (which outlines the requirement to undertake microbiological testing) has, however, opened the door for a reduction in processing doses. This standard allows devices with low bioburden to be sterilised by minimum processing doses of 15 kGy, or even lower in some cases, and through regular auditing of bioburden. As such the efficacy of the sterilisation dose can be maintained whilst conforming to the standard.

### Temperature Control and Inert Atmospheres

Even a 5-10% increase in temperature seen during Gamma and Electron Beam processing can cause degradation in some cases, so this needs to be checked during validation of the process. However, it has been proven that keeping the product at a reduced temperature through the use of dry ice prior to and during irradiation (Gamma only), helps to protect the drugs from the effects of free radicals and dampens the chemical reactions these cause in the drugs.

A major negative effect of the Gamma and Electron beam sterilisation technique is the production of the highly reactive compound, ozone, which occurs through the ionisation of air. The use of sealed packaging filled with inert gases, such as nitrogen, stops or severely reduces the production of ozone in the proximity of the drug and reduces the potential damage to efficacy even at doses of 25 kGy using Gamma.

A consideration with both temperature control and inert atmosphere approaches is control of packaging and shipping, cost of manufacturing, and the ability of the sterilisation provider to handle either low-temperature products or the risk of handling pressurised containers.

The methods outlined above have allowed combination devices to be manufactured and sterilised routinely for many years. However, the expected large increase of these products over the next 20 years, along with the complexity of drugs and devices, has meant that manufacturers and contract sterilisers are looking for a new regulatory route to make terminal sterilisation easier to achieve.

## KEY CONSIDERATIONS

It is important that the manufacturer gets input from the contract steriliser at an early stage of development to ensure that the prefilled syringes can be sterilised using an appropriate technique.

Other areas for more detailed consideration are:

- Drug stability with chosen sterilisation technique.
- Development trials to establish processing parameters and product limitations.
- Packaging configuration – orientation during sterilisation.
- Temperature sensitivity and transportation requirements.
- Timelines between manufacturing, sterilisation and delivery to market.
- Regulatory compliance: UK MHRA, US FDA and other notified bodies.

## FUTURE REGULATORY CHANGES

A major discussion within the industry relates to the fact that SALs (security assurance levels) of $10^{-3}$ or $10^{-4}$ are commonplace for vaccines and other pharmaceuticals produced by aseptic processing. This has therefore opened up a potential for the industry to select the appropriate SAL for a healthcare product scientifically, rather than taking the arbitrary $10^{-6}$ currently used by the medical device industry. This SAL of $10^{-6}$ is seen as overkill in some cases rather than a level required for safe use.

The subject of drug device systems continues to be an area of interest for all related industries. The International Irradiation Association (iiA) (www.iiaglobal.org) sponsored three workshops on drug combination devices held in San Diego,

CA, US, in December 2006, in Washington DC, US, in June 2007 and in London, UK, in 2008. These workshops brought together experts in the field of medical device manufacturing, sterilisation, drug development and regulatory approval to review the technical and process challenges associated with drug-device combination products, many of which are outlined earlier in this article.

## CONCLUSION

The development of drug delivery systems which require terminal sterilisation has meant that the contract sterilisation industry has needed to develop ways of processing drugs through tight control of dose, bioburden, irradiation source and packaging, whilst not aversely affecting the efficacy of the drug. These techniques allow manufacturers to routinely sterilise drug delivery systems.

With a detailed understanding of all medical device and pharmaceutical sterilisation requirements, from design to regulatory compliance, Isotron offers support and guidance to a diverse range of medical device manufacturers. Combined with an appreciation of the importance of sterilisation services to your business, Isotron endeavours to operate as an extension of your organisation, enabling you to offer a regulatory complaint and cost effective product to the market.

## ABOUT THE COMPANY:

With more than 30 years' experience, Isotron is the partner of choice for providing sterilisation solutions, validations and support services to the medical devices industry, including the prefilled syringes industry (Figure 1). Through a network of 19 sites (Figure 2) in nine countries across Europe, Asia and South Africa, Isotron operates the three principal sterilisation technologies of Gamma, Electron Beam and Ethylene Oxide. A schematic of the Electron Beam processing plant at Daventry, UK is shown in Figure 3.

In addition to the core technologies, Isotron also operates a network of laboratories to satisfy the microbiological needs of the industry. With a solid foundation of technical expertise and involvement with standard development and industry working groups, Isotron is uniquely positioned to provide an experts' insight into sterilisation technologies.

## REFERENCES:


1. *Kifford, Tracey 2006, Prefilled: The Future for Parenterals? Packaging Gateway.*
2. *Frost & Sullivan 2005, Future of Prefilled Syringes: Manufacturer's Perspective – Challenges and Opportunities.*


**Figure 1: With more than 30 years' experience, Isotron has the technologies and expertise effectively to sterilise complex drug-combination devices such as prefilled syringes.**


**Figure 2: As a multinational supplier of sterilisation services, Isotron employs a global network of experts.**

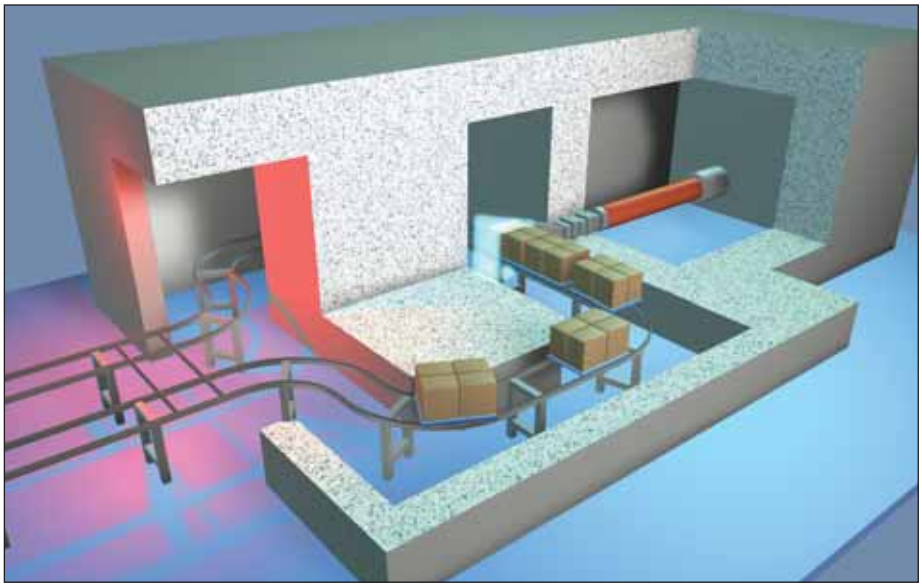

**Figure 3: A schematic of the Electron Beam processing plant at Isotron, Daventry, UK.**

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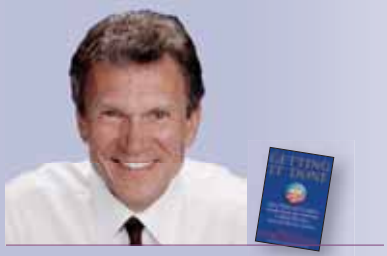

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# Dividella

Pharma Packaging Technology

# LINE IT UP THEN FILL IT UP!
## DEVELOPMENTS IN THE PACKAGING OF PREFILLED SYRINGES

**The prefilled syringe is an increasingly attractive presentation for both new and established parenteral pharmaceuticals and vaccines. In this article, Andrew Longworth, General Manager of Körber Medipak UK & Ireland, explores how innovative carton packaging solutions can enhance this presentation whilst meeting the stringent requirements of both product protection and environmental sustainability. He analyses recent developments in the packaging of prefilled syringes for pharmaceutical products and considers trends for the future.**

Biotech products are becoming increasingly important because of their extraordinary pharmaceutical potential. Even today, 45% of new approvals are for drugs that contain biotechnological additives. This trend will continue to strengthen in the future. In the next few years, a total of 200 new approvals are expected on the world market.

The active ingredients of biotech products are often too unstable to be incorporated into solid pharmaceutical products (tablets or powders). Well over 90% of these products are therefore packaged as liquids in syringes, vials or ampoules. Since the products are distinctly more expensive than other pharmaceuticals, they must be packed as securely as possible. Moreover, the products have to be transported in a precisely defined temperature environment. Special "cold-chain logistics" are needed to ensure that a product is transported at the correct temperature from manufacture through transport, and storage to administration.

Many pharmaceutical companies produce and market a wide range of products worldwide. The different demand in the respective market and product segments therefore requires a highly flexible packaging system which can handle a wide range of different items and, at the same time, provide optimal product protection. It is also essential to guarantee efficient, low-cost packaging of small, medium and large lot sizes.

Other requirements of a modern packaging system include item and code checks (vision systems), printing and checking of variable data, the shortest possible machine set-up times and compliance with GMP standards.

### THE PREFILLED SYRINGE

Since its introduction in the mid-1970s, the prefilled syringe has gained wide acceptance. This acceptance is based upon lifecycle benefits that can be identified as follows:

- The prefilled syringe is simple for healthcare professionals to handle. The risks of spillage, contamination and ampoule cuts are reduced or eliminated. Furthermore, the potential risks of misidentification or dosage error are greatly reduced.
- The potential risk of needlestick injury, associated with all methods of injection, is greatly reduced by the addition of a safety needle device to the syringe. The availability of such devices enables compliance with current and envisaged legislation.
- Self-administration by patients on long-term therapies is practical.
- For the pharmacist, requirements for storage, preparation and ultimate disposal are simplified.
- For the pharmaceutical manufacturer, the prefilled syringe offers advantages in both marketing and distribution.
- For the prefilled syringe there is no overfilling required, as it is filled with less drug substance per dose than a vial or ampoule, hence leading to significant cost savings.

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**Figure 1: A TopLoad carton for prefilled syringes**

Prefilled syringes are being used more, so that syringe application of liquid pharmaceutical products at the doctor's surgery, by nursing personnel or patients, can be more simply and reliably handled. In the simplest case, it is necessary only to remove the needle protection prior to injecting the drug. There is no longer any need to break off the heads of ampoules, with the possible ensuing injuries, or for troublesome handling of vials or syringes.

The reduced logistical costs which can be achieved with optimised packaging solutions represent another argument in favour of prefilled syringes.

## REQUIREMENTS OF THE PACKAGE

All packages must safeguard the product throughout its route from manufacture to final point of use. The package must also convey sufficient information to ensure that the product is used correctly. Each package provides the vital link between manufacturer and consumer; it is an essential component of the product itself.

The prefilled syringe is an example of a high-value product that must be safeguarded throughout a long shelf-life and yet be readily and accurately used whenever required. The proper selection of the package and the attention to its design will promote the benefits of the product in addition to fulfilling these fundamental functions. The syringe is not viable without a primary package.

The package must enable rapid access to each of the prefilled syringes it contains, and must remain intact until the last of the syringes has been removed, if that last syringe is to be safeguarded. The printing of the package will clearly present essential product information. Further features may confirm that the syringe is untouched until required for use.

A re-closable package can be retained for subsequent use without difficulty (Figure 1). If the package contains a course of treatment for a single patient, features to assist dosage compliance are appropriate. If the contents are to be used over an extended period, opening features that release only one syringe at a time can assist the user (Figure 2). In other cases, prefilled syringes are packed individually, as shown in see Figure 3.

Concerning the logistics of distribution, costs are affected by the volume of the package itself. Where the product must be held in a temperature-controlled environment, it is particularly important to adopt a package of minimum volume relative to its contents. Minimising package volume also benefits storage immediately prior to use; for example in a hospital pharmacy.

The immense cost pressure within the medical sector encourages the increasing trend towards self-medication. The branch of liquid pharmaceuticals is also drawn into this development with the use of prefilled syringes on the increase. They are not only easy and safe to handle by the patients themselves, but are also favoured by both doctors and hospitals. The potential dangers involved with breaking the ampoule are therefore avoided. Another important factor for this development is found in the low logistical costs which, thanks to optimal packaging solutions, are easily accomplished.

## FOCUS ON PACKAGING COSTS: CARDBOARD VS PVC

Inevitably, over the last few years, sober economic considerations have put the spotlight on packaging costs. Indeed, pressure on costs is affecting the packaging industry in particular. Some companies only take the costs of packaging materials into account, whilst others have a more holistic approach, which also encompasses operating and investment costs, personnel, set-up times, the cost of format parts and material losses.

A good example is Dividella, which has been able to demonstrate cost benefits in terms of the packaging material alone. Dividella's NeoTOP solution, which comprises a flat blank and partition, both cardboard (see Figure 4). It wins out against PVC blisters and the additional horizontal folding box which is required. The key principle is, that the more product in the folding box, the greater the cost saving.

One of the reasons for this is the low volume of the pack in comparison with PVC blisters (see Figure 5). One study by Dividella has shown that savings of up to 30% in volume are possible, if using the NeoTOP concept for disposable syringes. If this is applied to the annual production of just one product, it corresponds to considerable financial savings. If the product has to then be refrigerated until it reaches the patient, a smaller pack is another major cost benefit.

However, looking at packaging costs alone is short-sighted; the greater benefits lie on the machine, or rather the process side. These include:

- Only one installation instead of a thermoforming machine and a cartoning machine.
- No thermoforming process.
- Fewer personnel required.
- Setup in 30 minutes.
- Packaging of mono-material/independent of changes in oil prices.
- Higher machine efficiency.
- Flexibility in machine allocation.
- Retrofitting/conversion of installations is very

**Figure 2: TopLoad carton with side-opening feature**

**Figure 3: Unit TopLoad carton for outputs of 240 cartons per minute**

**Figure 4: Flat blank and partition from which the TopLoad carton is formed**

**Figure 5: TopLoad carton *vs* Blister for a combination of products**

simple thanks to machinery's modular construction. Figure 6 shows the TopLoad cartoner, Dividella NeoTOP 804.

## COUNTERFEITING PROTECTION & TAMPER-EVIDENT SEALS

Dividella has been concerned with guaranteeing originality for many years and has solved the problem quite simply by applying a spot of hot-melt in the right place. If the box has been opened, this is immediately apparent to the user – and it involves virtually no extra machine costs and has no effect at all on performance.

## COUNTERFEITING PROTECTION AS LIFE INSURANCE

Biotechnology products in particular require a lot of effort to produce and are therefore expensive to manufacture. However, the risk of these products being counterfeited or manipulated is unfortunately omnipresent and has already become a major issue on some continents. If a counterfeit product is used for cancer therapy, or even for antibiotic therapy, the consequences for the patient could be fatal.

Concepts relating to guaranteeing originality and counterfeit protecting have been developed, which can also be implemented in the short term on existing packaging solutions. An invisible code for the pack, and product and information on usage ensures the necessary security – and also permits effective "track and trace".

## ENERGY AND ENVIRONMENTAL FACTORS

Until very recently, it was seriously frowned upon to discuss the energy and environmental aspects of a packaging concept. The argument

**Figure 6: TopLoad Cartoner Dividella NeoTOP 804**

frequently given was along the lines that the topic had no resonance among the management … but, personally, individuals clearly see the importance of the topic and the advantages of addressing it.

Today, if a manager in the pharmaceutical industry were to try to sweep this topic under the carpet, it would certainly not be advisable – for the following reasons:

- Energy costs are rising – a difficult variable to predict.
- Production costs (including packaging costs) are clearly a competitive advantage.
- Customers decide whether packaging is environmentally friendly.
- Costs of disposal are rising.
- Major consumers such as hospitals will exert pressure.

For example, Germany's Federal Office for the Environment has made figures available that clearly show that merely to manufacture one kilogram of PVC in granulate form generates the equivalent of 2.2kg of $CO_2$ and requires approximately 500 litres of water. Today these figures perhaps do not mean much to us, but in the medium term these values will become an instrument for industry regulation.

Managers in the pharmaceutical industry make a far-reaching strategic decision when they opt for mono-material solutions and give them preference over PVC and paperboard variants. However, this decision is likely to bring commercial advantages, both in the day-to-day packaging process and in terms of greater systems flexibility.

One point is absolutely clear – switching over existing products packaged in PVC without question involves considerable effort. But the market looks at things differently and asks whether, in the long term, the potential short-term savings of not switching can be sacrificed in view of longer-term lower costs and greater flexibility from making the switch?

## CONCLUSION

We have seen that the prefilled syringe is of increasing importance because of the range of benefits it confers throughout its lifecycle. The packaging needs of the prefilled syringe are rigorous as it must perform safely and effectively. The TopLoad carton more than meets these packaging needs, whilst enhancing the benefits of the prefilled syringe.

The distinguishing advantages are the low volume, the easy user handling, low production costs and the high flexibility of the packaging solution. Furthermore, the small volumes are reflected in the low transport costs within the cooling chain.

There are a number of additional advantages, such as opening the packaging from the top (top loading), meaning that the user has an immediate overview of the remaining product. The leaflet or information brochure can be extracted without any problem, and can be read and placed back. The packaging is suitable for printing additional information on the package interior and exterior, and needles or vials can also be integrated into the package without any problems.

Opening protection is provided either by the opening mechanism itself or by means of additional relevant labels. These packaging systems also widen their remit through being not only suitable for syringes (with or without needle protection), but also for pens, injectors, inhalers and other similar products.

## ABOUT DIVIDELLA:

Within the KÖRBER MEDIPAK Group, as specialists in the development and manufacture of machinery for the pharmaceutical industry Dividella has established itself as the centre of competency for parenteral product packaging.

Starting from your products and specifications, our team of packaging specialists design complete solutions and above all solutions which are suitable for machine use. Ampoules, injection bottles, complete syringes, cylindrical items or other products which are difficult to stack, such as tablet blisters and patches – whatever the problem, you will always find the right TopLoading solution from Dividella!

As the leading systems supplier for innovative wallet machines, we also develop handy

# Dividella

Pharma Packaging Technology

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## THE INNOVATIVE AUTOMATION PROFESSIONALS

Dividella's packaging lines are in use worldwide and are known for their problem-solving and customer-specific design features.

They are applicable throughout the range of production volumes, from <1 million to >24 million packs/year as shown in Figure 7.

These are complemented by product characteristics such as operating safety, a high degree of reliability, user-friendliness, short conversion times and fast format changes.

Packaging systems with all the advantages of series production.

The system packs developed by Dividella are erected on the packaging line from supplied flat blanks, then filled and provided with a tamper-evident seal. Mono-material packs produced in this way provide for:

**The Patient:**
- overview (leaflet/Product)
- easy access
- re-closable

**Production:**
- 100% verification after loading
- optimal product protection
- quick and easy format changes

**Marketing:**
- cardboard on both sides printable
- brand recognition
- sustainability

**Regulation:**
- tamper-evident closing
- product-protection RFID etc.
- security options

**Logistics:**
- flat carton and partition blanks
- compact package dimensions
- low material and logistics costs

The creativity of the packaging development centres at Rondo, our sister company, and Dividella from the basis for your packaging solution. This is how our combined efforts produce highly functional solutions which can be produced efficiently on modular packaging machines. Depending on your requirements, the packs can be produced manually, semi-automatically or fully automatically. Joint development by Rondo and Dividella ensures that our products combine a high degree of functionality and maximum productivity.

Dividella's unique platform concept, based on a tried-and-tested modular system, allows customised automation solutions to be built.

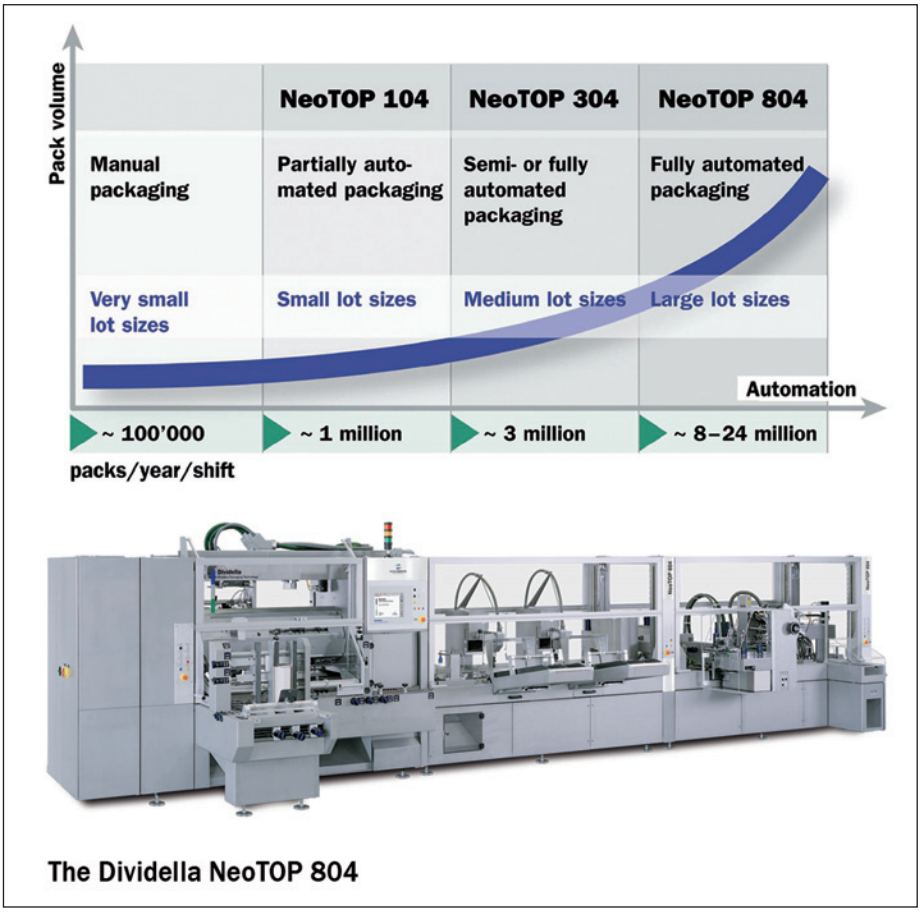


**Figure 7: Packaging solutions across the product lifecycle.**

Mechanical packaging lines, which include process elements such as carton forming, carton transport, item feed, item handling, pharma-standard code and presence checks, insertion of patient information leaflets and the application of variable data, help ensure your projects are highly efficient.

## DIVIDELLA FEEDING TECHNOLOGY

One of the most difficult tasks involves a gentle, flexible feeding system for items such as syringes, vials, pens, softblisters etc. In this area, Dividella is able to apply a very wide range of feeding technologies.

On the basis of Dividella's many years experience of object handling, we have developed new modular feeding systems. This means that up to 500 objects per feeding unit per minute can be packaged; before they are inserted they can also be aligned, spread and individually checked.

Apart from the actual pharmaceutical products, placing inserts can present major challenges. The handling of inserts is a critical area, especially in the case of high-output machines such as the Dividella NeoTOP 804, which can produce up to 240 packs per minute. Dividella has developed a wide range of scalable feeding systems for this purpose. Consequently, very large, thick inserts can be fed in at full speed, using minimum labour.

In recent years, Dividella has developed many different customised feed systems, linked to upstream machines – for pens, prefilled syringes, plungers, soft blisters etc.

Dividella feeding systems are also used successfully by its sister company MediSeal which specialises in thermoformers. These synergies ensure that systems are used in many different situations, field-tested and further developed to guarantee maximum operational reliability.

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3. *Guidance for Industry and FDA Staff - Medical Devices with Sharp Injury Protection Features, US FDA, August 2005.*
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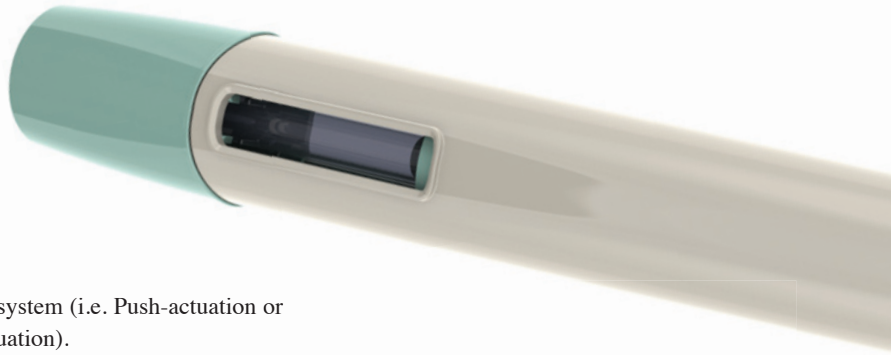
bespak Injectables



Bespak Injectables specialises in the design, development and manufacture of innovative devices for delivering injectable drugs. Benefitting from a programme of user-assessments and designed to accommodate prefilled syringes, Bespak Injectables' auto-injectors enable patients and other non-clinicians to easily undertake comfortable, safe injections.

## OTS™ DISPOSABLE AUTO-INJECTOR DEVICE

Based on the patented ASI™ auto-injector technology platform, the OTS™ auto-injector is designed to incorporate a 1ml 'long' prefilled syringe with staked needle. Bespak Injectables can supply the OTS™ auto-injector within short lead times for user assessments and clinical studies, as well as for commercial supply.

## OTS™ AUTO-INJECTOR OPTIMISATION

The innovative design of the OTS™ auto-injector and its associated manufacturing systems provides both a standardised product and devices adapted to a partner's needs in relation to:

- Operating system (i.e. Push-actuation or Button-actuation).
- Injection volume.
- External device geometry.
- Liquid viscosity.

Variation of injection volume is achieved within the existing OTS™ auto-injector design, thus offering a range of dosing options without the costs associated with extensive re-design and replication of production systems. In addition, a simple means for tailoring the external geometry of the OTS™ auto-injector device makes it possible to vary ergonomic and aesthetic features of the product, whilst avoiding time-consuming and costly device customisation programmes.

Building on Bespak Injectables' considerable experience with delivery of viscous formulations, the OTS™ auto-injector can also deliver viscous drug products which may otherwise prove difficult to inject without risk of damage to syringes.

## OTS™ AUTO-INJECTOR APPLICATIONS

As well as providing a cost-effective delivery device for specific drugs, the OTS™ auto-injector can support the delivery needs of drug product pipelines and lifecycle management programmes.

The OTS™ auto-injector is one of a number of injection technologies developed by Bespak Injectables. For more information on these technologies, or to discuss your specific requirements, please contact Bespak Injectables using the details below.

## ABOUT BESPAK INJECTABLES

Bespak Injectables (formerly The Medical House PLC) was acquired in 2009 by Consort Medical PLC. Consort operates state-of-the-art medical device manufacturing facilities in the US and UK and its Bespak division is a leading supplier of drug delivery devices to global pharmaceutical industry clients. At its 650,000 square-foot facility in the UK, Bespak manufactures over 450 million medical devices each year.

In addition to its patented drug delivery device technologies, Bespak offers comprehensive design, development and manufacturing capabilities taking device projects from early stage development through to commercialisation and long-term supply.

| | |
|---|---|
| Syringe | 1ml 'long' barrel |
| Needle | ½ inch; staked |
| Syringe Fill Volume | Up to 1ml |
| Delivery Volume | Fixed dose; up to 1ml |
| Drug Viscosity | Up to 40 Cps* |
| Actuation Mechanism | Push or Button |

**OTS™ Disposable Auto-Injector Specification**

Bespak Injectables' ASI™ auto-injector platform can deliver liquid viscosities in excess of 40 Cps. Please contact Bespak Injectables for further information.

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