

PREFILLED SYRINGES

INNOVATIONS THAT MEET THE GROWING DEMAND



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“Prefilled syringes: innovations that meet the growing demand”

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Full contact information appears alongside each article. Contributing companies would be delighted to hear from interested readers directly. ONdrugDelivery would also be very pleased to pass on to authors, or answer as appropriate, any queries you might have in relation to this publication or others in the series.

Contact:

Guy Furness, Managing Director

T: +44 1273 831 370

E: guy.furness@ondrugdelivery.com

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INTRODUCTION

The use of prefilled syringes is a modern way to apply parenteral drugs. With the achievements in science and technology in the past twenty years an increasing number of injectables apply prefilled syringes. The benefits compared with vial-disposable syringe concepts are obviously convenience and ease of handling as well as advantages in safety and a reduction of drug overfill.

The currently existing market of prefilled syringes is in the range of US\$1-2 billion. The growth rate is to be expected to remain at a high level of more than 10% annually.

In the future, the pharmaceutical and biotech industries will ask for prefillable drug delivery systems for valuable potent drugs. Particularly, for biologicals the parenteral application will remain the most important route of application.

These valuable new drugs will need application systems that allow for accurate dosing and safe handling. There will be an increased use of drugs in home-care situations, which will result in a need for prefilled syringes, given the inherent benefits in convenience and safe handling.

In this publication you will find a compilation of papers that cover a broad range of topics on prefilled syringes. Descriptions of

the basic components of prefilled syringes like glass, needle and stoppers are given and special aspects of quality are addressed. In addition, handling and safety issues as well as auto-injector features are described. One article deals with manufacturing and outsourcing strategies.

The papers are written by experts in the field, giving an insight into the capabilities and services of their companies.

Overall, this compilation of papers is not covering every aspect of the field of prefilled syringes, but aims to provide the reader with a better understanding of this dynamically growing field of parenteral application systems.

The idea to create such a brochure was born at the October 2004 PDA meeting: "The Universe of Prefilled syringes", in Hanover, Germany. The next PDA meeting on prefilled syringes will take place in Munich, Germany, on October 17-18, 2005. For details please visit the website, www.pda.org, or contact Gautam Maitra (maitra@pda.org).

Georg Roessling, PhD
Schering AG
Board Member of PDA



STERILE PREFILLED SYRINGES: MARKET DYNAMICS AND CURRENT ISSUES IN MANUFACTURING AND QUALITY CONTROL

With the potential for filling up to 300 million syringes annually at its facility in Bloomington, Indiana, US, Baxter BioPharma Solutions is the leading parenteral contract manufacturer of prefilled syringes in North America. In order to understand Baxter BioPharma Solutions' expertise in prefilled syringe filling, say Karim Abdelkader, Ryan M Akers, and Michael J Akers, it is necessary to understand the reasoning behind the growth in this market sector and why the bio/pharmaceutical industry increasingly prefers prefilled syringes to traditional packaging in vials and ampoules.

MARKET DYNAMICS

The worldwide prefill market is estimated to be one billion units ¹. Prefilled syringes in the US market have been growing at a rate of 20% per year for at least five years ². Studies indicate that the majority of healthcare professionals are demanding the convenience and safety that prefilled syringes provide ¹.

In addition, conversions into a prefilled syringe system (from a vial) and/or supplementing lyophilised drugs in a vial with a prefilled diluent syringe are becoming more and more apparent in antithrombotics, vaccines, anti-infectives, and other biotech drugs indicated for chronic conditions such as rheumatoid arthritis, multiple sclerosis, psoriasis and Crohn's dis-

- for home use; easier in emergency situations
- reduction of medication errors, misidentification; better dose accuracy
- increased assurance of sterility
- better use of controlled drugs such as narcotics
- lower injection costs—less preparation, fewer materials, easy storage and disposal
- elimination of vial overfill for products transferred to syringes for direct injection or addition to primary diluents
- removal of preservatives (i.e. thimerosal) from vaccine formulations
- product differentiation

Most lyophilised drug products are filled into vials. While options such as dual-chambered delivery systems are on the market and

continue to be created, such devices are not compatible with many lyophilised protein drugs because of increased silicone exposure when the rubber

ONE OF THE MOST CHALLENGING ASPECTS OF SYRINGE QUALITY CONTROL ENSURING CONTAINER/CLOSURE INTEGRITY.

separator is activated to mix diluent with powder. For silicone-sensitive proteins, the protein product lyophilised in the vial and the prefilled diluent syringe is a best option to assure long-term and reconstituted protein stability.

At Baxter BioPharma Solutions, our offering for prefilled diluent syringes has been enhanced. We have streamlined the approach to process

The primary driving factors behind the growth of prefilled syringes include:

- ease of administration; more convenient for healthcare professionals and end users; easier



Karim Abdelkader
Marketing Manager



Ryan M Akers
Senior Marketing Communications
Associate

T: +1 812 355 7136
F: +1 812 332 3079
E: ryan_akers@baxter.com

Baxter Pharmaceutical Solutions LLC
P.O. Box 3068
927 S. Curry Pike
Bloomington, IN 47402-3068
United States

www.baxterbiopharmasolutions.com

validation for prefilled diluent syringes – resulting in time, cost, and resource savings. In addition, we have established Drug Master Files for prefilled diluent syringes (bacteriostatic water for injection, water for injection, and saline). With a Drug Master File already in place, we can readily fill and kit diluents with your lyophilised product. The enhanced prefilled diluent syringe offering may result in significant savings in costs and resources and accelerate your drug products into the marketplace.

QUALITY CONTROL CHALLENGES

Like any other sterile dosage form, major quality challenges for syringe filling include achievement of and maintenance of sterility, assurance of freedom from particulate contamination, and freedom from pyrogenic contamination. Quality control also includes assurance of drug product potency, identity, safety, and stability³. However, one of the most challenging aspects of syringe quality control is the assurance of container/closure integrity during and after filling and terminal sterilisation.

The standard test to evaluate the container/closure integrity of a syringe involves challenging the syringe container/stopper interface with micro-organisms in very high concentrations. A suspension of at least one million cells (1×10^6 cfu/mL) of *Brevundimonas diminuta* (0.3 to 0.5 μm in size) is prepared and into this suspension are placed several sterile trypticase soy broth filled syringes. It is important to process the syringes and plungers just as they would be processed during normal manufacturing (for example, sterilisation, storage and shipping conditions) in order to capture any potential changes in the tightness of fit of the closure interface with the container.

The syringes are cleaned and incubated for one week at a temperature range optimal for the challenge organism to proliferate. Positive and negative controls are prepared and incubated along with the challenge syringes. After the incubation period, the challenge syringes are inspected for bacterial growth in comparison with the positive and negative controls.

If the controls are acceptable and the challenge syringes are sterile, the criteria of the container/closure integrity challenge are met. Meeting these criteria provides assurance that the integrity of a sterile syringe product will remain intact during normal production conditions as the extremes of vacuum and pressure are a worst case set of conditions.

Dye challenges are also performed with similar stresses to determine any leakage where the dye will penetrate into syringes filled with clear solutions. The dye test uses the same procedures

as the microbiological test, except that coloured dye is used rather than a suspension of microorganisms, and the syringes are either empty or filled with product. The physical dye test should correlate with the microbiological challenge test (i.e. poor container-closure integrity should fail both tests).

CONCLUSION

The future of prefilled syringe usage worldwide is projected to increase with the movement towards more potent dosage forms and home-use products. The need for precise dosing is met with prefilled syringes, whereas vials add a level of manipulation to the administration process, not to mention cost.

Syringe processing and quality control requires unique techniques providing significant challenges to the syringe manufacturer, including the need to demonstrate sterility assurance via sound container/closure integrity testing techniques as described in this brief article.

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PREFILLABLE SYRINGES

TRENDS AND GROWTH STRATEGIES

The pharmaceutical and biotech industries have seen a remarkable growth in the demand for prefilled drug delivery systems over the past ten years. Not only have prefill volumes now reached over one billion, but also the range of drug delivery technologies has expanded significantly. Glenn A Thorpe, Director of Marketing and Business Development at BD Medical - Pharmaceutical Systems, a division of BD (Becton Dickinson), explains how BD, during its long history and with wide experience, has maintained its position of strength in the sector.

MARKET GROWTH AND THE LESSONS LEARNED

Today, prefills can be introduced at any point during a product's lifecycle to make it more desirable. Switching from vials to prefilled syringes, syringes to a nasal spray or a self-injection system, prefills can work easily for products in development and those already on the market. At the same time, drug delivery systems must evolve and adapt to meet tomorrow's demands. Prefilled syringes have many advantages – medical, marketing, and manufacturing – that help drive their growth in popularity.

MEDICAL ADVANTAGES

Healthcare professionals benefit from accurate, pre-measured doses, reduced dosing and medication errors, and reduced risk of microbial contamination. Prefills are convenient for emergency use and have potential for duplicate peel-off labels, which facilitate patient charting. Single-use prefilled syringes typically do not require preservatives. In fact, in studies conducted by BD recently, nine out of ten healthcare professionals preferred prefills to conventional needles and syringes.

MANUFACTURING ADVANTAGES

Another key advantage is that prefills require less overfill. For example, for a 0.5 ml vial, the USP recommends 20-25% overfill. In contrast, for a 0.5 ml BD Hypak dose, required overfill is less than 2%. As a result, potentially 18-23% more doses can be produced.

Simple and flexible processing formats make prefills easier to incorporate into a pharmaceutical company manufacturing line. BD manufactures prefilled drug delivery systems at our six plants worldwide - in France, the UK, Mexico, Japan, Singapore, and the US. BD has expert staff dedicated to supporting our products around the globe. We developed the world's largest prefill supply chain with the knowledge and flexibility to deliver a customisable solution when and where our customer needs it.

MARKETING ADVANTAGES

Not only do healthcare providers prefer prefills, but BD healthcare products are also accepted and well known globally. BD products can be found in virtually every hospital in the US and many overseas. This enables BD associates to gather first-hand knowledge from the end-users of the current drug delivery practices, healthcare trends, and obstacles that a drug delivery system may face. This real-time exposure gives us a unique opportunity to develop products for our customers that will be well accepted by their ultimate recipients – end-users, doctors, and other healthcare professionals.

WHAT YOU NEED FROM YOUR PREFILL PARTNER OF CHOICE

In our division's 40-year history we have learned that it is not enough simply to deliver a quality prefilled device. BD goes much further in helping the customer to select the product that specifically fits its drug or vaccine's need and is well accepted by patients. We provide our



Glenn A Thorpe
Director, Marketing and Business
Development

European contact:
Laurence Grassano-Raymond
European Communication Specialist

BD Medical - Pharmaceutical Systems
11, Rue Aristide Berges
38800 Le Pont De Claix - France

T: +33 4 76 68 36 36

US Contact:
Glenn A Thorpe
Director, Marketing and Business
Development

BD Medical - Pharmaceutical Systems
1 Becton Drive MC 407
Franklin Lakes, NJ 07417

T: +1 800 225 3310

www.bdpharma.com



Figure 1: Examples of BD prefilled products

customers with service, technical support, regulatory, R&D, and clinical expertise, as well as marketing support worldwide.

TECHNICAL SUPPORT AND REGULATORY EXPERTISE

We believe that anticipating customer questions and prompt attention to their requests is an essential part of a well managed and successful business operation. We provide expert advice with quality planning, design and development to ensure our products meet the physical, chemical, and functional specification requirements. Our quality requirements are assured through process validation, process control, and in-process and end-product testing.

Our specialists provide advice in choosing suitable component material for customer applications. To accomplish this, we create project teams to help develop innovative solutions, assist our customers in process design and validation, collaborate with machine suppliers, and work with a range of contract manufacturers.

Our regulatory experts assist our customers in their dialogues with the regulatory authorities and supply the necessary information to meet regulatory requirements worldwide, in addition to providing access to the Drug Master Files (DMFs) and Technical Dossiers for product registrations.

R&D AND CLINICAL EXPERTISE

In order to provide our customers with innovative drug delivery solutions, we conduct extensive clinical studies and have the flexibility to develop a customised product that lets them meet specific end-user needs.

MARKETING SUPPORT

We conduct multiple market research surveys with the drug manufacturers, end users, and healthcare professionals to support customers' market research needs. We also closely track therapeutic areas to understand fully the pharmaceutical marketplace and stay ahead of the changes in healthcare practices.

KEY PREFILL INNOVATIONS

BD Medical - Pharmaceutical Systems markets a broad range of customisable, prefilled solutions for parental drug delivery. We develop these products with a global vision of both the pharmaceutical process and end-user functional requirements and have a full array of the prefilled drug delivery systems available for the customers worldwide.

Our key product is the BD Hypak™ glass prefilled syringe. During the development of this product line, we concentrated on needle performance improvements, introduced latex-free formulations and expanded customisation options for the syringe components such as plunger rods and backstops. We also developed the isolation technology-friendly BD TSCF™ advanced stopper packaging for sterile pharmaceutical processing. Our nasal spray delivery system, BD Accuspray™, is another example of BD Hypak line extension. It offers a unique drug delivery route to our customers while remaining an easy-to-process and familiar product. BD Sterifill SCF™, a premium plastic prefilled syringe system in BD Crystal Clear Polymer, has also been launched. Figure 1 shows photographs of some of these products.

BD's commitment to healthcare workers' safety led to the development of BD Preventis™ – an automatic needle-shielding system, which was launched in 2002. BD Preventis provides a safety solution for staked prefilled syringes.

To improve product handling by healthcare workers further, the company recently launched BD Hypak PRTC with an ergonomically designed tip cap. We also have an extensive array of the self-injection systems created to meet drug manufacturers' and patients' needs. These are full-featured, high-quality products offering reliability and value. Light, compact, and easy-to-handle, BD self-injection systems are in growing demand. We plan to expand our self-injection system offer to our customers while fully supporting this platform with the same level of BD's expertise in drug delivery system development, manufacturing, and processing, that our customers come to expect of all our products.

BD HYPAK PHYSIOLIS™ GLASS PREFILLABLE SYRINGE



Figure 2: The BD Hypak Physiolis

With more than 15 billion needles sold each year, BD has developed significant expertise in needle quality and performance. We produce the world's thinnest and sharpest needles and have worked to find solutions to continue improving patient comfort. We concentrated our continuous research

efforts for those patients receiving subcutaneous injections, the main route for chronic disease treatment requiring frequent injections long-term. The result, our BD Hypak Physiolis syringe, sets a new quality standard for prefilled disposable syringe systems by making injections easier and more comfortable (see figure 2).

The BD Hypak Physiolis syringe features a patented needle-point geometry and a new latex-free needle shield material. The needle has five bevels and, at 29 gauge, is thinner than previous offerings. Its unique design results in a needle point that, while being thinner, is actually stronger. In combination with a new needle-shield material, the BD Hypak Physiolis syringe needle is sharper and penetrates the skin more easily, which enhances patient comfort.

As part of the development process, BD conducted clinical trials of the syringe system to detect and characterize the effect of the BD Hypak Physiolis syringe. Participating nurses reported that it took 70% less force to penetrate their subjects' skin than before. Patients also responded positively: they reported a 40% decrease in perceived pain associated with injection (trial data on file at BD).

BD™ TSCF PACKAGING



Figure 3: BD™ TSCF Packaging

Pharmaceutical industry demand for higher sterility assurance level, withdrawal of preservatives from selected vaccines, introduction of new sensitive drugs incompatible with terminal sterilization, and high speed processing led BD to develop a new safety standard in transfer technologies, BD TSCF (see figure 3).

It is a very simple system to introduce conventional sterilized BD BSCF stoppers into sterile areas. The system guarantees sterility during transfer and transport and is equipped with validated single-use door. It has multi-layer packaging to ensure low particulate levels, and is designed for high-capacity processing. BD TSCF is easy to handle and it does not require bag cutting inside isolators.

BD™ HYPAK PRTC

The tip cap of BD Hypak PRTC is designed for luer lock prefilled syringes (see figure 4).

Figure 4: BD Hypak PRTC
– Plastic Rigid Tip Cap



The device maintains optimum integrity of the syringe tip and the contents. The rigid cap is securely attached to the BD Luer-Lok tip to prevent inadvertent cap removal and the rib tip cap firmly seals the syringe tip aperture.

The unique tip cap design helps healthcare professionals maintain aseptic technique during cap removal. It is intuitive, with a familiar twist-off mechanism, and features a textured cap surface, which facilitates easy opening and removal.

A transparent BD Luer-Lok tip promotes proper needle hub attachment, enabling healthcare professionals to inspect the needle hub connection visually. PRTC is also compatible with conventional and safety-engineered needles.

PREFILL MARKET TRENDS

Clearly the prefill industry continues to grow and evolve with the pharmaceutical and biotech industries market trends, such as continued growth in vaccines, blood-stimulant drugs, and therapeutic proteins; conversion to devices with safety features; shift to unit-dose packaging/removal of preservatives; strong growth in self-injection with very different end-user needs. Other trends

include geographic expansion, evolution of processing and isolation technology, as well as high line speeds (300+ per minute).

At our research facility in Raleigh, North Carolina, US, BD continues to develop technology platforms that can meet the delivery needs of complex drugs beyond what is available today. It is one of the reasons why, over the past 10 years, BD has been able to make great strides in improving the efficacy of drugs and vaccines. From targeted therapies to the broad application and administration of vaccines, millions of patients benefit from healthcare innovations and advances. BD has been at the forefront of the technological development of drug delivery systems that support the progress made in improving patient outcomes.

CONCLUSION

As this article shows, the concept behind BD parenteral drug delivery systems is to continuously improve and reassess its drug delivery products to keep ahead of changes in healthcare. Innovating to meet customer and market demands has made BD Medical - Pharmaceutical Systems the industry leader in prefills.

With more than 100 years of expertise in manufacturing and processing technology for parenteral drug delivery systems, BD understands how best to meet the pharmaceutical industry's delivery requirements for injectable medications. Over the years, we have gained unrivalled knowledge of the prefill concept – its medical benefits, economic value, marketing advantages, technical aspects, and processing requirements. More than 200 pharmaceutical companies have already chosen BD prefillable systems for their injectable products and we continue to develop and provide quality prefillable parenteral drug delivery systems for the pharmaceutical and biotech industry. BD is recognised as worldwide prefill expert because of the unique expertise and experience of our dedicated team.

If your business goals include improving your bottom line with increased sales and more cost effective production, delivery of greater medical and clinical benefits to end-users, differentiation of your product among competitors, or effective break-in to new markets, we would like to offer the BD Prefill Advantages to you and your company.

BD expert teams are ready to work with you to meet your specific drug delivery needs. Please call us to discuss your next project or visit our website www.bdpharma.com for more information. We look forward to hearing from you!

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PREFILLED SYRINGES:

WHY NEW DEVELOPMENTS ARE IMPORTANT IN INJECTABLE DELIVERY TODAY

Within the almost \$100 billion injectables market, one such injection format – the prefilled syringe – is becoming increasingly popular. But, as prefilled syringe manufacturers and fillers are required to deal with an ever-growing number of new types of compounds in new therapeutic classes, they encounter new obstacles, and must devise methods of overcoming them. In this piece, Dr Thomas Brachtendorf and Mathias Romacker, Directors of Business Development at Buender Glas (a division of Gerresheimer pharmaSystems), outline some of the advances and innovations that have enabled the prefilled syringes sector to keep ahead of rapid changes and growing demand.

Some view the injectables market as the traditional, more conventional side of drug delivery. As such, they do not tend to associate it with the level of cutting-edge science and technology that is readily linked with other delivery methods, such as advanced inhalers.

In reality though, the experience of anyone close to the injectables sector would lead them to take a quite different view. The number of injectable products is rocketing – not least because injection is currently the only viable way of delivering many of them. As a consequence, demand for technologies that improve the production, administration, and the experience of receiving injectable products, is strong.

The first products presented in prefilled-syringes were heparins, launched in Europe by Sanofi and Rhône Poulenc-Rorer in the early 1980s. At that time, the prefilled-syringes market was viewed as a relatively insignificant niche area within the huge injectables market. Therapeutically, prefilled syringes were limited to a narrow range of applications in a few vaccines and anticoagulant products. Their use was also limited geographically to Europe.

Initial interest, during the 1980s and 1990s, was sparked primarily by the clear advantages prefilled syringes have over traditional vials and ampoules. The procedure for using a prefilled-syringe product often involves nothing more than removing the syringe from the packaging and injecting the formulation. In contrast, anyone administering a traditional injection from a

vial might typically have to: read the required dose from the physician's dosing directions, withdraw from the vial slightly more formulation than is required, invert the syringe to allow any air bubbles to reach the top, depress the plunger slightly to expel any air and, finally, depress the plunger slightly further still to leave precisely the required dose, which they measure using the scale along the syringe barrel.

Prefilled syringes, with their single-use, disposable format, together with the fact that they eliminate several of the procedures required prior to administering a formulation presented in a vial, are significantly quicker and more convenient. Ease of use, in addition to simply making them more convenient, means that prefilled syringes are safer.

The major safety benefit is the reduced likelihood of dosing errors – which can occur at each of the steps in the vial/ampoule procedure. The fixed dose in a prefilled syringe is filled mechanically and is checked electronically during quality control.

As well as reducing errors in the dose quantity, prefilled syringes reduce the risk of administering the wrong product because the syringe and packaging are clearly labelled with the drug name. For syringes filled at the point of administration, there is a period – between filling and giving the dose – when the syringe can be left full of drug but completely unmarked, on a tray ready to use. This is a danger period since the identity of the drug in the syringe is typically known only to



Dr Thomas Schoenknecht
Director of Business Development

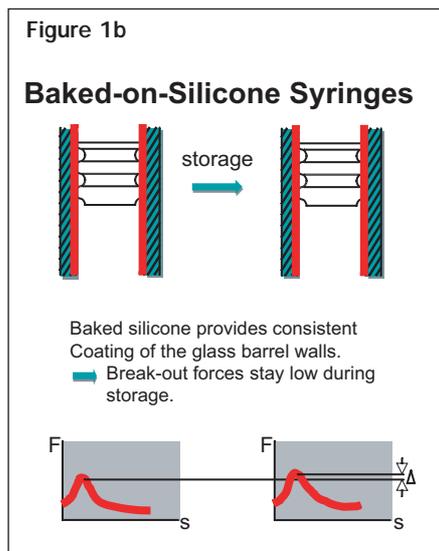
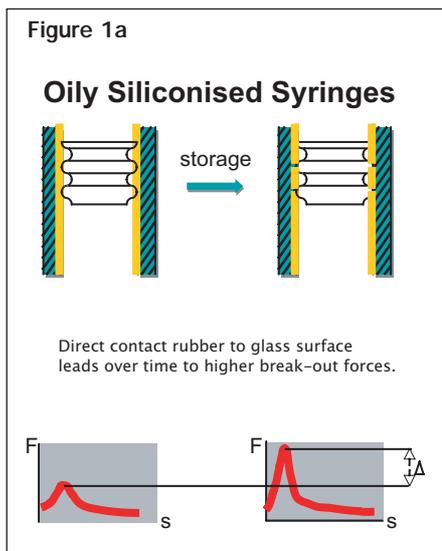


Mathias Romacker
Director of Business Development

T: +49 (0) 52 23 16 44 01
F: +49 (0) 52 23 16 43 16
E: m.romacker@gerresheimer.com

Buender Glas GmbH
Erich-Martens-Strasse 26-32
32257 Bünde
Germany

www.buenderglas.com



Figures 1a and 1b: the break loose effect

the person who filled it and the information only exists in the memory of that person. If they are distracted during the danger period, or are perhaps called away to an emergency and have to hand over to another person the job of giving the injection, there is a real risk of a mistake occurring.

Another safety benefit is the reduced risk of needle-stick injury. Accidents are more likely with traditional formats because the user is required to expose the needle tip for longer, while performing a series of actions requiring dexterity and concentration. The fact that prefilled syringes are single-use devices also eliminates the possibility of cross-infection arising from needle re-use.

Prefilled syringes contain the precise amount of drug that is to be injected, but vials and ampoules have to contain more liquid than the actual dose in order for the correct amount to be withdrawn. The excess formulation is wasted and, especially with expensive biotech products, elimination of wastage allows the manufacturer to make significant cost savings

As demand increased, and the range of viable applications of prefilled syringes broadened, the market began to grow. Notably, the US market, with its shorter history of prefilled syringes, was particularly keen on the advantages this format gave, to the extent that it is now exclusively an RTF syringe market.

The emergence of biotechnology drugs in the early 1990s gave demand for prefilled syringes a colossal boost worldwide and this product class today still represents the highest potential for future growth. In Europe, new drugs that have been presented in prefilled syringes include: erythropoietins such as Recormon and Eprex; interferons like Betaferon, Avonex, Copaxone and Rebif; and rheumatoid arthritis drugs like Enbrel and Humira, to name just a few.

Crucially, biotech provided a late but very

profound entry into the previously untapped US market, where many of the aforementioned products, and many other biotech products, were developed and launched first – often in prefilled syringes.

RECENT INNOVATIONS

The continually increasing demand for prefilled syringes has maintained pressure on manufacturers to devise methods for increasing production capacity and driving down costs. Alongside these ongoing advances, which focus on improving the overall efficiency of the production process, recent trends in the industry, and in the healthcare environment generally, have given rise to several specific innovations that improve the quality of prefilled syringes.

Like many manufacturers, Buender Glas has experienced a rapid expansion in the number of therapeutic classes its prefilled syringe products must serve, and foresees a continuation of this trend. Its novel technologies broaden the range of products that can be presented in prefilled syringes and, crucially, increase the acceptability of prefilled syringes among the patients and medical professionals that use them.

BAKED-ON SILICONE

Among the most important innovations are those that have overcome the compatibility and stability issues that arise when dealing with biotechnology formulations. One particularly common problem has been that such products can react with the oily form of silicone, which is used as a lubricant to coat the sliding components of the syringe.

The propensity for silicone to react with the formulation is dependent on the concentration

of silicone in the syringe and its chemical activity. The latter is determined by the number of terminal hydroxyl groups, which is greater the shorter the silicone polymer chain length.

Baking-on the silicone – which involves heating the silicone-coated syringe to a specific temperature for an appropriate time – results in longer chains that are more closely adhered to the surfaces they coat. Thus the concentration of silicone in the syringe and its chemical reactivity are both reduced and the product's stability is increased.

The second benefit of baked-on silicone is that it reduces the frequency of the “break loose” effect. The effect can occur during storage when the rubber closure, inside the syringe barrel, expands outwards so that eventually it displaces the low-friction silicone coating and comes into direct contact with the inner glass surface (see figure 1a).

The user cannot detect the problem until the point of administration when they try to depress the plunger. Because the rubber closure is essentially stuck to the inside surface of the syringe, a high initial force is needed to shift it. The needle has already penetrated the patient's skin and the tip is positioned in their tissue at this point, so the lack of control as the extra force is applied, and the potential for a sudden movement as the rubber closure is freed up, is clearly undesirable.

As shown in figure 1b, baked-on silicone provides a more consistent coating of the syringe walls, which prevents the expanding rubber closure from touching the glass wall. Lubrication is maintained so that the initial force required to inject using prefilled syringes with baked-on silicone remains consistently low before and after storage.

Syringes with staked-in needles have yet another advantage from the baked-on siliconisation process. Until now, baked-on silicone was not available with staked-in needle syringes since a needle could not be glued into the channel of a syringe after baking process or the baking process itself would soften the glue in the channel, resulting in a bad fixation of the needle.

The key to producing staked-in needle syringes with baked-on silicone lies in the inactivation of silicone located in the channel where the needle will be glued in. For this purpose Buender Glas had developed a patented process.

AVOIDING PH CHANGES

Another challenge has been to prevent the undesirable pH change that sometimes occurs in liquids stored in prefilled syringes. It has been observed in solvent syringes containing water for injection (WFI) or saline solution, in diluent prefilled syringes, which contain WFI for reconstituting lyophilised products, and in syringes con-

taining non-buffered drug solutions. For WFI, the upper pH limit specified in the USP is 7.

The shift in pH occurs because the USP Type 1 glass used in prefilled syringe manufacture is a borosilicate glass, which must be subjected to various temperature changes during the glass tube production process (see Figure 2). Around the beginning of the cooling phase, at 580°C, sodium oxide forms and remains in the glass. During storage, sodium ions are released into the WFI and, as shown in figure 3, increase the concentration of hydroxide ions, thus increasing alkalinity

Sodium oxide is transported during the tempering process to the surface of the syringe glass barrel. Over time, the ions on the inside of the syringe are released into the WFI. This results finally in an increase of the concentration of hydroxide ions, yielding a change in the pH.

Buender Glas has developed an ammonium sulfate pre-treatment process that solves this problem. Ammonium sulphate is sprayed into the glass barrel before the tempering process of the formed syringe is started. During the following heating process, the formed sodium oxide reacts with the ammonium sulphate by forming highly soluble sodium sulphate plus water and ammonia.

A study compared the pH increase in bi-distilled water in an untreated glass syringe with that of water in an ammonium sulfate treated syringe. After being heated to 121 °C for one hour, the pH of the water in the untreated syringe increased from 5.5 to 6.6 while the pH of the liquid inside the treated syringe increased from 5.5 to 5.9. This effect was checked in stability studies and long-term data is expected soon.

INCREASING FOCUS ON THE PATIENT

The general trend in the wider healthcare sector, increasingly to place the patient more at the centre of treatment strategies, rather than focusing purely on their disease, is having a considerable impact on the prefilled syringes sector and prompting new thinking.

The requirement from consumers for more convenient treatments is one of the factors driving the prefilled syringe market en masse. However, this demand for convenience also gives companies within the sector an opportunity to differentiate themselves.

Uppermost in the thoughts of many patients receiving injections are pain and discomfort. The needle is clearly the main component that determines how pleasant or unpleasant a patient finds the injection. Buender Glas has identified three parameter sets that exert the greatest influence.

The first are the basic needle-quality characteristics, such as the requirement for a hook-free

needle tip and smooth surfaces. These are achieved through a validated, reliable production process. Secondly, there are less critical, subtler factors such as the number of bevels at the needle tip, the angle of the bevels and the bevel length. Thirdly, the coating substance and method of application, for example siliconisation, have been recognised as key in determining the pain of injection.

The increase in the number of prefilled syringes being used to self-inject, often at home, is in part a reflection of the trend towards more patient-centred treatments, but equally due to the application of prefilled syringes in new indications, such as rheumatoid arthritis and multiple sclerosis.

Prefilled syringe manufacturers are developing design features that take into account that in diseases such as these, the self-injecting patient is likely to be physically impaired in terms of the force they can apply and their degree of manual control. Relatively simple, though important, new features include a larger finger flange on the syringe barrel and a larger thumb plate on the plunger, to make the device easier to handle.

LONG-TERM VIEW

Looking ahead, the continual progress towards ever cheaper and quicker production processes, which has been underway from the first days of prefilled syringe manufacture, will no doubt continue in the background.

One specific development predicted in the coming years is an increased interest in the use of plastics, instead of glass, for the syringe body. Plastic is already widely used in syringes, but its application has hitherto been limited to large-volume (20-50 ml) syringes for delivering contrast media, for example.

For smaller volume syringes (0.5-2.0 ml) glass is the material of choice. However, prefilled syringe manufacturers are investigating the potential of plastic in their products perhaps for use in certain niche areas yet to be identified. Buender Glas, for example, has a plastic product ready for initial testing.

Finally, the predictions made in the 1990s that invasive drug delivery was nearing its end were clearly somewhat premature. However, those involved in the production of invasive

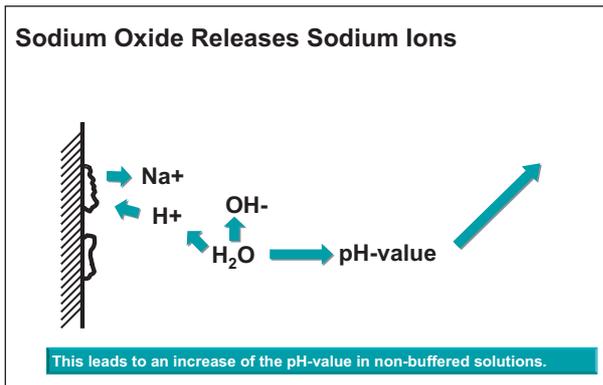


Figure 2: pH shift in all-glass syringes

delivery systems such as prefilled syringes are perhaps mindful that, one day, the predictions are likely to be fulfilled. Like its peers, Buender

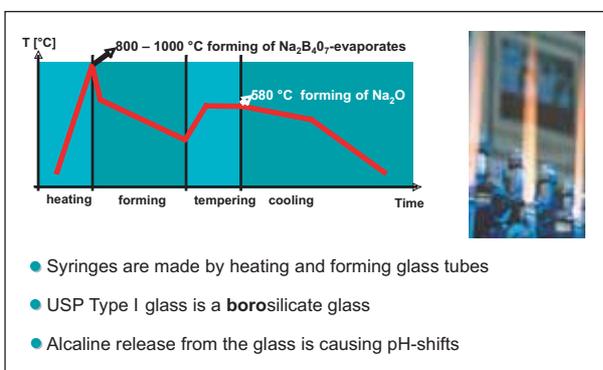


Figure 3: Sodium oxide releases sodium ions

Glas is forging links and building expertise outside prefilled syringes. Indeed, specific applications of its core technologies in the areas of needle-free injection and nasal delivery are already being explored internally and with partners.

CONCLUSION

The examples of innovations given above are just a few among many new technologies and processes that have been adopted in prefilled syringe production. Others involve, for example, increasing further the sterility of the finished product and decreasing the number of particulates found in the formulation; optimising the design, composition and coatings for elastomeric components such as plungers and needle shields; and even ingenious advanced labelling technologies, including peel-off tabs and radio frequency transmitters, to increase product safety and security.

The need for prefilled syringe producers to innovate and make real breakthroughs has never been greater than in recent years. With the market for prefilled syringes estimated to have grown by more than 20% annually in the US since 1999, to reach its current size of \$200 million, and by around 8% annually in Europe to reach \$1 billion, we appear to be rising to the challenge.

THE NEXT GENERATION OF SAFETY PREFILL DEVICES:

NMT'S SAFETY PREFILL NEEDLE UNIT ENTERS THE COMMERCIAL STAGE

In order for it to develop, manufacture and deliver drugs to the market, the pharmaceutical industry must continue to satisfy increasingly tighter regulations. In November 2000, the US implemented the Needlestick Safety and Prevention Law. This was followed up in 2003 by Germany issuing legislation to prevent needlestick injuries and more recently the UK has issued guidance in 2005. In his article, Ian Littleton, Business Development Manager, at NMT Group PLC provides some background on the problem of needlestick injuries, and describes one possible solution from NMT – the Safety Prefill Needle Unit.

A new industry has developed in response to recent legislative changes, to provide safe technology to reduce sharps injuries. Pharmaceutical companies are beginning to adopt this technology and, interestingly, are discovering that the

THE SOLUTIONS ARE OFFERING FAR MORE THAN JUST THE SAFETY BENEFITS THAT WERE INITIALLY EXPECTED OF THEM.

solutions are offering far more than just the safety benefits that were initially expected of them.

In today's pharmaceutical market, medicines are hard to differentiate and the competition increases year on year. Pharmaceutical companies have always utilised packaging as a product differentiator and the application of a safety device provides further opportunities to achieve this. NMT Group PLC is using its experience to provide a solution to the large and growing market of prefill syringes. At present there are no passive safety needle unit devices available on the market to satisfy the needs of the clinicians, pharmaceutical companies and legislative requirements.

NEEDLESTICK INJURIES

In Europe, the number of needlestick injuries is now estimated at one million per annum

(Eucomed 2004). Apart from the trauma of the initial injury, the victim has the potential to contract a fatal disease as there are more than 20 blood-borne pathogens that can be transmitted by a needlestick injury. Of these pathogens,

human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) are of the largest concern and are potentially life threatening. The resultant

costs of treatment, litigation and other direct and indirect costs of a needlestick injury are considerable.

Recent research conducted by NMT with UK nurses in face-to-face interviews found that 100% of nurses interviewed would like a device to stop needlestick injuries and that 64% of nurses interviewed stated that they had suffered from at least one needlestick injury.

LEGISLATION

Whilst the US pioneered legislation to mandate safe needle technology in healthcare settings, the uptake of safety devices for the syringe market has been gradual. Encouragingly, the most recent data from the US would indicate that the rate of needlestick injuries is falling as the implementation of safer devices and safe



Ian Littleton
Business Development Manager

T: +44 (0) 1506 445 000
F: +44 (0) 1506 430 444
E: sales@newmedicaltechnology.com

NMT Group PLC
Unit C2, Fairways Office Park
Deer Park Avenue
Livingston EH54 8AF
Scotland

www.newmedicaltechnology.com



Figure 1: The Safety Prefill Needle Unit

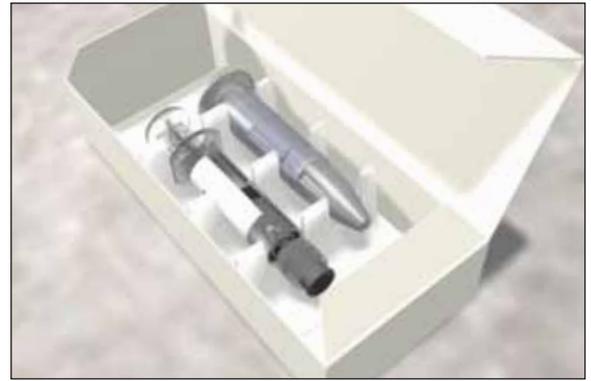


Figure 2: NMT can incorporate many customer-specific options

practice gathers momentum. As the risks of contamination are clearly global, it could be reasonable to expect that many other countries may adopt needle-safety legislation.

PHARMACEUTICAL REQUIREMENTS

In general, pharmaceutical companies are increasingly realising that for new and existing drug portfolios there is a benefit to have a safety device for injectables, to prevent needle sticks. During the last few years NMT has conducted a series of meetings with injectable drug manufacturers to identify the criteria that would form the basis of a “pharmaceutical company wish list” for the ideal device. This wish list is now integral to the design and development of all NMT devices.

PRODUCT AND APPLICATIONS

During 2003, NMT acquired intellectual property for a passive safety needle system – The Safety Prefill Needle Unit – and developed it to be applicable for the prefill syringe market (see figure 1). The flexibility that this unit offers, allows it to be fitted to virtually all non-staked needle prefill syringes and it can be adapted to some staked needle syringes. A key feature of the technology is that NMT can readily incorporate customer-specified options for specific drug pipelines (see figure 2).

The Safety Prefill Needle Unit operates using automatic needle re-sheathing technology, for which the original IP was awarded *preferred* status by ECRI (www.ecri.org). During the process of injecting, the device is automatically activated and a shield covers the needle as it is withdrawn from the skin. This shield deadlocks, aiding in the prevention of needlestick injuries.

NMT’s market research with the Safety Prefill Needle Unit found that 74% of nurses interviewed considered it to be a significant innovation or breakthrough product.

One design criterion requested by pharmaceutical companies was that the safety device

should require little or no training. NMT’s market research has shown that this requirement has been met, as more than 90% of nurses found that the device was both intuitive to use and was used in a similar manner to conventional devices.

PRODUCT VERSATILITY

The Prefill Safety Needle Unit is highly versatile, fulfilling another of the prerequisites from the pharmaceutical wish list. The main body of the device – and hence its operating mechanism – is standardised, whilst the needle length and gauge can be specified according to application, as can the connectors (see figure 3). Furthermore, the design can take into account whether the injection is intradermal, subcutaneous or intramuscular. From a practical point of view it is possible to specify the device to cover the needle completely before injection, which is of particular relevance for needle phobic patients.

NMT is currently developing intellectual property that can provide safety solutions for pen needles, cartridge systems and staked needle prefilled syringes.

Our in-house product design and development expertise allows us to provide bespoke solutions to suit the needs of our customer base. We would welcome any prospective partner to approach us directly in order to allow us to demonstrate our design and development capabilities.

ABOUT NMT GROUP PLC

NMT Group PLC is a licensing and development company for safety needle-based medical devices, including drug delivery systems. Technology such as NMT’s Automatic Retraction Technology and Automatic Re-sheathing Technology ART, has been developed with the objective of significantly reducing the chance of accidental needlestick injury. Since its foundation in 1996, NMT has built up an impressive intellectual property base for safety devices via in-house development, and acquisition. NMT designed, developed and manufactured in high volume one of the world’s first automatically retracting syringes, and has emerged as a global leader in safe needle technology. NMT’s first-generation safety syringe was recognised by the well-respected ECRI group, as the preferred choice.



Figure 3: Various combinations of sheaths and connectors can be specified



OUTSOURCING AS A STRATEGIC DECISION

Pharmaceutical companies these days are under growing pressure from several directions. First, process costs have been rising exponentially owing to stricter criteria for quality control and the growing need for new technologies. Secondly, the standards issued by regulatory authorities the world round have been sharpened over the past years. In order to maintain or expand market shares, pharmaceutical companies are being compelled to devise new strategies to remain competitive. One highly successful option is contract manufacturing or outsourcing, which was very popular in other industries during the 1990s. Max Horn, Managing Director at Vetter Pharma-Fertigung, describes how over the past few years, it has been tried by the pharmaceutical industry with success.

Outsourcing has several advantages. In the short term, for example, it can relieve the strain of a pharmaceutical company while a drug is taking off on the market. If the drug is failing, the manufacturing process can be switched off quickly. Critics of outsourcing for the pharmaceutical industry say that these short-term measures are in fact inefficient, for the most part, and only incur additional expenses. Standard products that are manufactured in large batches need not be outsourced. Specialised products requiring new technologies, however, might be developed faster and with less difficulty by another company that already owns the special skills and equipment.

This approach is far more promising and it avoids having to scramble in the case of a bottleneck or other emergency. A contract manufacturer is sought and hired as part of the company's overall strategic plan. This requires a careful screening and selection process but, in the end, it pays up. One of the crucial criteria for selecting a contract manufacturer is simply experience with outsourcing. The more experience, the smoother the collaboration.

The pharmaceutical company can focus on its main business, namely R&D and marketing, while the contractor takes care of, say, the entire manufacturing process, including validation, license application and packaging. A successful outsourcing partnership will cut expenses considerably.

MEETING THE CHALLENGES

When producing new drugs, pharmaceutical companies face the difficult task of ensuring consistent quality and quantity. During the

launch stage, it is difficult to determine the exact demand for a product, so production and distribution must be managed carefully. To guarantee an adequate supply, a company can look for one or two partners who use the same systems. What if the newly launched drug requires special technology though? A contract manufacturer prepared to set up a back-up production line is the best answer. And if the drug fails, the production facility can be shut down fairly easily. In both cases, success or failure, the company can at least plan with greater security.

THE HARDWARE FACTOR

New systems and technologies are critical cost and time factors in the development of drugs. Indeed, designing and implementing innovative technologies and processes in-house can be an extremely costly business. It can also pose a problem when it comes to calculating investments with any degree of precision. Licensing authorities also have their standards, which must be respected. Here again, a company can only benefit from an experienced contract manufacturer who has all the systems in place and already approved. This guarantees smoother production processes and higher margins of profit from high-priced, high-tech substances improved.

FINANCIAL BENEFITS

Manufacturing drugs – especially new, innovative, “high-tech” substances – involves considerable risk. The first question, already touched upon above, is whether to invest in set-



Max Horn
Managing Director

Contact: Suzan Frohmann
T: +49 751 3700 0
F: +49 751 3700 4000
E: info@vetter-pharma.com

Vetter Pharma-Fertigung
GmbH & Co. KG
Schuetzenstrasse 87
88212 Ravensburg
Germany

www.vetter-pharma.com

ting up a new production facility from scratch, or to rely on the existing facilities and expertise of a trusted partner. Furthermore, no company can say for sure whether its newest product will achieve a breakthrough on the market and when.

The contract manufacturer can alleviate much of the pressure on the company by handling the processes involved in designing and installing facilities. Once the product is launched, the contractor will then be responsible for harmonising production and demand. Indeed, in the event of a boom, the partner can increase production. Should the product encounter problems, production can be simply slowed or halted. Success and risk are then shared. What is important, however, is that overall costs can be better planned.

THE KNOWLEDGE FACTOR

Trial and error are the parents of experience and know-how. When a pharmaceutical company decides to invest energy and money in new and innovative technologies, it will have to take setbacks into account. The learning process demands it. An experienced partner – one with decades in the field and with well-founded knowledge in today's technologies – can help a company avoid setbacks and save money and time. The reason is simple: the contractor, has already gone through the ups and downs of the learning process.

THE OFFICIAL FACTOR

One of the necessary stumbling blocks in the production and marketing of drugs is the state. Regulatory agencies, like for example the FDA in the USA or EMEA, apply strict standards when it comes to manufacturing substances. No matter how effective its products are, if a pharmaceutical company does not have the internal knowledge and experience of working with regulators, it will have to work with a partner with the experience needed to expedite the filing process. This will shorten time-to-market, which is especially critical in the pharmaceutical field. The best partner, of course, is one with filing experience in a variety of countries, since the success of a drug depends on whether it can reach the international markets.

THE POSITIONING FACTOR

When a product is launched on international markets, it will be either as a commodity or a technology. This must be determined at an early stage, since it will influence a company's strategy. The main features differentiating technolo-

gy and commodity products are simple handling that avoids any errors in dosing and guarantees the product's quality and protection from falsification. Many outsourcing firms offer standard products and standardised processes. It might even be worthwhile collaborating with

several providers. A specialised solution is preferable for a company seeking safety and user-friendliness. Choosing the correct system is vital in standing out from the competition, particularly in the technology sector.

For processes and products that require special technology, one will need a partner who can provide a particularly broad range of services. A "one-source" concept reduces time-to-market and the management capacities and skills needed to set the production processes in motion.

FINDING THE RIGHT PARTNER

A long-term partnership must be developed with care and requires the investment of time and money. The preceding paragraphs show clearly that a potential outsourcing partner must meet a certain number of criteria. On the physical level, it must have the technical infrastructure and innovative talent to handle a broad spectrum of projects. This includes dedicated teams to see each project to completion. The partner must guarantee stable and secure production processes that can deliver at all times. It must also have the capacity and flexibility to respond quickly to changes in demand.

On another level, a contract manufacturer must have the experience with global markets and especially with regulatory agencies in key countries. The optimal partner will also be open to work with the company's other partners. Financial stability is also a fundamental criterion if the partnership is to be productive and lasting. The last thing a pharmaceutical company needs is a partner running into financial difficulties and ceasing production. Above all, an outsourcing partner must be independent, meaning that his own brands and products – if any at all – will not create a conflict of interest with its partner's products.

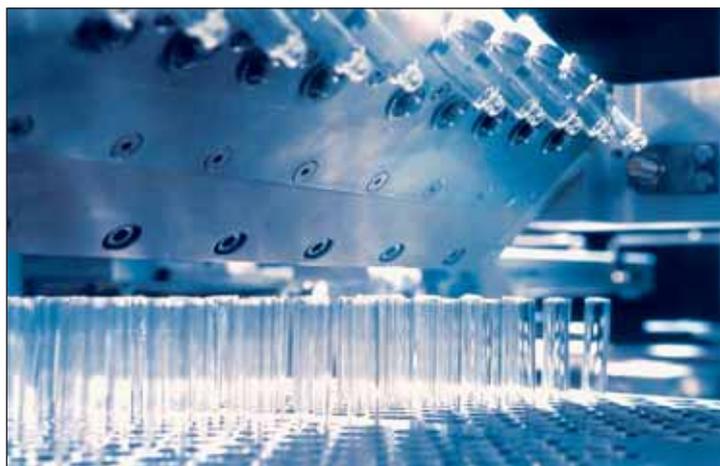


Figure 1: Vetter commercial manufacturing

COMMUNICATION BUILDS TRUST

Adopting a sustainable outsourcing strategy is an important step for a company, and can lead to a perfect win-win situation. But it does make certain demands on both parties. Integrated management is required to make sure each project is being handled properly and communication channels are open. Regular planning sessions must be held to ensure that each party is fully informed of any potential roadblocks. All processes carried out by all parties involved must be carefully documented for future reference. In fact, the best way keep track of a project's progress is jointly to establish performance measures that can be easily quantified using objective data. These are simply best practices. Ultimately, however, a company seeking to outsource production processes will be dependent on its partner, to a certain extent. Confidential information and knowledge is shared. In the end, therefore, the true core of any partnership is trust.

INVESTING IN PARTNERSHIP

For 25 years Vetter Pharma Fertigung, a specialist in manufacturing and related pharmaceutical services, has collaborated and worked closely with leading companies in the pharmaceutical and biotechnology industries in the US, Europe and Japan as a partner in manufacturing and related pharmaceutical services. Vetter's customers rely on our independence and loyalty and benefit immeasurably from our company's experience. Vetter does not produce its own products so can focus completely on the customer. Its state-of-the-art technology with the FDA, as well as that of other regulatory agencies in Europe, Asia and North and South America, and approved products and processes, are proven to help our customers cut costs. This means that new products can be introduced into



Figure 2: Hand fill under flow bench for chamber I

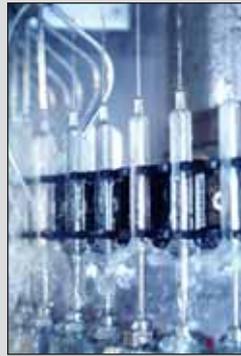


Figure 3: Syringe washing

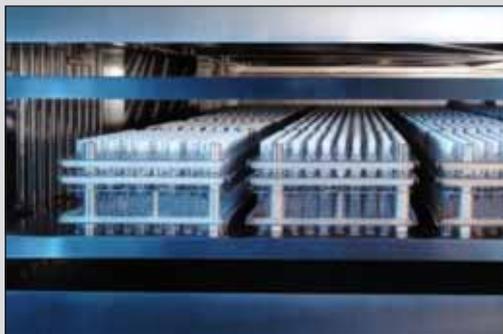


Figure 4: Freeze drying of dual chamber cartridges

the market faster and deliverability is assured at all times.

Vetter is an expert in working with new and highly sensitive products such as monoclonal antibodies, interferons and GNRH-analogues. Vetter's own innovative and patient-friendly solutions are designed to give the partners a competitive edge in all international markets. There is the Vetter Lyo-Ject, dual chamber one-way syringe, for example, or the award-winning tamper-evident needle shield V-OVS NS®. The Vetter Identification System (V-IN®) is another intelligent solution that allows each individual product to be tracked during the entire production process.

In order to maintain its high standard, Vetter invests eight-digit sums annually, as well as expending considerable sums in the continuous training and schooling of its personnel, internally at its own campus as well as at institutes and universities in Europe and the US. These investments are to expand capacity, for example, in new lines for vials, as well as syringes, and, of course, permanently to continue

improving overall quality and maintain state-of-the-art production. Besides investing in its R&D department, Vetter has also invested in enlarging its service portfolio by expanding the offerings from its Development Services.

SUMMARY

Every company must make a fundamental decision when deciding whether or not to outsource. The appropriate marketing strategy for new products must be established as early as possible in Phase I and II. An outsourcing manufacturing decision should always be considered a strategic decision and made within that same strategic timeframe. If this gives rise to a long-term partnership, as it should, it will be a win-win situation for both parties.

It is crucial to avoid spontaneous or last-minute selections of an outsourcing partner. Rather, a company wishing to make outsourcing part of its business strategy should make a selection early on and determine a suitable partner very carefully. Investments on the part of the company are of course also necessary – in the production process and in the partnership. After all, a partner is an ally with whom one shares the ups and the downs of working in a competitive field.



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THE INTRICACIES OF SELECTING AND EVALUATING PLUNGERS FOR PREFILLED SYRINGE SYSTEMS

A syringe system generally consists of a barrel, a needle, and a rod with an elastomeric plunger on the tip. The plunger contacts the drug during administration. In a prefilled syringe system, the plunger may also contact the drug during storage, which may last up to two years. Selecting a plunger for a prefilled syringe system is therefore an important consideration for pharmaceutical manufacturers, who must be aware of issues related to the compatibility of the plunger and the drug, and how the plunger affects the long-term stability of the drug product. Ms Frances DeGrazio, Vice-President, Quality Assurance and Regulatory Affairs, Americas, at West Pharmaceutical Services, explains.

An increasing number of pharmaceutical companies are packaging their drugs in prefilled syringe systems rather than vials. This development is especially evident in Europe and Asia. The prefilled syringe systems typically offer a major advantage – they are user friendly, which may encourage patient compliance, especially for self-administered drugs.

Manufacturers must understand the requirements for prefilled syringe systems included in the FDA's Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics. They should conduct the extractables/leachables testing that the guidance recommends. Further, pharmaceutical manufacturers should consider risk mitigation strategies such as the use of a barrier film on prefilled syringe plungers to minimise interaction between the plunger and the drug product. Finally, they may be able to reduce operational risks by specifying ready-to-sterilise syringe plungers.

UNDERSTANDING THE CONTAINER CLOSURE GUIDANCE

The FDA guidance, Container Closure Systems for Packaging Human Drugs and Biologics, addresses the evaluation of packaging and delivery systems for pharmaceutical drug products. According to the guidance, each NDA and ANDA should contain enough information to demonstrate that a proposed container closure system and its components are suitable for the intended use.

Packaging suitability is based on four attributes: protection, safety, compatibility and performance (function and/or drug delivery). For injectable dosage forms, the guidance specifies the procedures that must be performed to test the interaction between the drug and its packaging components. Associated components, such as those used only at the time a dosage is administered and secondary packaging materials, are also included in the review.

EXTRACTABLES AND LEACHABLES IN PRIMARY CONTAINER CLOSURE SYSTEMS

Primary container closure systems, including components such as syringe plungers, have the potential to interact with the dosage form. Factors that must be considered in evaluating container closure systems include the materials used to construct the components, surface treatments applied to the components, processing aids, the dosage form's active ingredients and excipients, sterilisation and other related processing and storage conditions.

The presence of extractables is determined through artificial means. An extractable is a chemical species that can be released from a container or component material of construction that has the potential to contaminate the dosage form. Under certain solvent, temperature and time conditions, extractables may be generated through an interaction with the closure system.



Ms Frances DeGrazio
Vice-President, Quality assurance
and Regulatory Affairs, Americas.

Contact: Jennifer L Riter
Business Development Manager
T: +1 610 594 3137
E: jennifer.riter@westpharma.com

West Pharmaceutical Services
101, Gordon Drive
Lionville
PA 19341
US

www.westpharma.com

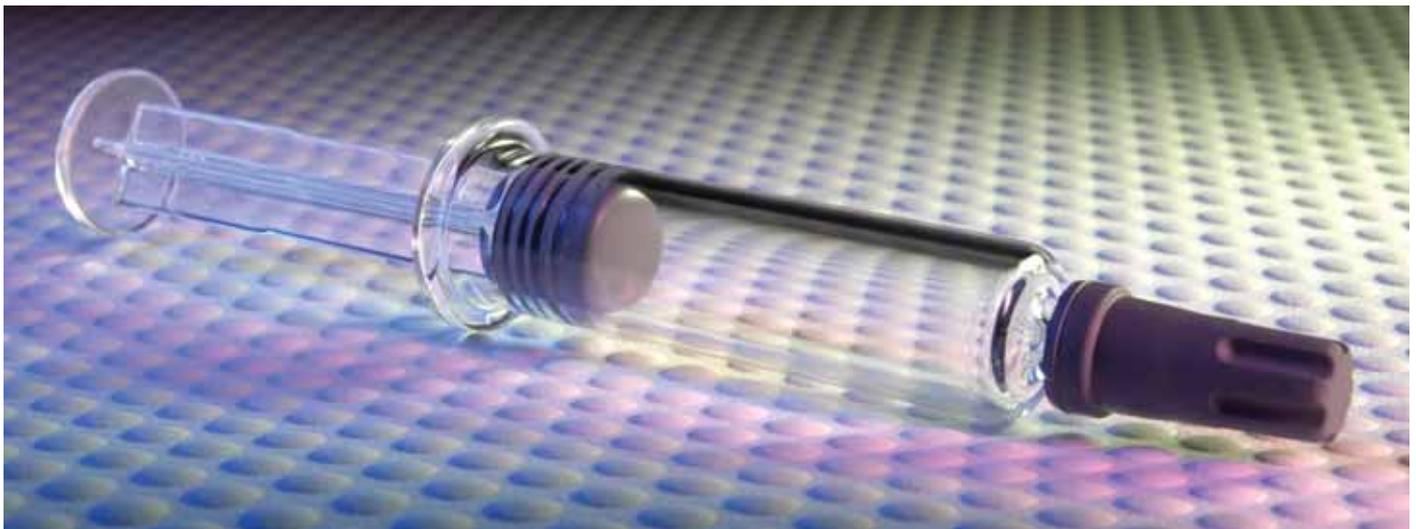


Figure 1: Interaction between the drug and the plunger can affect the long-term stability of the drug product

Extractable testing studies are recommended even if containers or components meet compendial suitability tests. Extensive testing for extractables should be performed as part of the qualification of the container closure system components. Testing under stressed conditions should demonstrate that the extractable profile is acceptable for the specific dosage form and that levels observed will not be approached or exceeded during the shelf life of the drug product.

A leachable is a chemical species that has migrated from packaging or other components into the dosage form under normal conditions of use or during stability studies. Leachables are substances identified in a defined laboratory regimen by simulating use conditions. The industry is focused on potential problems associated with the leaching of species from packaging materials into drug product. Typically, leachables are a subset of extractables.

EXTRACTABLE AND LEACHABLES TESTING CRITERIA

Extractables/leachables testing determines:

That the materials of construction of the container closure system components are safe for their intended use. This is usually done by a chemical analysis for extractables, and if necessary, toxicological evaluation of the extractable substances.

That the container closure system components are compatible with the dosage form by demonstrating that the dosage form does not interact sufficiently with the container closure components to cause unacceptable changes in the quality of either the dosage form or the packaging components. Such reactions might include degradation of the active ingredient induced by a chemical leached from the packaging component or a reduction in the concentration of an excipient because of absorption,

adsorption or leachable-induced degradation.

That the container closure system provides the dosage form with adequate protection from factors that can cause degradation in the quality of the dosage form over its shelf life; these factors include seal integrity and the ability to reseal when applicable.

That the container closure system functions in the manner for which it was designed. This is especially important in respect to prefilled syringe systems, where an understanding and evaluation of functional aspects of the system, such as breakloose and extrusion force of the plunger in the barrel, is critical.

Leachables have the potential to interfere with drug product assays.

For instance, leachables might have the same retention time as a drug in a High-Performance Liquid Chromatography (HPLC) assay.

Leachables also may interfere with medical diagnostic tests, increase the impurity level of a drug product to an unacceptable range or increase the toxicity of a drug product. If leachables react with one or more drug product components, they could cause a precipitate, pH change or other unexpected interaction.

TESTING PROCESSES

Extractable screening during safety studies is an important step in choosing the appropriate plunger for a prefilled syringe. A screening study can minimise the time and money needed for future suitability studies. Because test methods must be specific to the extractable, the laboratory performing the testing must use the cor-

rect techniques. Test methods must be specific to the drug product or placebo in order to evaluate interferences, linearity and other critical factors accurately. In addition, evaluators must test the final packaging/drug combination for leachables during stability studies.

Prescreening procedures should begin with a basic evaluation of syringe plunger options. The protocol can involve multiple temperatures and conditions for acceleration. It should be designed to identify the appropriate plunger candidate for inclusion in stability programs. Identification of extractables can be achieved through analytical testing, such as Liquid Chromatography/Mass Spectrophotometry (LC/MS), Gas Chromatography Spectroscopy/Mass Spectrophotometry (GC/MS), Inductively Coupled Plasma (ICP) and Infrared (IR). Suppliers of these systems may be able to pro-

THE READY-TO-STERILISE PROCESS ALLOWS THE DRUG MANUFACTURER TO FOCUS ON DRUG DEVELOPMENT, NOT COMPONENT CLEANING.

vide some information on testing procedures or the contract laboratory that performs the analysis may have recommended screening methods for use. The testing laboratory can then develop extractable-specific methods and complete validation of them.

Using a plunger for a prefilled syringe as an example, the laboratory would identify a potential extractables list for the rubber formulation composing the plunger. This list would include chemicals that can leach into the product from the base rubber formulation.

These extractables have a direct relationship

with the materials in the plunger. If the laboratory has prior experience with certain potential extractables, previously used methods are chosen for the study. Otherwise, the laboratory will engage in methods development and conduct an assessment to determine the potential for analytical interference, the limits of quantification (LOQ) and typical percentage of recovery of spiked extractables in non-degraded and degraded drug product or placebo.

If there is significant interference during method feasibility testing, such as HPLC column deterioration evidenced by peak fronting, peak splitting, retention time shortening and poor recovery after multiple injections for leachables, the laboratory determines that these leachables cannot be detected by that particular method. If issues with column performance are noted, dilution of the drug product with an organic solvent and cleanup injections between sample injections may be investigated, and analysis of these leachables by other methods with a new sample preparation technique may be attempted.

Sometimes methods development studies are expanded to improve sample preparation before analysis with a particular instrument. In one case of certain leachables analysed by HPLC, it was determined through several organic solvent investigations that client samples require dilution with an equal volume of tetrahydrofuran (THF) to enhance the solubility of the leachables. Samples were then centrifuged at a preset time and speed to allow presence of a clear THF top layer. The laboratory then analysed this layer to allow for proper detection of compounds at required concentrations. It was also determined that the cleanup step between sample injections should be made with acetonitrile to maintain column performance. For some leachables, new sample preparation techniques are investigated.

Once appropriate methods are developed and verified through multiple sample preparation repetitions and varying factors, formal procedural methods are written in detail for method validation.

Methods validation for detection of leachables in placebo or drug product is based on recommended industry practices and International Conference for Harmonisation (ICH) guidelines. A validation plan for each identified test method should be developed and approved by the client. Each plan includes detailed standards and sample preparation techniques, system suitability, validation criteria and pass/fail specifications.

Once the appropriate test methods are validated, samples are analysed for leachables. Then testing of development and stability lots is per-



Figure 2: Each NDA and ANDA must include information that demonstrates that drug container components are suitable for intended use

formed under accelerated and long-term conditions. If leachables are found, a toxicological evaluation should be conducted and routine testing, or testing of the annual stability lot, may be necessary. Typically, three lots of each dosage strength will be tested at predetermined conditions. The leachables testing may be incorporated into the master stability study protocol. This “next phase” testing allows for monitoring of leachables during long-term storage conditions and will assess any negative or positive impacts that may occur with the primary packaging components.

RISK MITIGATION STRATEGIES

Risk mitigation strategies for pharmaceutical manufacturers using prefilled syringe systems include barrier films and ready-to-sterilise components.

Syringe plungers with a fluorocarbon barrier film can help reduce the risk of product loss caused by interaction of the drug and the plunger and the loss of the drug through adsorption and absorption.

A barrier film can:

- Protect the shelf life of packaged drugs
- Enhance drug/plunger compatibility
- Have exceptional lubricity for enhanced machineability and processing

A fluorocarbon film provides an effective barrier against organic and inorganic extractables to minimise interaction between the drug and the plunger and maintain the plunger’s seal integrity. The fluorocarbon film reduces absorption and adsorption of the drug product, an important benefit for maintaining the full strength and shelf life of most drugs. In addition, the low surface energy of the film provides lubricity without the need for silicone oil, eliminating one source of particulate contamination.

THE ADVANTAGES OF READY-TO-STERILISE COMPONENTS

Another industry trend is the growing use of ready-to-sterilise elastomeric components for which the component manufacturer performs the washing and preparation steps usually done by the pharmaceutical manufacturer.

The ready-to-sterilise process allows the drug manufacturer to focus on drug development, not component cleaning, and brings the additional benefit of a standardised process for component preparation. A component manufacturer’s ready-to-sterilise process should be fully validated by pharmaceutical GMP standards and the manufacturing should be completed under CGMP standards.

Items such as cleaning validations of the washer should be completed and a certificate of analysis should be supplied with each wash load.

The certificate of analysis should provide bioburden, endotoxin and particulate test data on each wash load; product should not be released without meeting the standard specifications for the process. Ready-to-sterilise components should be washed in a pharmaceutical-grade washer with a final rinse in USP water for injection.

Final packing of the components into carriers suitable for introduction into sterilisation units is typically performed in a Class 100 clean room. To improve cleanliness, component manufacturers may ship the products in plastic cartons packed on plastic pallets to minimise particle contamination.

CONCLUSION

The FDA guidance, Container Closure Systems for Packaging Human Drugs and Biologics, defines suggested criteria for extractable and leachable testing of container closure packaging components. To obtain this information, pharmaceutical companies may have to initiate testing methods not previously completed within their manufacturing environment. This testing will require time and money that must be built into the qualification and stability studies of the container closure system early in the product development cycle.

Container closure prescreening of plungers for prefilled syringes helps assure their suitability for use with the dosage form and establishes appropriate methodology to test leachables using validated methods. These tests minimise risk and allow for a successful product launch in a timely manner.

Pharmaceutical manufacturers may reduce risks associated with the container closure system by selecting syringe plungers with fluorocarbon barrier film and by specifying ready-to-sterilise components.



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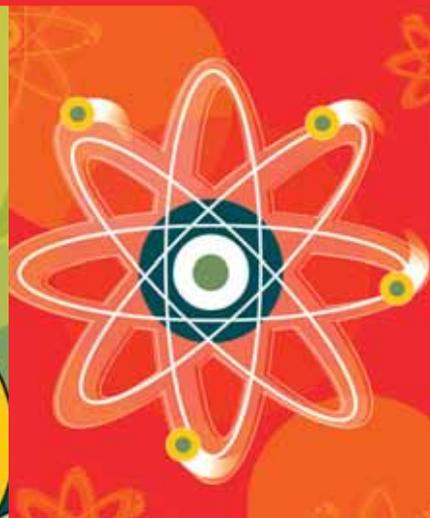
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NEW-GENERATION AUTO-INJECTORS: TAKING SELF INJECTION BEYOND PREFILLED SYRINGES

The market for prefilled syringes continues to grow for the convenient injection of anti-coagulants and a range of biotech products. One area where their convenience is particularly appreciated is by patients who need to self-inject. In this article, Ian Thompson, Manager of Business Development at Ypsomed AG, describes how prefilled syringes are becoming more widespread for self-injection and how Ypsomed has developed and is continuing to perfect auto-injectors to facilitate injections using prefilled syringes in new and existing therapeutic areas.

The market for sophisticated self-injection devices really began in 1984 with the introduction of the first insulin pen injector. Pen injectors are essentially sophisticated syringes, which were developed for the reliable and accurate injection of the first wave of biotech molecules, mainly hormone replacement therapies, such as

insulin (and human growth hormone (hGH) and osteoporosis (PTH – parathyroid hormone) for which pen injection systems have recently been introduced.

The pen injector is a cartridge-based device designed for the frequent (usually daily) manual injection of hormone replacement therapies. These therapies often require weight-based dosing or dose titration and injections are repeated until the cartridge is empty - usually after one or two weeks. The drugs in the multiple-dose cartridges require the use of preservatives, while individual doses are typically 0.5 ml or less in terms of injection volume.

The pen injector patients are accustomed to injecting themselves manually with 29-31G pen needles and the need for automated needle insertion or injection has traditionally been outweighed by the patient's desire for discreet and easy-to-use devices. The market for pen injectors continues to grow significantly (see figure 2) while the whole market for self-injection systems is changing with the increased use of prefilled syringes and auto-injection devices in new therapeutic areas.

ONE OF THE KEY MARKET CHANGES THAT HAS INCREASED THE INTEREST IN AUTO-INJECTORS IS THE DEVELOPMENT OF LIQUID-STABLE FORMULATIONS IN PREFILLED SYRINGES

insulin and human growth hormone (hGH). Today, insulin still dominates the market for self-injection devices, followed by hGH and newer therapies such as fertility treatment (FSH – folli-

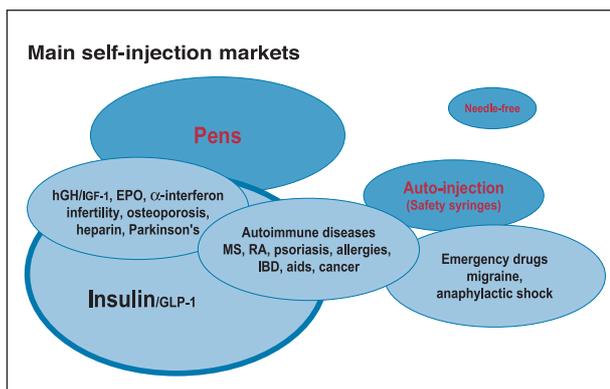


Figure 1: Main therapeutic areas for self-injection devices



Ian Thompson
 Manager, Business Development

Phone: +41 34 424 32 23
 Fax: +41 34 424 31 51
 ian.thompson@ypsomed.com

Ypsomed AG
 Brunnmattstrasse, 6
 CH-3401
 Burgdorf
 Switzerland

www.ypsomed.com

Pen market trends

- Growth of new markets in diabetes and other hormone replacement therapies
- Segmentation of markets requiring different platforms for different patient groups
- Increased interest in disposable pen systems
- Pen needle safety and handling systems
- More sophisticated devices e.g. needle-covers, electronics, automated needle insertion and injection

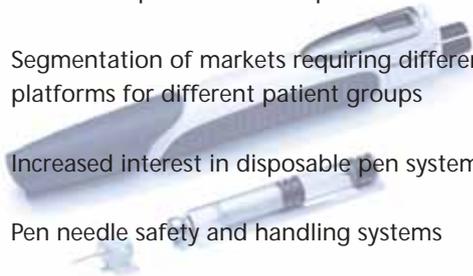


Figure 5: Ypsomed Auto-injector designed for SSI's UltraSafe Passive Delivery System

Figure 2: Pen market trends



Figure 3: Early auto-injectors – EpiPen and Imigran auto-injector

Auto-injectors, as their name implies, automatically insert the needle and perform the injection, and are usually designed for use with fillable or prefilled syringes. Auto-injectors have been on the market as long as pen injectors but their use until the 1990s was restricted to emergency situations such as epinephrine for treating anaphylactic shock (EpiPen®) where the prime focus was less on a painless delivery of the drug, but rather on simply ensuring that the injection was completed. The first prefilled syringe-based reusable auto-injector was launched in the 1990s by Glaxo for treating migraine (Imigran®/Imitrex®).

Reusable auto-injectors have also been used since the late 1980s for syringe-based hormone replacement therapies and increasingly for newer waves of biotech molecules such as alpha-interferon for treating multiple sclerosis (MS). Some of these drugs are injected daily, but many therapeutics – particularly those for treating autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis – are now injected weekly or less frequently.

Most of these newer therapies involve drugs that do not have a preservative (monodose formulations) and comparatively large injection volumes of up to 1 ml. One of the key market changes that has increased the interest in auto-injectors is the development of liquid-stable formulations in prefilled syringes. Other influencing factors are listed in figure 4.

Not only is there more interest in auto-injectors, but their operation and safety features are being improved. Currently marketed auto-injectors do not have complete needle safety as they are generally used with standard prefilled syringes with pre-attached needles. But, in the normal clinical environment, it is the need for needle safety, which has given rise to new safety syringes and other safety devices, which are being fitted to prefilled syringes. Increasingly, patients who self-inject are also concerned about the risks of needle-stick injuries to friends or family in their midst and for the easy and safe disposal of the used product. They look for safety – whether it is a syringe or an auto-injector that they are using.

The first-generation safety syringe devices were “active”, requiring the user to make them safe after injection, whereas the newer “passive” devices automatically provide needle-safety after the injection has been completed. Passive devices not only provide needle-safety but they are injection aids, which make it easier to perform injections.

The passive devices, with their low activation forces, can also be used in conjunction with new-generation reusable auto-injectors. For this reason Ypsomed has teamed up with Safety Syringes, Inc (SSI), based in Carlsbad, California, US, to develop reusable auto-injector technology which is compatible with SSI's UltraSafe® Passive™ Delivery System safety technology (figure 5).

The UltraSafe® Delivery System has the advantage that they can be used by healthcare professionals and patients alike and thus only require the drug company to offer a single stock keeping unit (SKU) for both. If the patient is still fearful of performing a manual injection then a compatible reusable auto-injector can be made available. Recent patient studies performed by SSI confirm that in a daily self-injecting MS patient population, approximately 50% use a prefilled syringe on its own and 50%

use a prefilled syringe on its own and 50% use a reusable auto-injector.

Main factors increasing the interest in auto-injectors

- Reformulation of first generation biologicals → liquid-stable pre-filled syringes
- Needle safety regulations driving need for safety syringe systems and auto-injectors
- Growth in number of new biologicals suitable for self-injection
- Increased competition in MS, RA and psoriasis
- Pressure on healthcare costs increasing need for self-injection



Figure 4: Main factors increasing the interest in auto-injectors

Ypsomed Disposable Auto-Injectors

Main pre-requisites:

- Safety mechanisms: safe activation and locking needle-cover
- Patient feedback: intuitive handling and visual feedback of injection process
- Reliability: injection must be completed every time, very low failure rate required
- Patient population requires close to 100% self-injection
- Costs can be prohibitive: weekly injection or less frequent



Patient Considerations

Main patient considerations regarding self-injection devices

- Lifestyle flexibility, less dependence on healthcare professionals
- Safe, easy and reliable
- Obvious and intuitive handling
- Know that the injection is complete and accurate
- Size, shape and design for use, discreet
- Needle covers to counter needle phobia
- Avoid inadvertent injections or injury
- Safe disposal
- Minimal waste

Figure 6: Ypsomed Disposable Auto-Injector

Figure 8: Main patient considerations regarding self-injection devices

"Scale of convenience"

1 Lyophilised formulation



6 Luer syringe



7 Pre-attached needle syringe



8 Safety syringe



9 Reusable auto-injector + safety syringe



10 Disposable auto-injector



Figure 7: The "scale of convenience" created by prefilled syringes, safety delivery systems and auto-injectors

also use the compatible forming reusable auto-injector.

The obvious gold standard for auto-injectors – where ease of use and convenience are 'king' – is the fully disposable device, where the prefilled syringe is already packaged in the auto-injector (figure 6). The patient only needs to remove the rubber needle cap and press the device against the skin. The device performs the injection and the needle is automatically covered and made safe as the device is removed from the injection site.

Although there has been increased interest in fully disposable auto-injectors, there are none on the market today for use with therapeutic proteins. A key prerequisite is the need for reliability (i.e. a very low incidence of failures), particularly when injecting expensive drugs. Another is that the majority of the injections should be self-administered – healthcare professionals may require needle safety when per-

forming injections, but not a fully disposable auto-injector.

If the injection frequency is greater than weekly the device costs can become a relevant factor, since such auto-injectors consist of more than ten components and cost significantly more than a basic safety syringe. For weekly or less frequent injections the annual costs for the devices become negligible compared with the annual therapy cost.

To summarise, we believe that a "scale of convenience" is being created by prefilled syringes, safety syringes and auto-injectors (see figure 7) with "1" corresponding with the lyophilised drug in a vial and "10" with the fully disposable auto-injector.

A simple prefilled syringe alone can bring much convenience to an injection therapy: this has been well illustrated over the last year following the successful launch by Abbott of Humira® in a prefilled syringe for the treatment of RA. But auto-injectors in combination bring an additional degree of ease-of-use and safety. Therefore, Ypsomed is developing auto-injector platforms that are compatible with increasing levels of convenience which are, in turn, dependent on the drug formulation, the competitive environment, the proportion of patients self-injecting and their specific needs (see figures 8 and 9).

This wide range of needs can only be met with customised designs taking into considera-

Different patients have different needs

- Visual:
diabetes, elderly patients
- Motor disabilities:
MS, RA, cancer
- Age issues:
hGH, osteoporosis
- No handicap:
psoriasis, allergies
- Short therapy duration:
lmw-heparin, infertility
- Emergency situations:
anaphylactic shock, migraine
- Needle issues:
HCV, aids and 10-15% of all patients



tion indication-specific patient characteristics. In particular, patient groups with motor disabilities or cognitive impairments are particularly challenged when having to perform self-injections. To minimize the risk of poor compliance dedicated device ergonomics are developed to make the injection process as easy and intuitive as technically possible.

At Ypsomed our injection devices are exclusively customised for our partners based on patent-protected technology. We develop new platforms and work strategically with our partners to customise technical solutions that complement the lifecycle planning for the individual drug product.

The production of sophisticated injection devices requires a deep understanding of the technical design and manufacturing processes. At

Ypsomed we have more than 15 years of experience working with state-of-the-art moulding and assembly equipment. Our long-term working relationships with contract fillers and syringe and cartridge suppliers are also key with the development of more disposable devices (combination drug/device products). Ypsomed is therefore ideally positioned to provide pharma and biotech partners with a complete service for the growing demand for both pen and auto-injector systems.

Ypsomed develops and manufactures its custom-made injection pens, compatible pen needles and auto-injectors for a wide range of pharma and biotech partners. All products are developed and manufactured in Switzerland, where internal capabilities include R&D, tool making, injection moulding, clean-room production and assembly facilities. Ypsomed provides not only the marketing and technological expertise, but also the production expertise according to the latest regulatory requirements for both low- and high-volume production. Ypsomed manufactures in FDA-registered facilities, is inspected regularly, and supplies devices approved for all leading markets including the US, Europe and Japan.

Figure 9: Different patients have different needs



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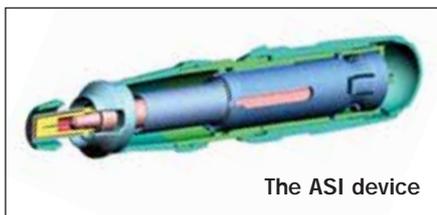
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COMPANY PROFILES



Company Description:

The Medical House (TMH) has developed a range of devices, which enable safe, comfortable and simple self-injection of liquid drugs. Its current portfolio includes reusable and disposable, needle-based and needle-free injection systems. A number of these devices have been



The ASI device

licensed by pharmaceutical companies (including BioPartners and Serono) in order to create a competitive advantage for their products. A

common feature is that these devices are designed to accommodate existing drug presentations and formulations, ensuring efficient regulatory approval processes and timescales.

AUTOSAFETY INJECTOR (ASI) FOR PRE-FILLED SYRINGE

The ASI AutoSafety Injector is a disposable, needle-based delivery device, which incorporates drugs in pre-filled syringe presentation. It provides a completely automated delivery (needle insertion, injection, needle retraction), which achieves a consistent outcome without the need for specialist expertise, making it particularly suited for self-injection. An optimal needle insertion depth ensures a comfortable, complete delivery, whilst the needle is hidden at all times thus addressing patients' injection anxieties. The needle retracts back into the unit after use, permitting a safe and easy disposal of the used ASI. A single use device, the ASI provides a reliable, low-cost, disposable system for the safe injection of liquid drugs.

TMH has a growing reputation for providing innovative, cost effective injection systems

Mr David Urquhart
Managing Director

T: +44(0) 114 261 9011
F: +44(0) 114 243 1597
E: durquhart@themedicalhouse.com

Miss Laura Hancock
Product & Marketing Support
lhancock@themedicalhouse.com

The Medical House Plc
199 Newhall Road
Sheffield
S9 2QJ
United Kingdom

www.tmh-drugdelivery.com

that can be brought to market in short timescales. A customer-focused provider of solutions to the global healthcare industry, TMH can create competitive advantage for any product portfolio.



The goal of Imprint Pharmaceuticals is to provide technologies that transform the performance of injectable therapeutics. Our clients know that with the help of our technology they can develop products that perform beyond those of their competitors. The company was founded by Dr Kevin Maynard and Peter Crocker, who each have over 20 years' experience in the pharmaceutical industry. They have assembled a



The DepotOne tip (above), compared with a conventional needle

world-class team of engineers, formulation scientists, regulatory and clinical personnel with proven ability to deliver products to market. Using this depth of experience, Imprint has

developed unique drug delivery technologies for complex injectable formulations.

The first, DepotOne, is a small needle which can replace large needles. This patented technology enables a small needle to be used in many circumstances where previously an unattractive large needle was required. It can be used for example to: deliver highly viscous materials; reduce the force required to inject (important for elderly and arthritic patients); and reduce the trauma caused by large needle injections. The technology is CE Marked and compatible with all standard syringes, luer hubs, and auto-injection devices.

The DepotOne tip is a half the size of a normal needle with a much smaller cutting blade, and is likely to cause substantially less damage and pain if it does touch a nerve or blood vessel. It transforms the fluidics of a small needle, delivering 50-100 times the fluid under the same conditions as the equivalent conventional needle.

Imprint is also developing new injection devices that have the potential to transform microparticulate formulations by substantially

Dr Kevin Maynard
Director Business Development

T: +44 (0) 1865 811 135
F: +44 (0) 1865 209 044
kevin.maynard@imprintpharma.com

Imprint Pharmaceuticals Ltd
Oxford Centre for Innovation
Mill Street
Oxford
OX2 0JX
United Kingdom

www.imprintpharma.com

increasing the dose that can be injected without the risk of a blockage occurring. Imprint has discovered that there are more than 15 needle-clogging mechanisms, each requiring a different needle design feature to reduce blockages. Many designs are possible, combining different features. Identifying the right needle to use is not simple, so Imprint has developed a unique testing system. Given a particulate formulation, Imprint's analysis can identify the mechanism by which that formulation is most likely to clog a needle and syringe, and thus identify the most appropriate needle design.



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