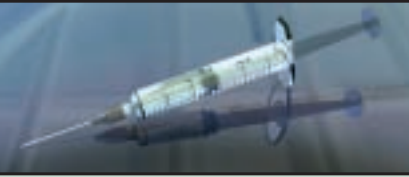


PREFILLED SYRINGES:

DEVICE SUPPLIERS MEETING PHARMACEUTICAL STANDARDS



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“Prefilled syringes: device suppliers meeting pharmaceutical standards”

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INTRODUCTION



PREFILLED SYRINGES: WHERE HAVE WE GOT TO ?

The mood in the prefilled syringes segment was upbeat when I first started writing about it four or five years ago, and it has continued to be positive since. Current evidence shows that the prefilled syringes market is still, and will carry on, expanding steadily.

However, this is not new information for most readers. The major drivers for growth have been written about often, continue to be written about often, and still apply today as they did several years back. (For a quick reminder of the many factors driving the prefilled syringes sector, see the summary box on page four.) So, in this article, instead of going over old ground I want to focus on some of the more recent developments.

First though, just a few reassuring figures to confirm that there has indeed been no let up in the prefilled market's growth since last time we checked! In his article on page six of this issue, Bernie Lahendro, Vice-President of Daikyo Crystal Zenith Technologies at West Pharmaceutical Services, states that over the past three years, unit sales of prefilled syringes have risen almost 22% from US\$1.19 billion to US\$1.45 billion. In an April 2007 article in P&MP, Patrick Grueninger of Schott forma vitrum said: "We see strong movement to prefilled syringes from vials and ampoules on new and existing products with sustainable growth rate between 10-15%." And a recent study conducted by IMS Health and Becton Dickinson predicted growth at more than 12% per year in the prefilled syringes market. In 2006, 1.4 billion prefilled syringe units were sold and this, the study said, would grow to 2.4 billion units by 2010.

AN INCREASINGLY INTERESTING SECTOR

Over the past few years, at the same time as it has become larger and more valuable, the prefilled syringes sector has also become more interesting, on various fronts.

We have seen the numbers of pharmaceutical products launched onto the market in prefilled syringe formats growing, and as such the pharma industry is tending to view these systems, and the technologies and services associated with them, as "market proven". As anyone involved in drug delivery technology partnering will know, a proven market track record is one of the most important boxes that pharma wants ticked before entering into relationships with suppliers and partners.

The prefilled syringe has gained broad acceptance in the pharmaceutical industry – often as the format of choice for many injectable products.

Furthermore, from an initially narrow range of therapeutic applications in the diabetes, growth hormone, heparin and emergency injections markets around ten years ago, the application of prefilled syringes has broadened into the rheumatoid arthritis, osteoporosis, multiple sclerosis, cancer, fertility, anaemia and haemophilia markets, among others.

While the commercial success of prefilled syringes has continued, the anticipated wave of products based on non-invasive drug delivery technologies – especially those for biologics – has still not arrived. Not in a big way in any case. Exubera's launch, which I myself once wrote could signal the opening of the floodgates for systemic pulmonary protein and peptide products, and the dawn of a new age of non-invasive drug delivery, has not registered as the key event it might have been. The lack of a boom in non-invasive drug delivery has, to some extent, left the way clear for prefilled syringes to go from strength to strength.

WHERE ARE THE INNOVATIONS TO BE FOUND?

Earlier this year, at the Pharmaceutical Technologies Arden House Conference in West Point, NY, US, Dr Donna French, Executive Director of Drug Delivery Engineering at Amgen, made the following two observations about current developments:

- Injection devices are becoming increasingly utilised as competitive tools
- Technology advancements are overcoming previous limitations and conventions.

Dr French's presentation was on the topic of parenteral devices generally, but these two points are very much valid for prefilled syringes. The two are also intrinsically linked, as it is often the drive for a competitive edge that brings about the technology advancements we see.

THE ARRIVAL OF PLASTIC

One of the most fundamental changes taking place right now is that the pharma industry is coming round to the idea of prefilled syringes made from plastic, rather than glass. This has been on the horizon for some time – the first polymer syringes, although they were made from polypropylene and thus had their pitfalls, became available in the 1990s.

As is often the case, pharma companies – while happy to talk about the potential benefits of a new idea – moved slowly to begin with. But now instead of just talking about plastic syringes, we are seeing

the pharmaceutical industry act, and real commercial progress is underway.

In summary, barriers that prevented polymer syringes from entering the market, such as lack of optical clarity and questions about shelf life of products stored in polymer containers, have now been overcome. At the same time the benefits that polymer syringes could bring, compared with glass, have been recognised. These include:

- increased resistance to breakage
- elimination of the need for silicone
- reduction in piston release force
- reduction in travel force variation
- reduced risk of leachables and extractables
- lighter weight
- greater potential for adding functional elements into the syringe manufacturing process
- application in a broader range of therapeutic areas

On page six of this issue, you will find more detailed information about plastic syringes from the point of view of one commercial supplier, West Pharmaceutical Services (Lionville, PA, US), which licensed the rights to Daikyo Seiko's (Tokyo, Japan) cyclic polyolefin, branded Crystal Zenith.

Other suppliers of plastic syringes and/or the polymers suitable for their manufacture include: Zeon Chemicals (Louisville, KY, US), which supplies its Zeonex cyclo olefin copolymer; Schott forma vitrum (St Gallen, Switzerland), which manufactures TopPac syringes made from Topas, a cyclo olefin copolymer supplied by Topas Advanced Polymers (Frankfurt-Höchst, Germany); Baxter BioPharma Solutions (Round Lake, IL, US), which manufactures a line of syringes and vials made from a copolymer and branded ClearShot; and BD (Franklin Lakes, NJ, US), which launched its Sterifill SCF line of syringes in 2004. The latter are made from BD's proprietary Crystal Clear Polymer.

INNOVATIVE FILLING TECHNIQUES

Another aspect of prefilled syringes where new ideas are being put into practice to improve the end result is the filling process. One could be forgiven for supposing that syringe filling, as long as it is conducted safely, is – compared with drug discovery or drug delivery R&D, for example – quite a rigid process where it is difficult to think of ways truly to innovate, apart from the obvious angles for improvement such as reducing cost or increasing speed.

It is for this reason that contract fillers naturally tend to differentiate themselves in the marketplace by highlighting the quality of their service – their track record, reliability, robustness, ability to be flexible, deliver on time, offer competitive pricing, and perhaps a network of facilities across the globe.

However, in his article on page 17, Dr Shaun Kinney, Founder and President of Hyaluron Contract Manufacturing (Burlington, MA, US), provides detailed evidence showing significant advantages from employing a different syringe filling method.

HCM's patented method of syringe filling involves online vacuum filling coupled with online vacuum stoppering. Known as Bubble-free filling™, it eliminates the air bubble inside the syringe (known as "head space"), that results from traditional filling methods.

In summary, the benefits that reducing the size of the bubble brings are: more reliably accurate and precise dosing, and increased sterility. Furthermore, totally removing the gas bubble improves the stability of oxygen-sensitive compounds.

Another advantage is that Bubble-free filling is compatible with coated stoppers. This benefit arises from the nature of the filling process rather than anything to do with the gas bubble itself. Conventional filling processes use a rod to push the stopper into place, but this can damage stopper coatings. In Bubble-free filling, a vacuum (or, more accurately, differential pressure) is used to place the stopper.

INJECTION DEVICES AND THE COMPETITIVE EDGE

To those outside the industry – physicians and patients – perhaps the most tangible change that is occurring with prefilled syringes at present relates to injection devices. Over the past few years, a broad variety of auto-injectors have emerged where before they were limited to a few niche applications.

Nowadays auto-injectors are becoming increasingly popular with pharmaceutical companies and

they are proving successful on the market.

Auto-injectors offer patient benefits in two key areas: eliminating the elements of self-injection that cause them to delay or skip their injections; and ensuring proper administration of the drug, explains Mike Kasprick, Vice-President, Business Development, Devices Group at Antares Pharma (Ewing, NJ, US), whose article can be found on page 23.

Dr French's comment mentioned earlier about the increasing use of injection devices as competitive tools goes some way to explain the success of auto-injectors further. If launching largely undifferentiated new pharmaceutical products onto an already crowded market, an innovative auto-injection device offers an excellent opportunity for pharmaceutical companies to gain the edge. And the kinds of features that distinguish one auto-injector from another are not obscure, technical nuances that mean little to patients, rather they are clear to see – operational sequence, safety mechanisms and low-price are three examples Mr Kasprick gives.

Mr Kasprick makes another important and telling point about how things have changed. In the past the feeling was that injection devices were an aid to help the true needle-phobics, "those who were extremely afraid to self-inject", he writes. But nowadays, there is a growing awareness that "most patients prefer products that help reduce the challenges of self-administration they face on a daily basis". The word "prefer" is crucial there, as it fits directly with the point about competition. Today, the choices patients make about their treatment are important and, therefore, so are attractive delivery devices.

One additional area of progress mentioned by Mr Kasprick in his article is that, in order to allow the successful development and commercialisation of a diverse range of auto-injectors, a working group has been set up to work on a draft document and establish ISO standards for the auto-injector industry. One of its main objectives is to ensure that devices will fit the standardised prefilled syringes for which they are designed.

MEETING PHARMA STANDARDS

The title of this issue is "Prefilled Syringes: device suppliers meeting pharmaceutical standards" and this is the essence of the final comment I would like to make about recent changes in the prefilled syringes sector. The point is highlighted by Stelmi in its article on page 10.

Pharma companies, Stelmi explains, used to carry out the preparation procedures for plungers themselves since they regarded these procedures to be part of the pharmaceutical process. Then, suppliers of device components in effect raised their game in terms of the levels of quality and cleanliness they maintained, in order to comply with the requirements of laboratories and regulatory authorities. So, many now supply clients with "ready-to-sterilise" components.

The most recent evolution in this trend is for the component supplier to meet the quality and cleanli-

ness standards and regulations necessary to bring the sterilisation process in-house too. This is what Stelmi has done and it now provides "ready-to-use" guaranteed sterile plungers to its clients.

A similar trend for erstwhile service providers and device developers beginning to work on a more equal footing with pharma is exemplified by the way in which pharma companies are increasingly forging pharmaceutical-type development agreements with device developers for disposable injection devices. Contract manufacturer, HCM, provides another example of players in the industry looking towards the higher end of the value chain. Instead of offering a standard, conventional service, HCM offers a proprietary, patented filling process that even has potential to improve therapeutic efficacy.

CONCLUSION

The examples given in this short commentary, many of which are taken from the more substantial articles that follow in this issue, show that while rising injectable product sales continues to be the underlying engine for growth in the prefilled syringes market, there is a lot more going on than just sales growth. The sector's success means that it is becoming rich not just in the financial sense, but also rich in variety, new ideas and techniques.

AND WHAT ABOUT THE FUTURE?

Mike Kasprick sums it up well: "The trends are quite clear; we will see a growing number of injectable products being launched over the next several years, an increasing number of these products will be self-administered, and the container of choice for many injectable products has become the prefilled syringe."

If the age of non-invasive drug delivery systems had arrived already, much of the focus and investment would have turned away from prefilled syringes in favour of the safer, less painful, simpler non-invasive alternatives. As it is though, innovations have enabled injections to break through barriers (real and perceived) so that they are no longer seen as particularly dangerous, painful or complicated.

Nonetheless, it is important to remember that the success of the prefilled syringes sector – like all areas of drug delivery – is ultimately dependent on the success of the pharmaceutical industry it serves.

Finally, one more undeniable trend in the global prefilled syringes sector that I wanted to highlight here, is the impressive year-on-year growth in attendance that PDA's annual Universe of Prefilled Syringes meeting has experienced in recent years. Perhaps alongside all the sales figures, financial analysis and market modelling, this is just as good a measure of how the prefilled sector is doing? This year's conference takes place in Berlin, Germany on November 27-28, and I look forward to seeing you there.

Guy Furness

Publisher, ONdrugDelivery

DRIVERS FOR GROWTH: IN A NUTSHELL

- Continuing rise in number of biotech compounds reaching the market
- The trend towards home health care and self-injection
- The relative ease of use, and fewer steps involved in prefilled syringes compared with using vials and ampoules
- Reduced risk of needle-stick injury
- Reduced risk of administering the wrong drug
- Reduced risk of giving the wrong dose
- Reduction in overfill and wastage compared with vials
- Better dose precision compared with vials
- Continued lack of many alternative (non-invasive) delivery methods
- Auto-injectors are a good differentiator in crowded market

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THE NEXT GENERATION OF PREFILLABLE SYRINGES: SPECIALISED PLASTICS LEAD THE WAY

For high-value injectable drugs, plastic prefilled syringe systems represent a compelling, cost-effective delivery solution rooted in simplicity, accuracy, durability, flexibility, and quality. Bernard Lahendro, Vice-President, Daikyo Crystal Zenith Technologies writes.

With their ability to provide convenient, pre-mixed, sterile fixed dosages, prefilled syringes are increasingly becoming the delivery vehicle of choice. Prefilled syringes are often considered for makers of vaccines and biotechnology drugs used to treat diseases and chronic conditions such as multiple sclerosis, infertility, osteoporosis, hepatitis, rheumatoid arthritis, oncology, anaemia and haemophilia. Worldwide, over the last three years, unit sales have risen nearly 22% from US\$1.19 billion to US\$1.45 billion.

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

THE POPULARITY OF PREFILLABLE SYRINGES

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

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

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

EXTRACTABLES AND LEACHABLES: THE CONTAMINANT CHALLENGE

To date, most prefilled syringes have used borosilicate glass barrels, rubber pistons, nozzle caps and silicone lubricants. However, glass barrels despite their cost advantages are not without some noteworthy disadvantages such as breakage, flaking glass, and potential pH shifts. Most problematic has been the introduction of extractable and leachable contaminants.

An extractable is a chemical that can be released from a container or syringe component that can potentially contaminate the dosage form. Under certain solvent, temperatures and time conditions, extractables can stem from an interaction within the prefilled container system. Similarly, a leachable is a chemical that migrates from packaging or other components



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Figure 1: A selection of syringes and containers manufactured from Crystal Zenith®

into the dosage form under normal conditions of use or during stability studies.

Unlike a vial, in a prefillable syringe, the drug and diluent are in constant contact with the primary container closure systems (including, for instance, the piston for months or years. With the increasing prevalence of protein- and peptide-based drugs that can bind to the surface of glass surfaces and be more susceptible to degradation from silicone oils, prefillable syringes present design and manufacturing challenges. It is essential to consider the materials used to construct the components, the surface treatments applied to those components, processing aids, the dosage form's active ingredients and excipients, sterilisation processes, storage conditions, and other factors.

To meet the need for lubricity, syringe manufacturers use silicone to coat the elastomers components and glass barrels and have recently started to bake silicone layers onto glass barrels. This is an effort to limit the amount of free silicone that may interact with the drug product. However, pharmaceutical manufacturers have found that too often the result has still been unacceptable levels of extractable, aggregated

contaminants. While there have been no studies showing a measurable loss of efficacy or undesirable side-effects resulting from this aggregation, it has still presented market challenges. Patients often are reluctant to proceed with injections of a product that looks less than pristine (with particles as large as 50 microns in size). This can lead to wasted products and clinical compliance issues.

Pharmaceutical manufacturers have responded to this challenge with the addition of surfactants (polysorbate, for example) that add cost, introduce chemical-interaction uncertainties, and run the risk of denaturing the proteins. These detergents can potentially spawn peroxide at time zero or within six to 12 months, as accelerated conditions frequently used to test pharmaceutical products can often exacerbate the aggregation phenomenon.

Drug product can also degrade when exposed to the tungsten residuals – the leftover traces of metal that remain after the glass-forming processes. During barrel manufacture, heat-resistant tungsten pins are used to form the glass syringe luer cone. Many bio-pharmaceutical companies are finding that tungsten extractables

can cause aggregation in their protein formulations. They are unable to use stacked-needle glass syringes where tungsten tools were used in the fabrication of the glass because the process leaves a small amount of tungsten that reacts with the drug product.

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

PLASTIC SYRINGES: SIGNIFICANT ADVANTAGES

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

Aiming to address unmet market needs, plastics makers developed a new class of thermo-

elastic polymers: cyclic olefin polymers that are as clear as glass but are lighter and less prone to breakage. These resins are also more resistant than polypropylene to water transmission, which lengthens the shelf life of the drugs they contain. One of the most popular is a cyclic polyolefin (COP) called Crystal Zenith (see figure 1).

Crystal Zenith (CZ) provides an impressive array of physical and chemical properties that are attractive to drug makers:

- High heat resistance – autoclavable
- Excellent low-temperature characteristics, including tolerance of freeze drying and liquid-nitrogen exposures
- Easily disposable and environmentally safe – the syringes can be incinerated with virtually no residual ash
- Excellent drainability – CZ offers a non-wettable surface with low surface energy and a contact angle of 80°, compared with 7° for glass
- High break-resistance
- High transparency
- Low extractables – there are virtually no metal extractables from CZ
- Unique solvent resistance
- Wide pH range – from 2 to 12.

Prefillable syringe manufacturers have redoubled their efforts to minimise silicone to facilitate piston action in these designs. With CZ syringes, for example (see figure 2) the manufacturer uses a proprietary fluoropolymer barrier film on syringe components to provide excellent travel force without the use of silicone – and its attendant concerns about leachables and extractables from elastomeric components. The film is moulded to the surface of the piston and inside surface of the nozzle cap and provides an effective barrier against



Figure 2: Crystal Zenith® syringes

organic and inorganic contaminants.

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

Furthermore, as pharmaceutical companies incorporate end-of-line vision systems in their manufacturing process, they are discovering that the silicone oil used in traditional syringes creates a significant increase in the number of in-line rejects.

THE CHALLENGES FOR CURRENT SYRINGE SYSTEMS

The trend toward home healthcare and the associated desire for competitive medical device differentiation has created a very significant opportunity for the adoption of auto-injectors – single-use devices that simplify patient administration. With an auto-injector, the patient typically does not see the needle throughout the administration process. Interest in auto-injectors is expected to grow in the near term as pharmaceutical companies further explore how to differentiate drug device delivery products.

Auto-injectors contain a pre-filled syringe with a staked needle or in some cases, a pre-filled cartridge. The use of traditional syringes

inside auto-injectors, coupled with more viscous pharmaceutical preparations, has created a new series of challenges for auto-injector and device manufacturers, such as the variability of piston release force. Variability can be attributed to dimensional tolerances coupled with silicone dissipation over time. This variability could result in a force that breaks the glass within the auto-injector.

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

CONCLUSION

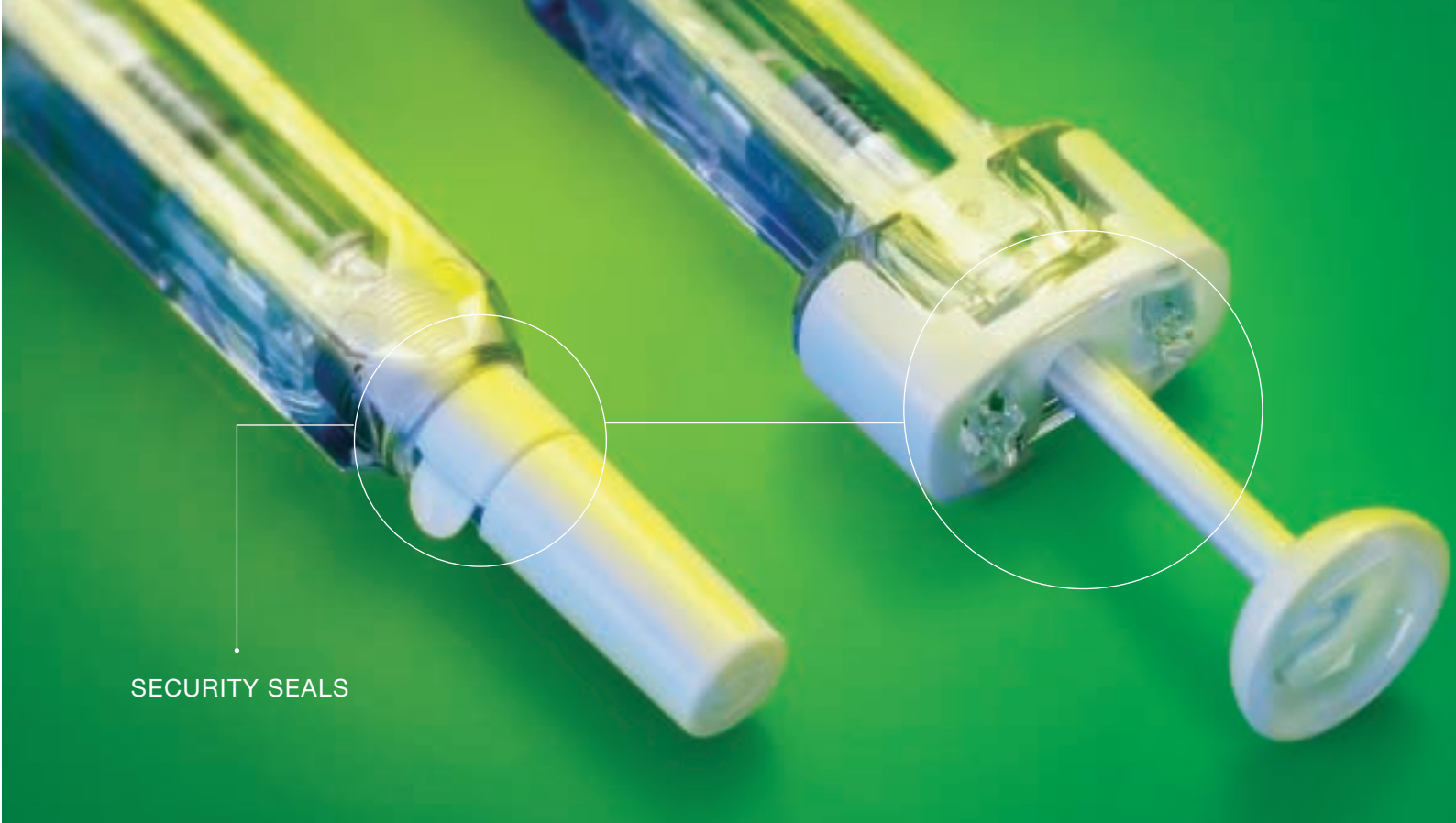
Ultra high-quality plastic syringe systems provide a compelling alternative to existing syringe systems. Through simplified usage, support for new classes of biopharmaceutical products, reduced waste, break-resistance, dosage precision, and the elimination of extractables and leachables, plastic prefillable syringes present attractive benefits that are gaining increased attention from manufacturers seeking new answers to today's and tomorrow's drug-delivery and administration challenges.

Crystal Zenith® is a registered trademark of Daikyo Seiko, Ltd.

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

IDEAL USES FOR PREFILLABLE PLASTIC SYRINGES

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



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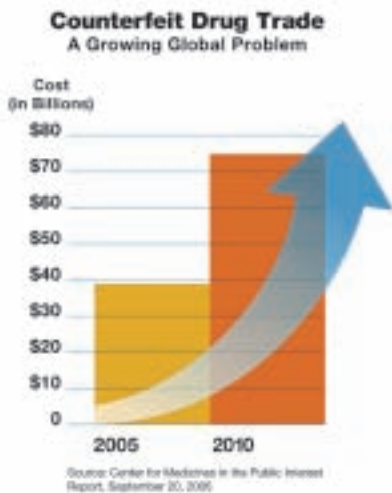
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The counterfeit drug trade is incredibly lucrative and alluring to criminal networks. Leading reports estimate counterfeit drugs to be a \$75 billion industry by 2010, an almost doubling from 2005. As much as 10% of the world's medicines are counterfeit; while in developing countries, the WHO estimates this number at least 25% of the total supply, and as high as 50% in some regions. The potential danger to patients is immeasurable.

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PRE-FILLED SYRINGE PLUNGERS FROM RTS TO RTU: CLEANLINESS & CONVENIENCE

Preparation procedures for the elastomeric closures of parenteral products were previously carried out by the laboratories themselves, as they considered these procedures to be pharmaceutical and part of their entire process. Progress made by the suppliers of primary packaging components has made it possible to obtain a level of quality and cleanliness compatible with the requirements of laboratories and regulatory agencies. These procedures are therefore now largely undertaken by manufacturers of components who generally offer “ready-to-sterilise” products. The follow-up to supplying “ready-to-sterilise” elastomer components is to supply “ready-to-use” items. Since the end of 2003, Stelmi has therefore been offering guaranteed sterile plungers, greatly simplifying use for its clients.

Indispensable validation and revalidation conditions are necessary for supplying sterile components and being able to issue pharmaceutical laboratories with sterility certificates and not merely irradiation certificates.

As one may expect, delegating a key operation such as sterilisation to a supplier requires the highest degree of assurance:

- Documentation proving conformity
- Efficiency of validation procedures
- Quality of components

I. RTU PLUNGERS, THE FUTURE TREND

Apart from the practical aspect and flexibility that it brings, the transfer of washing and sterilisation operations from the laboratory to the supplier of stoppers has several advantages for pharmaceutical laboratories:

- Reduction in the number of human operations.
- Improved productivity: the stoppers (see figure 1) may be used immediately, without any additional operation (time savings and better allocation of resources).
- Economic advantages linked to the reduction of investment in equipment for washing and sterilising components, eliminating the costs of maintaining the validations for these operations
- Reduced stock levels.

Ionising Radiation

Gamma sterilisation has proved to be an efficient means of sterilising stoppers for injectable solutions:

- Ionising radiation has the advantage of sterilising the syringe plungers while they remain in their packaging. Possible risks of contamination (unavoidable at each transfer) are therefore limited to handling when transferring the components to the sterile zone where the drug products are packaged. This may be done by means of a tunnel, in which the exterior of the double packaging is chemically decontaminated before it is removed. Another option is the use of containers equipped with a double port transfer system (Rapid Transfer Port - RTP) for the aseptic transfer of materials and components in isolators. The parts remain fully identifiable and therefore their traceability is assured.
- Radiosterilisation takes place without moisture. Therefore, the stoppers do not have to be dried before use.
- Gamma rays are highly penetrating and can be used for treating whole pallets.
- The exposure dose is well controlled and can be easily recorded.

Compatibility of the elastomer formulation

In a same category of rubber, the irradiation influence on a given property can be substantially dif-

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ferent according to the formulation considered. Indeed the resistance to gamma sterilisation can be modified by the selection of ingredients. Some formulations are therefore more sensitive to radiosterilisation and it is interesting to note that the evolution of the property affected is not necessarily proportional to the level of radiation received.

Thus, the influence of gamma irradiation has to be studied with regard to the mechanical properties, the chemical properties, the functional properties and the biological properties of the formulation for irradiation levels of 25 and 50 kGy, corresponding respectively to one and two radiosterilisations according to the recommendations of the standard pharmacopoeias.

II. THE VALIDATION PROTOCOL

Obtaining “ready-to-use” syringe plungers requires being in control of all applicable pharmaceutical requirements. These requirements mainly affect the finishing steps which are washing and sterilisation. All of the steps of the manufacturing process must be validated in order to ensure the required quality and to demonstrate this quality reproducibility.

1) Validation of washing process

Washing rubber parts effectively requires equipment specially designed for this purpose. Stelmi has therefore developed its washing technology and uses machines of its own design.

The cleanliness of elastomer components is particularly important for pre-filled syringe components, especially plungers where there is a large contact surface between the drug and the plunger and where contact is prolonged. The cleanliness of elastomer sealing systems principally concerns the parameters of visible and subvisible particles, bioburden and endotoxins.

Regulatory requirements mainly concern the quality of the fluids used, the environment and the validation of the procedure.

The quality of water to be used is clearly defined in the Guidelines issued by the FDA and the EMEA.^{1,2} In both cases, it must comply with the “Purified Water”, USP Monograph for the washing and first rinsing operations and the “Water for Injectable Product” Monograph for the final rinsing.

The environment should not allow any recontamination after washing. The sensitive area is packaging, which will take place in an ISO 5 standard classified zone. In order to meet these requirements, Stelmi uses the UltraClean 6 *evolution* washing process for plungers, which allows the highest particulate and microbiological cleanliness to be obtained.

- Washing and first rinsing operations are carried out using Highly Purified Water, EP.
- The final rinsing is in WFI, USP.

Validation is divided into three successive qualification phases, each with a specific aim.

- Installation Qualification (IQ) consists of checking that all the equipment is installed in accordance with the manufacturer’s designs and specifications.



Figure 1: Selection of plungers

- Operational Qualification (OQ) consists of demonstrating that the equipment functions as anticipated under normal and extreme conditions of use.
- Performance Qualification (PQ) is carried out under real production conditions. Its purpose is to show that the product obtained clearly conforms to previously established specifications.

Performance Qualification mainly covers the following parameters:

- Minimum 3 log reduction of bacterial endotoxin contamination (Worst Case Challenge).
- Reduction of particulate contamination.
- Reduction of microbiological contamination.
- Absence of residual detergent.
- Homogeneity of siliconisation.

Qualitative and quantitative knowledge of the microbiological contamination is essential for plungers as contamination not controlled may call into question the validation of the sterilisation process.

In fact, testing particulate and microbiological cleanliness does not just rely on the washing procedure, and all manufacturing processes related to plungers must be optimised to fully limit risks of contamination. This optimisation allows contamination below 0.1 CFU/cm² before sterilisation to be absolutely guaranteed.

Moreover, UltraClean 6 *evolution* is part of a general programme of maximum endotoxin elimination based on the implementation of effective preventive and elimination methods, making it possible to guarantee exceptional levels: endotoxins < 0.03 EU/ml.

Stelmi has taken the option of regrouping all the information about pharmaceutical closure finishing in a Type-V DMF. The pharmaceutical laboratories may therefore refer to this DMF and simplify the registration of their own file with the FDA and it ensures that Stelmi’s production meets all the reference requirements in force.

Stelmi has prepared a unique DMF for its production sites, ensuring that the same quality is provided regardless of the production site and also allowing the availability of a second source.

2) Validation of the sterilisation process

Validation of the sterilisation process with gamma irradiation has four steps:

i Determining the maximum dose tolerated by the product

Determining the permitted maximum irradiation dose concerns the product itself and its packaging. The most relevant tests are those described in the European Pharmacopoeia and applicable to rubber closures.³ They reveal the effect of gamma sterilisation on the chemical and functional properties of the product. These tests may be augmented by measuring the mechanical properties in standardised test samples.

The results obtained from chlorobutyl rubber closures (see figure 2) show great stability of all the properties studied after exposure to 25 and 50 kGy.

With respect to the packaging materials, the measurement of mechanical properties gives interesting information about the behaviour of the chosen material. Integrity is checked at the time of determining the expiry date.

The elastomer-based formulations offered by Stelmi for sterile plungers are designed to be compatible with radiosterilisation. Exposing the stoppers to 25 and 50 kGy either does not affect the investigated properties or has a negligible influence on these properties. Even when irradiated and aged, these formulations do not approach the limits described in the principal norms and pharmacopoeias.

The influence of ageing was also studied. The tests listed in Figure 2 were performed after one and three years. No significant change in the chemical profile of the elastomer formulation was observed.

ii Determining the sterilising dose

To select the sterilising dose, Stelmi has chosen to use ISO regulation 11137 relating to the sterilisation of medical devices and more specific-

ly to use Method 1, which involves working from information on bioburden. The advantage of this method is accurate determination of the sterilising dose and therefore not exposing the product more than is necessary.

In practice, an estimate of the average bioburden is made from three different batches of syringe plungers and a table provides the dose at which SAL (Sterility Assurance Level) is 10^{-2} for this bioburden. This value is then used as the verification dose. A sample of 100 syringe plungers is then exposed to this verification dose and the sterility of each product is tested individually. If there are no more than two positive tests out of 100, the sterilising dose where SAL is 10^{-6} is determined using the same table.

Once the dose is determined, a periodic audit must be carried out to confirm the validity of this sterilising dose.

iii Determining dose mapping (irradiation dose received in each point of the batch to be sterilised)

Gamma sterilisation permits products on entire pallets to be treated, which simplifies handling considerably. Depending on the density of the product, this may lead to significant dose differences in different points within the load on the pallet. The first step therefore consists of determining the configuration which allows the most homogenous irradiation dose possible to be obtained between the different points within the load being treated. This is done by choosing the service provider and its plant, as well as by optimising the pallet-loading arrangement. Dose-mapping is then validated from three different loads.

Validation involves distributing the dosimeters to different points within each load and therefore determining the position of the “cold point” (minimum dose) and the position of the “hot point” (maximum dose) so that exposure relating to these points can be compared with a routine or reference point. Afterwards, a single dosimeter will be necessary for each load and will be placed at the “routine point”.

From the irradiation dose measured at the routine point, we can deduce the doses received at the cold and hot points and therefore ensure that each point within the load has at least received the sterilising dose without exceeding the set maximum dose.

iv Determining the expiry date

The expiry date is determined following an aging study conducted on the finished product.

GRADE DESIGNATION		STEMMI				
BASE ELASTOMER		CHLOROBUTYL				
<i>Gamma radiosterilisation (25 and 50 kGy) incidence upon the physicochemical and functional properties of the formula</i>						
Property	Unit	Procedure	0Gy	25 kGy	50kGy	Limit value
Appearance	class (NTU)	Eur. Ph.	I(0.9)	I(0.8)	I(0.9)	II(5)
Acidity	ml	Eur. Ph.	-	-	-	0.3
Alkalinity	ml	Eur. Ph.	0.03	0.03	0.03	0.8
Transmittance	DO max	Eur. Ph.	cf		spectrum	0.2
Reducing matter	ml	Eur. Ph.	0.2	0.3	0.2	3
Heavy metals	ppm	Eur. Ph.	<2	<2	<2	2
Soluble zinc	ppm	Eur. Ph.	0.5	0.6	0.8	5
Ammonia	ppm	Eur. Ph.	<2	<2	<2	2
Extracted non volatile solids	mg	Eur. Ph.	<2	<2	<2	2
Volatile sulfides	mg/20cm ²	Eur. Ph.	<0.154	<0.154	<0.154	0.154
Conductivity	µS/cm	ISO 8871	4.2	4.7	5.5	40
Fragmentation*	-	Eur. Ph.	0	1	0	5
Self sealing*	-	Eur. Ph.	conform	conform	conform	-
Penetration force*	N	Eur. Ph.	2.3	2.4	2.4	10
Hardness	Shore A	ASTM D 2240	43	44	46	-
Module 100 %	MPa	ASTM D 412	1.6	1.8	1.9	-
Tensile strength	MPa	ASTM D 412	7.3	5.8	4.9	-
Compression set	%	ASTM D 395	24	25	24	-
Density	-	ISO 8871	1.29	1.29	1.29	-

* Tests have been performed on 20 mm SVP stoppers (ISO 8362-2 type)

Figure 2: Summary of results from gamma irradiation from chlorobutyl rubber closures

This aging study allows us to check packaging integrity and the behaviour of the irradiated product. Packaging integrity is an essential factor in terms of preserving sterility. This may be demonstrated by periodically checking the vacuum level in the bags and this examination may be completed by performing sterility tests on the product itself.

A review of the physico-chemical properties of the product may be conducted at the same time to check conformity over time.

III. THE PARTIES INVOLVED

The sterilisation of rubber stoppers for parenteral use requires the close involvement of three different players:

1. The manufacturer of the elastomeric components who must document and validate:

- The compatibility of the elastomeric material with the selected ionising radiation (determination of the maximum acceptable dose).
- The minimum sterilising dose.
- The dose mapping, which includes the identification of the load areas where the exposure to the radiation is minimum and maximum, in collaboration with the sterilisation sub-contractor.
- The process specifications in collaboration with the sterilisation sub-contractor
- The product release and certification.

2. The sub-contractor carrying out the sterilisation who must:

- Be approved by the relevant national authorities
- Provide a comprehensive description of the sterilisation unit, including:
 - the radiation source type and the plant builder
 - the unit operating mode (batch or continuous operation)
 - the authorised and operational activities of the source
 - a short description of the plant indicating the product flow, the position and the geometry of the source and the conveyor system
- Organise the product loading, unloading and post-sterilisation handling as well as the process monitoring
- Issue a quality certificate proving that the product has received at least the sterilising dose, without exceeding the maximum acceptable dose
- Retain the process data and records

3. The pharmaceutical laboratory using the sterilised stoppers who must:

- Assess the compatibility of the container/drug product
- Approve the validation plan developed by the component manufacturer
- Implement the necessary audits
- Proceed to delivery acceptance

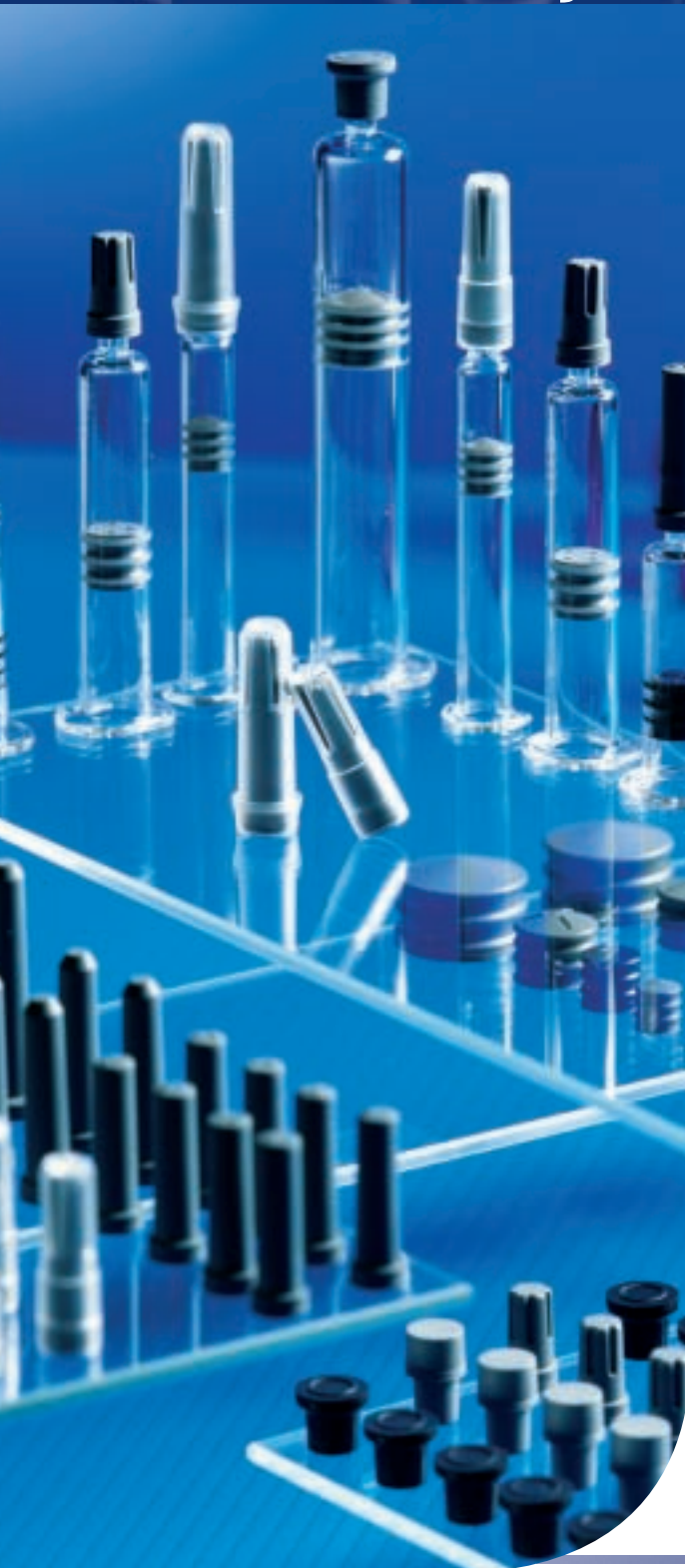
CONCLUSIONS

Supplying “ready-to-use” primary packaging materials is the logical next step resulting from the supply of “ready-to-sterilise” components. Gamma sterilisation, which is easy to validate, provides the pharmaceutical laboratories with all necessary safety. The issue of responsibility may be settled within a contractual context where the key points to consider are the validation procedure, the validation files as well as the data which led to the product being released.

REFERENCES

- 1 FDA Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. September 2004
- 2 EMEA Note for Guidance on Quality of Water for Pharmaceutical Use. May 2002
- 3 European Pharmacopoeia 5.0. 3.2.9. Rubber Closures for Containers for Aqueous Parenteral Preparations, for Powders and for Freeze-Dried Powders

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Ypsomed's core technology is constantly expanding to cover new therapy and patient needs. Its range includes a disposable auto-injector platform for the treatment of autoimmune diseases and other therapies. A broad-based technology platform and over 200 patents means that Ypsomed can meet virtually all partner needs in the growing market for self-injection systems.

Ypsomed was created in 2003 from one of the two divisions formerly owned by the well-known Disetronic Group. It employs over 1,100 people at several production sites in Switzerland and throughout a European sales and distribution network.

All products are developed and manufactured in Switzerland, where internal capabilities include R&D, tool-making, injection moulding, clean-room production and assembly facilities. It has production sites in Burgdorf, Grenchen and Solothurn. 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

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Ian Thompson's article, "Market Trends for self-injection: pens and auto-injectors" was published in ONdrugDelivery's 2007 "Delivering Injectables" issue, is available to download at:

www.ondrugdelivery.com/publications/ypsomed_2007.pdf

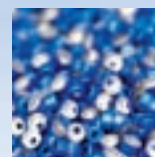
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A BETTER FILL FOR PREFILLED SYRINGES: APPLICATIONS & ADVANTAGES OF BUBBLE-FREE FILLING FOR TODAY'S PARENTERAL PRODUCTS

In this article, Dr Shawn Kinney, President, Hyaluron Contract Manufacturing, describes a method of syringe filling which eliminates “headspace” — the air bubble that results from conventional filling methods — and details the advantages that bubble-free filling confers.

Prefilled syringes are a fast-growing alternative to vials for many of today's parenteral products. According to recent estimates, the market for pre-filled systems has grown at a rate of at least 20% annually for several years, and will continue to experience double-digit growth into the near future. The increased interest in prefilled syringes is in large part driven by the many advantages they offer relative to vials. These include greater ease of use, reduced waste, improved dosing accuracy and enhanced product differentiation.

In a number of recent studies, Hyaluron Contract Manufacturing (HCM), a leader in aseptic manufacturing of prefilled syringes, found that the advantages of a prefilled syringe can be significantly improved upon by decreasing the size of the gas bubble inside the syringe. The gas bubble is not intrinsic to the syringe but is a by-product of traditional filling processes, and these studies showed that reducing its size offers greater assurances with regard to dosing accuracy and precision as well as product sterility. Additionally the HCM studies suggest removing the gas bubble entirely from a prefilled syringe can improve the stability of many oxygen-sensitive compounds as well as some proteins that rearrange due to the gas-liquid interface.

FILLING AND STOPPERING PREFILLED SYRINGES

Until recently, there were three processes for filling and stoppering prefilled syringes. They include traditional filling and stoppering; online vacuum filling and stoppering; and online vacuum filling followed by offline vacuum stoppering in a vacuum chamber. Recently, HCM introduced a new method for filling prefilled syringes, Bubble-free fillingTM, which uses online vacuum

filling and online vacuum stoppering in conjunction with proprietary technology to eliminate the bubble inside a prefilled syringe.

In traditional processes, syringes are filled and stoppered using conventional filling equipment. In these processes, a needle is inserted into a presterilised syringe and product is expelled. Next, the syringe stopper is forced into a tube — the insertion tube — which is narrower than the syringe. The insertion tube is then placed in the syringe above the liquid level line and a rod pushes the stopper out of the insertion tube into the syringe.

The advantages of conventional methods include minimal operator intervention as well as accelerated filling speed, which leads to considerable cost and time savings. The drawback, however, is that conventional methods leave a gas bubble inside the syringe which can pose significant challenges. Additionally, conventional methods which use insertion tubes are not suitable for coated stoppers since the force of the compression of the stopper and the action of the insertion rod can cause the coating to wrinkle or tear.

With vacuum filling and vacuum stoppering, syringes are first evacuated and filled under vacuum. Next, they are advanced to the stoppering position where a vacuum is again applied to the filled syringes, and a stopper is pushed into position by differential pressure. In this process, there is no compression of the stoppers and insertion rods are not required.

The primary advantage of online vacuum filling and online vacuum stoppering over more conventional methods is the reduction of the bubble which exists between the product and the stopper in traditionally-filled syringes. It also works well with coated stoppers since the stopper is placed using differential pressure rather than force.



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	<i>Hold-up volume</i>	<i>% of 0.30 ml dose</i>
1ml long syringe hub	0.0099ml	3.3%
16 gauge 1"	0.0391ml	13.0%
18 gauge 1.5"	0.0299ml	10.0%
26 gauge 5/8"	0.0011ml	0.4%

Figure 1: Summary results from HCM study measuring hold-up volumes in a 1ml syringe and three different sized needles

Filled syringes could, alternatively, be placed into an offline vacuum chamber for stoppering. However, offline vacuum stoppering requires increased operator intervention which raises the potential for contamination and can slow the process down.

It should be noted that online vacuum filling and online vacuum stoppering is a slower process for filling syringes and thus is more costly. These considerations, however, should be weighed against the proven benefits of a bubble-free syringe including enhanced dosing accuracy and precision, improved sterility assurance, and increased product stability.

ENHANCED ACCURACY AND PRECISION

One benefit of reducing or eliminating the air bubble inside a prefilled syringe is enhanced dosing accuracy and precision.

In a typical scenario, a prefilled syringe would be administered in an upright position. In this position, when the stopper is pressed, the product is expelled first, followed by the bubble. As product exits the syringe, the bubble moves into the hub, forcing any remaining product into the needle.

Conversely, when a syringe is administered in the inverted position, the gas bubble is positioned near the needle. As the stopper is pressed, the gas bubble is expelled, followed by the product. Once the stopper reaches the hub of the syringe there is no air bubble to force out the remaining product. Some product, or hold-up, can then be left behind, ultimately reducing the amount of product delivered to the patient.

To determine the hold-up volume in a traditionally-filled syringe, and its significance with regard to dosing accuracy, one HCM study measured the hold-up volumes in a 1ml syringe and three varying size needles (see figure 1).

The study found that in a 1ml syringe, the hold-up was 0.0099ml, or more than 3% of a 0.30ml dose. When the hold-up volume in a 26 gauge 5/8" needle was added to the hold-up volume of the 1ml syringe, a common configuration for prefilled syringes, the hold-up volume was 0.0011ml or nearly 4% of a 0.30ml dose.

Not surprisingly, the study found that as the

size of the needle increased so too did the hold-up volumes. In a 1ml syringe, with a 16 gauge 1" needle, a configuration frequently used with some viscous products, hold-up volumes jumped to as much as 17% of a 0.30ml dose when the syringe is not oriented properly.

In a related study, it was determined that with vacuum filling and vacuum stoppering, or bubble-free filling, the same reproducible dose was delivered again and again regardless of the orientation of the syringe.

In this study, 40 syringes with staked needles were each filled with approximately 0.3ml of a test media. Twenty of the syringes were filled using traditional online filling and stoppering, while the remaining 20 were filled using bubble-free filling.

Half of the syringes in each sample were expelled into vials in the upright position, or with the needle pointed down. The remaining syringes in each sample were then expelled into vials in the inverted position, or with the needle pointed up. Finally, the expelled weight was determined for each syringe.

Among the study findings was the fact that in bubble-free filled syringes more of the product was expelled in both the inverted and upright positions relative to similarly oriented, traditionally-filled syringes. Further, it was found that the range of the expelled weights in both bubble-free samples was approximately three-fold less than in the traditionally-filled samples. The range of expelled weights in the bubble-free syringes was 0.003g versus 0.013g, or greater than 4% of the average weight of 3g in traditionally-filled syringes

The study also showed that with a traditionally-filled syringe there is increased potential for product to leak out inadvertently when the tip cap is removed due to the vacuum that is created as the cap is pulled off. With a bubble-free syringe, conversely, no product is observed leaking from the needle because there is no bubble to expand as the tip cap is removed. No leaks mean that not only will the size of the delivered dose be more accurate, but less product will be wasted. It also reduces the potential for administrator exposure to cytotoxic and potent compounds which could prove hazardous.

Given that a number of today's parenteral products call for small volumes and many are intended

for use at home and in emergency situations, these differences in the delivered dose can be significant. For the end-user, both the patient self-administering a therapeutic and the clinician working in less than optimal circumstances, a bubble-free filled syringe offers added assurance that the delivered dose is accurate regardless of how the syringe is held. It also promises increased safety from limited exposure to the therapeutic. For the drug sponsor there is the additional assurance that less bulk product will be wasted when the syringe is in use.

IMPROVED STERILITY ASSURANCE

Another benefit of bubble-free filling is improved sterility assurance due to a reduced potential for microbial contamination, both through inhibited microbial growth as well as through limited stopper movement when the syringe is subjected to reduced atmospheric pressure.

Inhibiting Microbial Growth:

Many injectable drug products are produced by sterile manufacturing processes that have been validated to produce a sterile product. The validation of the process and the control of the manufacturing process, environment and equipment are relied upon to produce a sterile product because it is impossible to test every unit for sterility.

When considering manufacturing processes, final drug product container and shipping methods, the most rugged processes and containers available are preferable in order to prevent risks from undetected accidental contamination. A recent study conducted by HCM found that reducing or eliminating the gas bubble inside a prefilled syringe during the filling process can create an environment that is not conducive to the growth of aerobic microorganisms, the type most commonly found in "sterile" manufacturing environments. As a result, the study concluded that bubble-free filling prevents or at least inhibits the growth of microorganisms inside a prefilled syringe.

In this study, trypticase soy broth, a media which supports the growth of several microorganisms, was challenged with three different types of microorganisms: *Candida albicans*, a yeast, *Bacillus subtilis*, a bacteria, and *Aspergillus niger*, a mould. These microorganisms are the same microorganisms the USP requires in growth promotion testing of trypticase soy broth, the most commonly used media in media fill validations.

The challenged media was then filled into 1ml syringes. Half of the samples were filled using traditional filling methods, while the other half was filled using online vacuum filling and online vacuum stoppering, or bubble-free filling. They were then incubated under similar conditions for two weeks.

At the end of the test period, the syringes con-

taining media challenged with *C. albicans* that were filled using conventional methods showed significant positive growth. The syringes containing the same media that were filled using online vacuum filling and online vacuum stoppering, on the other hand, showed no signs of growth.

Likewise, the conventionally filled syringes containing media challenged with *B. subtilis* showed some cloudiness indicative of growth, while the bubble-free filled syringes containing the same media showed no sign of growth after 14 days.

Only the media challenged with *A. niger* showed signs of growth in both the conventionally filled syringe and the bubble-free filled syringe. The growth in the bubble-free filled syringe, however, was significantly less than the conventionally filled syringe. This was to be expected since, although *A. niger* prefers an aerobic environment, it can grow in both aerobic and anaerobic conditions.

Based on these results, the study concluded that bubble-free filling inhibits and/or prevents the growth of aerobic microorganisms, and while it does not prevent the growth of facultative microorganisms, it does inhibit or slow down their spread considerably. It is important to note that bubble-free filling is not intended to take the place of any of the controls, rigour or validation that are an absolute

necessity for sterile manufacturing. Rather, bubble-free filling provides an additional level of security in that, in the event of a low-level contamination by common cleanroom microorganisms, the organisms would not be able to grow inside the syringe.

Limiting Stopper Movement:

While manufacturers take every precaution to eliminate the opportunity for microbial contamination during the manufacturing process, a potential for contamination of prefilled syringes also exists during shipping if the syringes have been filled using conventional filling methods.

In a prefilled syringe, the stopper is free to move in order to allow the drug product to be administered to the end-user. This freedom of movement, when coupled with the gas bubble left in the syringe by conventional filling methods can potentially expose the drug to harmful contaminants when the syringe is subject to reduced atmospheric pressure, such as during air shipments, or transportation at high ground elevations, as demonstrated in another study conducted by HCM.

In this study, the impact of a bubble on stopper movement was determined using several syringes which were filled with gas headspaces of 2.5mm and 5mm respectively. The syringes were then placed inside a vacuum chamber where a vacuum was pulled to simulate reduced

atmospheric pressures. After a few minutes, the vacuum was released in order to restore the ambient pressure to its original levels. Finally, the process of pulling and releasing a vacuum was repeated several times in order to mimic the multiple exposures to reduced atmospheric pressure a syringe might undergo during shipping.

In the course of the study, it was observed that as pressure decreased, the bubble inside the syringe expanded, causing the stopper to rise into non-sterile areas of the barrel where it could potentially pick up contaminants. It was also observed that when the vacuum was released and the pressure returned to its original levels, the stopper moved back down into its original position with no indication that the stopper had moved into the non-sterile area of the syringe.

It was also discovered that the size of the bubble impacted the amount of stopper movement; the larger the bubble the greater the movement at any given elevation. Consequently, in syringes with a larger gas bubble, the stopper rose into non-sterile areas at lower elevations. In syringes with a smaller gas bubble, however, the stoppers entered non-sterile areas at much higher elevations.

Finally, the study found that in cases where the stopper moved multiple times, sterility could be compromised if the sum of the distances the stop-



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January 2006 HAS-1006

per moved each time equaled or exceeded the distance from the bottom of the stopper to the uppermost point at which it makes contact with the walls of the syringe, or the sterile barrier height, H_{sb} (see figure 2). Given that most products in today's market are shipped several times, this is an important consideration.

INCREASED STABILITY

One final benefit of vacuum filling and vacuum stoppering, or bubble-free filling, is increased stability of oxygen-sensitive compounds.

Dissolved gases can negatively impact the stability of some drug solutions. Likewise, the liquid-gas interface inside a traditionally-filled syringe can cause molecular rearrangement in some proteins, while air bubbles, in conjunction with silicon, may lead to protein aggregation. By eliminating the bubble inside a syringe, online vacuum filling and online vacuum stoppering makes it possible for more proteins and peptides – the foundation of many of today's biotechnology drugs – to be presented in a pre-filled syringe with a shelf-life that rivals that of a lyophilised drug in a vial.

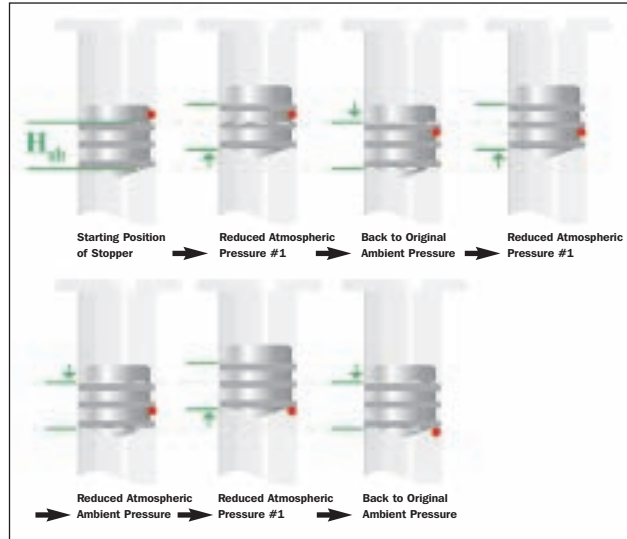


Figure 2: Illustration of stopper movement during changes in pressure, and the importance of the sterile barrier height (H_{sb})

CONCLUSION

As pre-filled syringes continue to find favour as the delivery method of choice for many of today's parenteral products, it is likely that vacuum filling and vacuum stoppering will become increasingly popular as the filling method of choice due to the many advantages it offers relative to traditional

filling methods. These include enhanced dosing accuracy and precision, improved sterility assurance and increased stability for many oxygen-sensitive compounds and some proteins that rearrange as a result of the gas-liquid interface.

Hyaluron Contract Manufacturing, an innovative leader in aseptic filling of vials and syringes, has conducted a number of studies to validate these advantages and has patented its own method for online vacuum filling and online vacuum stoppering known as Bubble-free filling™. Since 1999, HCM has been offering its customers – from newly established firms to large-scale commercial enterprises – innovative and unique solutions to all their aseptic formulation/fill needs. The company, located in Burlington, MA, is committed to working with clients in the global pharmaceutical and biotechnology industries, making it possible for more of today's groundbreaking parenteral products to reach more of the people who need them most, safely and efficiently. For additional information on the company and its patented Bubble-free filling™ technology, visit HCM's website at www.hyaluron.com.

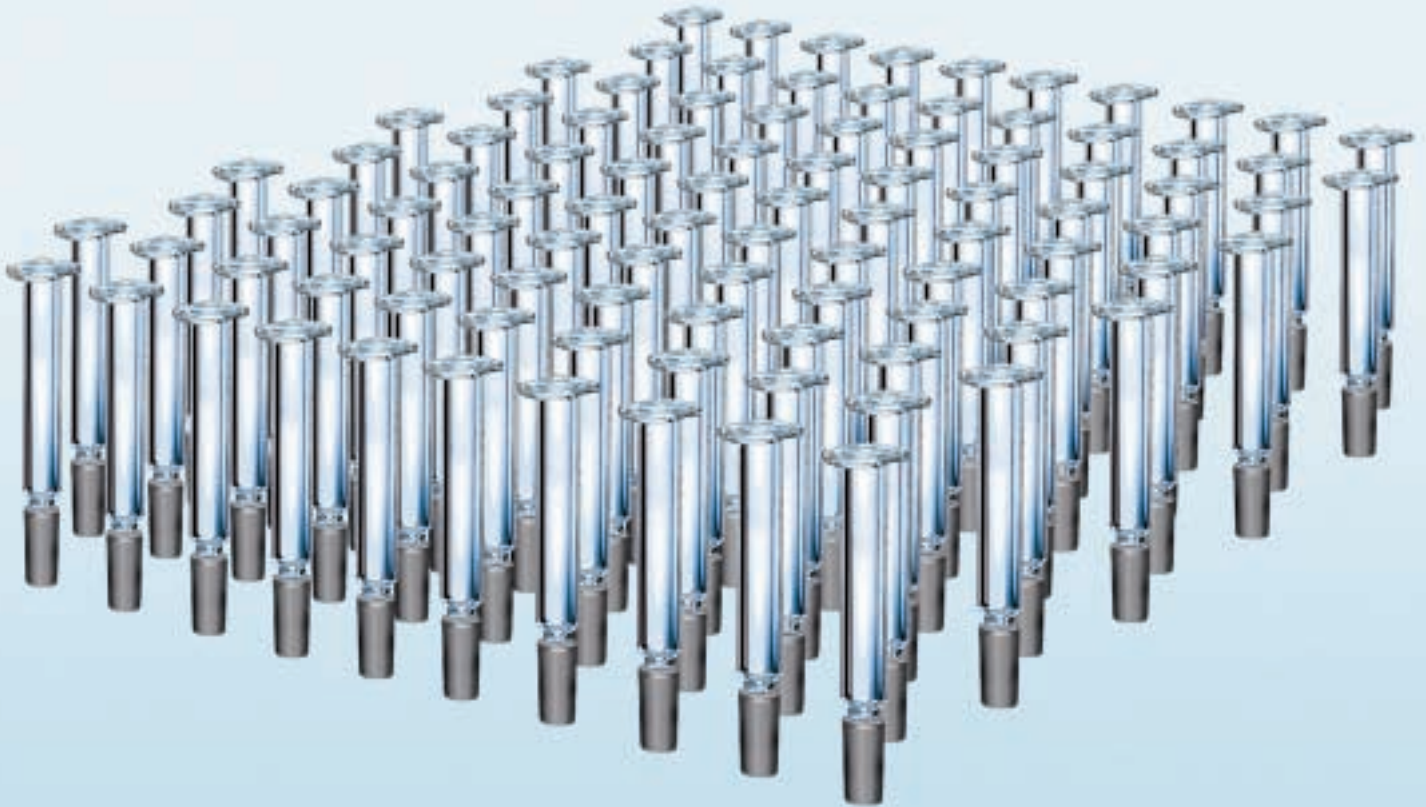
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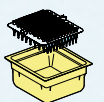
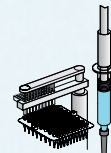
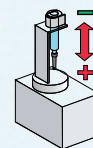
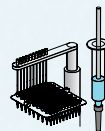
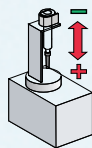
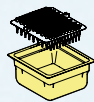
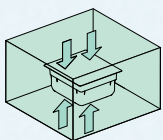
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AUTO-INJECTION DEVICES: CONVENIENCE ITEMS, OR A KEY COMPONENT OF INJECTABLE PRODUCTS?

As the number of self-administered injectable products being developed in prefilled syringes continues to grow, it becomes increasingly important to understand the role of auto-injection devices in ensuring the success of these products. Are they convenience items intended to make self-injection more tolerable for patients? Or do they play a more critical role as a necessary component of a combination product? The market's response to these devices suggests that the answer to both of those questions is "yes", argues Mike Kasprick, Vice-President, Business Development, Devices Group, at Antares Pharma.

The trends are quite clear; we will see a growing number of injectable products being launched over the next several years, an increasing number of these products will be self-administered, and the container of choice for many injectable drugs has become the prefilled syringe. Prefilled syringes provide a wide range of benefits for patients who must self-administer these injectable products including simplifying the preparation and administration of the injection, and helping to avoid dosing errors.

Another key trend that is just now becoming more evident due to some recent successful product launches is the introduction of injectable products in auto-injection devices. There are several drug delivery companies developing auto-injectors, each offering devices with unique attributes and advantages. But generally, these devices are designed to accept the most common prefilled glass syringes from the leading syringe suppliers, and they help to further simplify and standardise the delivery of self-injected products. Figure 1 shows an example of an auto-injection device alongside an illustration highlighting the "drop in" compatibility of these devices with a conventional prefilled syringe.

Most devices in the current class of auto-injectors are simple to use, requiring no more than three steps. The simplicity of these injectors is shown in figure 2.

Designed to be intuitive, easily understood and used by the general population, auto-injectors are starting to become recognised as a necessary component of an injectable drug

product that is targeted for self-administration. Let's look at some of the reasons why this has occurred.

POTENTIAL BENEFITS

Starting with a very simplified perspective of the category of auto-injection devices, there are two key areas where these devices can offer notable benefits to patients. First would be in eliminating the elements of self-injection that cause patients to delay or skip their injections, with the goal of improving compliance with their injection regimens. Second would be in ensuring proper administration of the drug, thereby helping patients achieve the expected efficacy from the product. Taken together, these two benefits indicate the potential for optimising the therapeutic outcomes of self-injected products based on the contributions of an auto-injection device.

PATIENTS' RELUCTANCE TO SELF-INJECT

In the past, I would often hear that injection devices were simply an aid to help a small subset of patients who were extremely afraid to self-inject ... the true needle-phobics ... and that the devices were not necessary for the mass market. Now, however, there is growing awareness that most patients prefer products that help reduce the challenges of self-administration they face on a daily basis and, if given a choice, they would select a product with a delivery system that helps

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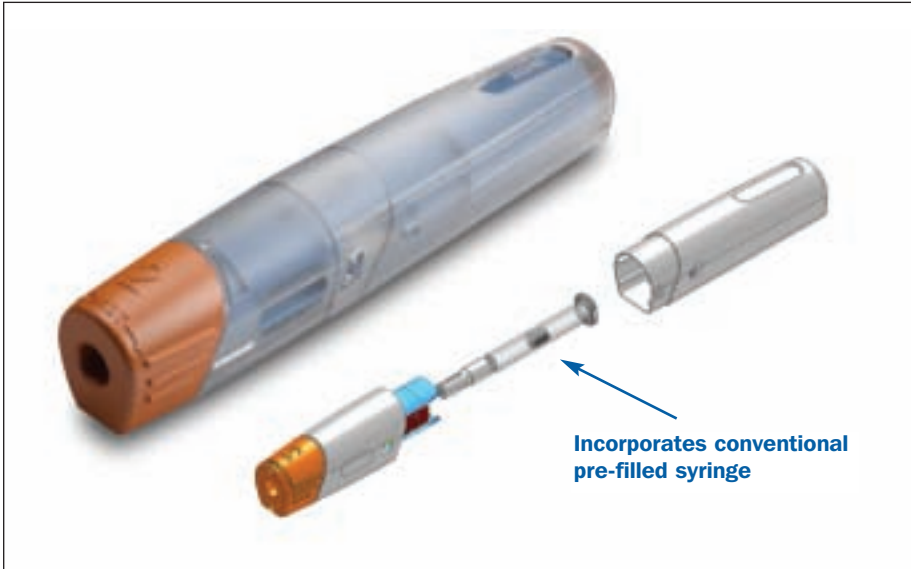


Figure 1: Antares Pharma's Vibex Injector

them overcome these barriers. It can be helpful to put yourself in the shoes of a patient to better understand their perspective regarding self-injection. While each individual might have unique concerns about injecting, there are generally four stages of self-injection that might introduce hesitancy and non-compliance for patients:

Stage 1: Seeing the needle. While most people won't suffer a reaction as severe as fainting, the sight of a needle does increase discomfort for many. This is addressed by most current auto-injectors as they conceal the needle through the entire injection process.

Stage 2: Inserting the needle. Manually insert-

ing a needle into your skin can be the most challenging element of self-injection. This is to be expected because our survival has depended on avoiding injury, so our natural instinct is to avoid actions that would result in a self-inflicted wound. Again, the current generation of auto-injectors typically feature auto-insertion of the syringe needle to overcome this challenging step.

Stage 3: Administering the drug. This is an automated element of virtually all auto-injection devices. However, they typically provide a long, slow injection, often requiring the needle to remain inserted for more than 10 seconds for a 1ml injection. Patients prefer a faster injection to help minimise the discomfort ... both psychological and physical. The longer the needle remains inserted into the skin, the greater the likelihood that it will be moved slightly and increase the physical sensation of the injection. In addition, a long duration injection increases the chances the patient will prematurely withdraw the injector, resulting in an incomplete injection. Antares Pharma has introduced its Vibex™ mini-needle injector which delivers 1ml in less than two seconds, easily addressing these potential issues. In addition, clinical results show the same very low pain sensation scores for both a 0.5 ml and a 1 ml injection at these injection speeds.

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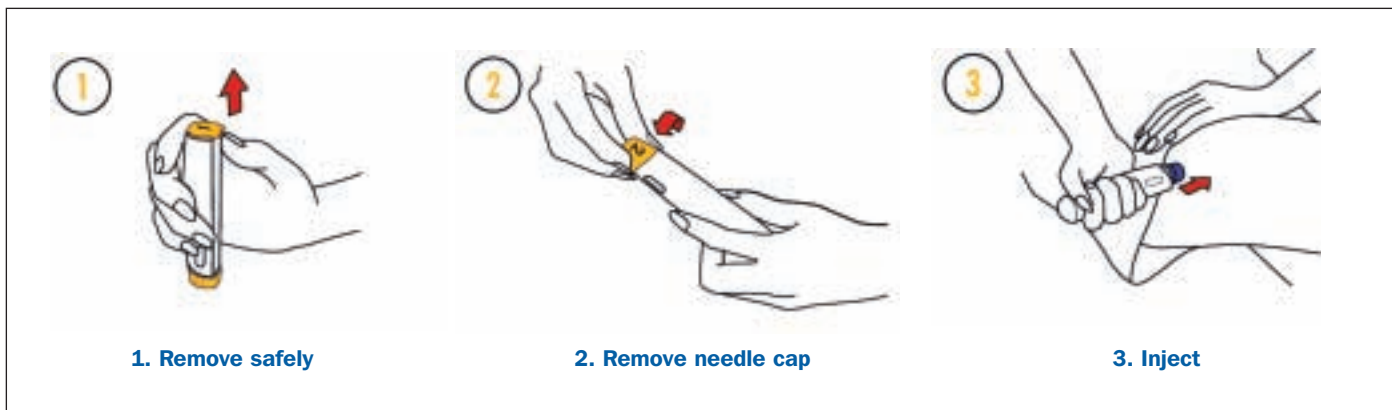


Figure 2: Simple three-step procedure for using auto-injectors

Stage 4: Handling contaminated sharps. Once the injection is completed, the patient must deal with any exposed, contaminated sharps. This potential hazard is addressed by most auto-injectors which utilise a needle retraction or protection mechanism.

AUTO-INJECTION DEVICES OFFER A NECESSARY SOLUTION

As described above, the current generation of disposable auto-injectors offers a very necessary set of benefits to patients. These devices are intuitive and simple to use, they can reduce the fear and anxiety that often leads to non-compliance, and they add safety to pharmaceutical products by concealing the contaminated sharps following completion of the injection. In view of these compelling benefits, it is clear that auto-injection devices can

make self-injection more acceptable for the vast majority of patients, providing the opportunity for improved compliance. And let's not forget about the potential to gain competitive advantage in our sometimes crowded product fields! This class of injection devices has clearly demonstrated its importance as an integral and necessary element of self-administered injectable products.

WHERE DO WE GO FROM HERE?

Many of the current auto-injectors are distinguished by features such as operational sequence (for example, is the drug ejected during or after full needle insertion), safety mechanisms, or low price.

Antares Pharma has taken an innovative approach with its Vibex™ mini-needle injectors by ensuring that the drug is delivered to the sub-

cutaneous tissue as intended, while avoiding inadvertent intramuscular delivery.

Achieving this result does not require a new or custom syringe with a short needle – the device simply restricts the portion of the needle that is exposed, allowing the tip of the needle to remain in the subcutaneous tissue – so pharma companies can use this as a “drop in” solution with their current prefilled syringe products.

Antares combined the short needle insertion with an increase in injection pressure to avoid leak-back of the drug at the injection site. This combination of short needle and higher injection pressure has resulted in a next-generation auto-injection device that offers several distinguishing characteristics:

- Quick, comfortable injections for patients
- Avoids the risk of unintended intramuscular injections

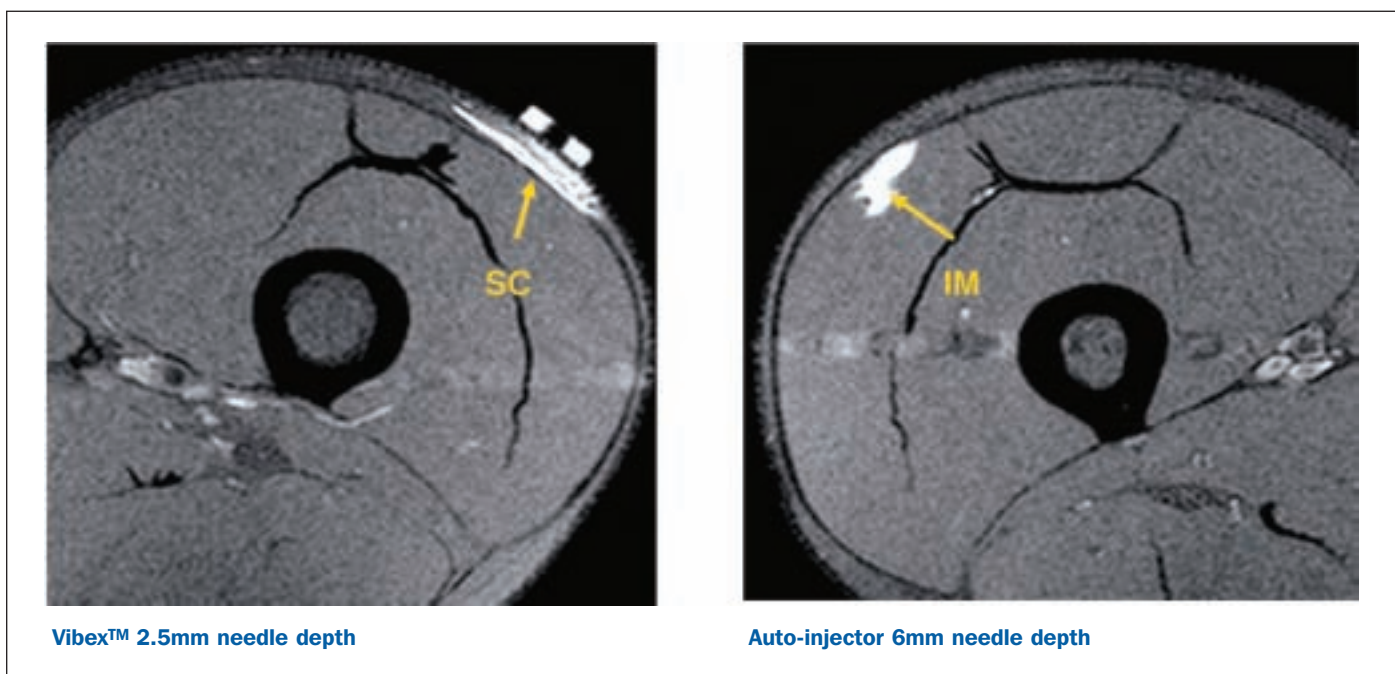


Figure 3: MRI images showing formulation deposition following injection with Vibex (2.5mm needle depth) and another auto-injector (6mm needle depth).

- Ability to effectively deliver high-viscosity drugs due to the higher spring forces.

ENSURING PROPER SC DELIVERY

Auto-injectors have removed much of the “human element” associated with self-injection. This is both beneficial and necessary if they are to be put in the hands of the general population. The devices must be intuitive and simple to use properly, without significant patient training requirements or special techniques for proper administration.

However, as these devices have been simplified to this degree, one step that is typically performed when injecting with a conventional syringe has now been eliminated. The “pinch up” technique was commonly used with conventional syringes and pen injectors to ensure sufficient subcutaneous thickness to avoid intramuscular penetration, but this technique is generally not recommended with auto-injectors. This places a greater burden on the patient to properly select an injection site with adequate subcutaneous tissue.

The mini-needle Vibex™ injector from Antares Pharma helps to overcome the issue of accidental intramuscular injections by limiting

the insertion depth of the needle. The nominal length of the exposed portion of the needle is just 2.5 mm, which is short enough to stay within the subcutaneous tissue of all but the leanest patients.

In comparison, a typical auto-injector might have a needle depth (fixed or adjustable) ranging from 12.7mm down as low as 6mm, but without increasing the injection pressure there will likely be a noticeable rise in incomplete injections due to leak-back as the needle insertion gets shortened further.

The MRI images shown in figure 3 illustrate the potential importance of needle length. In this study, five subjects were injected in alternate thighs with the Vibex™ injector at 2.5mm needle depth, and a conventional re-usable auto-injector with an exposed needle length of 6mm. This group of subjects presented a wide range of subcutaneous tissue thicknesses, from lean to obese, and the images below are from the leanest subject in the group.

The Vibex™ device deposited the injection at the intended subcutaneous depth whereas the conventional auto-injector penetrated the muscle fascia resulting in an intramuscular injection.

This is just one example of how auto-injection devices can help ensure proper delivery of injectable drugs, either ensuring

optimal efficacy or potentially reducing undesirable side effects.

EXPECT STANDARDISATION ... AND FURTHER INNOVATION

Evolving along a typical path to maturity and broad acceptance, the auto-injector industry is currently engaged in establishing international standards for this product category. A working group has been established and is working toward the development of a draft document that will establish ISO standards for the industry. This will prove to be a valuable step as it will ensure that certain performance criteria are met, and that devices will properly accommodate the standardised prefilled syringes they are intended to contain.

Clearly, innovative new auto-injection technologies will also be developed to provide benefits well beyond the expected patient benefits related to reducing fear and anxiety. In addition to the standard “off-the-shelf” offerings, you might expect to see more device customisation as pharma and biotech companies seek to differentiate their products, and as they search for injectors that can solve unique delivery challenges such as micro doses, very large doses, or highly viscous materials.



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