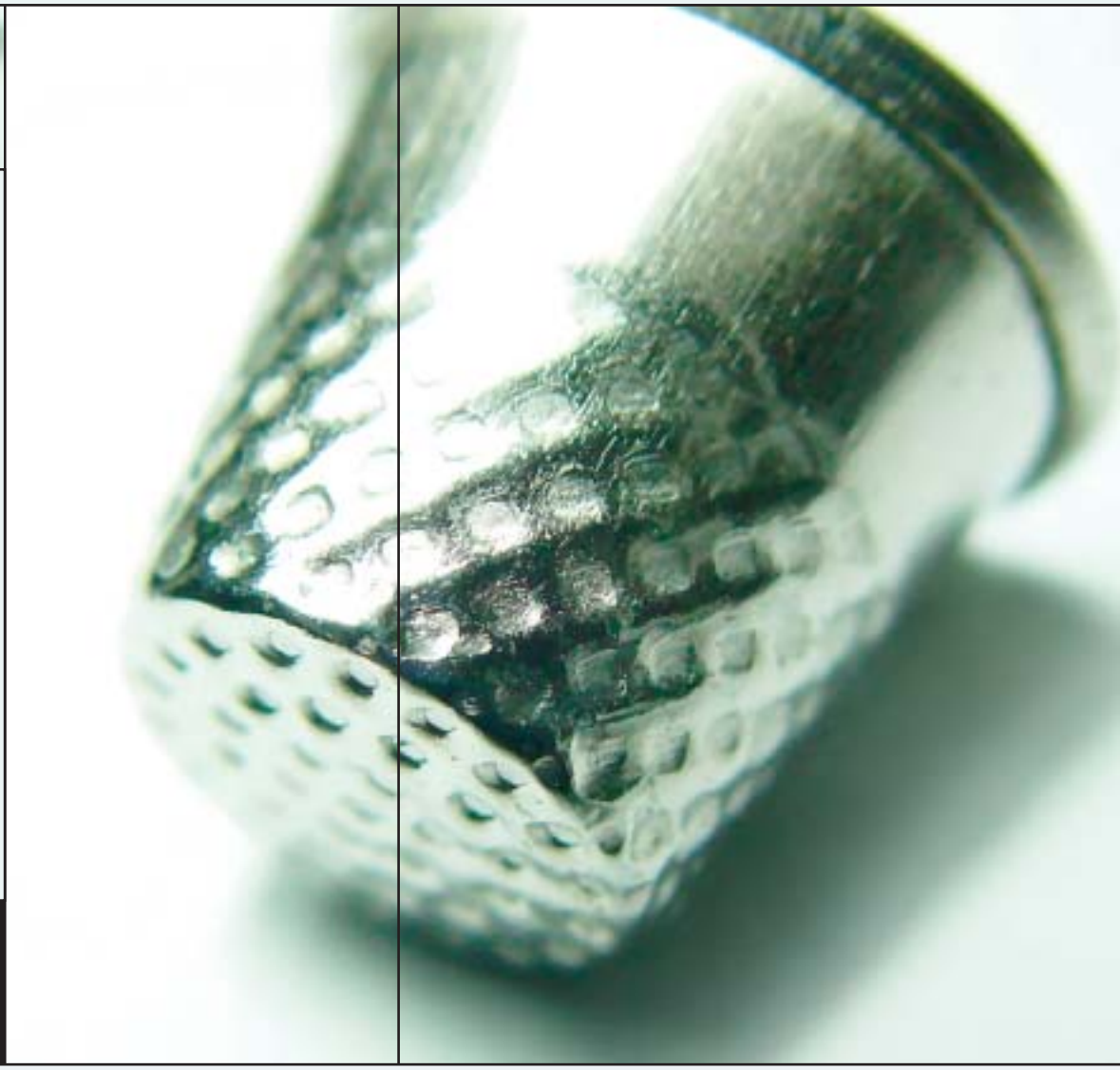
SAFER INJECTIONS

REDUCING RISK FOR NURSES, PHYSICIANS AND PATIENTS ALIKE



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"Safer Injections: reducing risk for nurses, physicians and patients alike"

This edition is one in a series of sponsored themed publications from ONdrugDelivery Ltd. Each issue will focus on a specific topic within the field of drug delivery, and contain up to eight articles contributed by industry experts.

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.

Forthcoming editions cover: drug delivery in diabetes; pulmonary delivery; advanced oral drug delivery; needle-free injection; prefilled syringes; nasal drug delivery; oral modified release; solubilising technologies; delivering injectables; and novel biomaterials for drug delivery. To find out more about receiving or participating with any of these issues, please contact ONdrugDelivery Ltd.

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"*Safer Injections: reducing risk for nurses, physicians and patients alike*".
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CONTENTS

INTRODUCTION

There are two major risks with needles and syringes. Perhaps the most obvious is that hypodermic needles are of course extremely sharp meaning that there is potential for accidental injury every second that the needle tip is exposed. The World Health Organisation estimates that there are three million accidental needlestick injuries annually worldwide but the real number is likely to be higher since many go unreported. Healthcare workers are reluctant to report when they suffer needlestick injuries because they often believe that it is their mistake and that they will be blamed.

Dr Ron Stoker, founder and executive director of the International Sharps Injury Prevention Society (ISIPS) said that there were an estimated 800,000 to one million needlestick and sharps injuries in the US alone each year and that more than 1,000 healthcare workers contracted serious infections such as hepatitis B and C, and HIV/AIDS from needlestick and sharps related injuries.

Over the past decade, the problem has come to the fore and has been recognised by major governments. US legislation requiring that all injections should be given using safety syringes, and guidelines in Europe recommending that safety devices should be used wherever possible, have led to a huge increase in the number of such devices on the market and in development. However, it is important to point out that in some European countries little has changed "on the ground" in hospitals and clinics as yet. Wholesale change is widely accepted as inevitable but the rate of change in the coming years is not certain.

The second major injection safety issue is the deliberate re-use of what should be disposable needles and syringes in mass vaccination campaigns in the developing world. The practice clearly carries the risk of spreading infection wherever it occurs, but it is potentially catastrophic in countries such as Botswana and Swaziland where the prevalence of HIV exceeds 40%. Dr Stoker illustrated the situation with the example of African doctor Warura Mogo who, in 1994, had 120 children waiting outside his office awaiting vaccinations, but had only 20 disposable needles and syringes available. He had two options. "He could immunise 20 children and send the rest away leaving them vulnerable ... to potentially lethal diseases," said Dr Stoker, "or he could vaccinate every child, quickly boiling the syringes after every injection knowing that if just one child carried HIV, hepatitis or another blood-borne virus, the others might get it too." In the end Dr Mogo vaccinated all of the children, a decision that troubles him to this day.

One safety solution to this problem is the auto-disable (AD) syringe – a device that is rendered irreversibly inoperable as soon as it has delivered its first injection. On page 18, Formosa Medical Devices describes a device that combines AD features with a needlestick prevention mechanism, hence addressing both of the risks – needlestick and needle re-use – described above.

These are not the only two risks involved in injectable delivery. Nowadays it is becoming increasingly common in healthcare policy for many patient groups to be given the option of self-injecting regularly. Although there is a risk of needlestick injury here, the consequences are less severe as there is little threat of cross-infection.

Nonetheless, in comparison with taking a tablet or inhaling a dose, self-injection is a complicated task with inherent risks. Selecting the correct dose, positioning the needle at the correct site, overcoming any anxiety, and inserting the needle to the correct depth for either intramuscular or subcutanoues delivery are tasks that can be dangerous if performed incorrectly. For example, hitting a vein with an intended IM depot injection can lead to rapid onset of a high dose. Even when the correct site is found, the consequences of incorrect doses injected are often more serious compared with other routes, and the margins between safe and dangerous doses are smaller, on account of the efficiency of the injectable routes.

As self-injection becomes more commonplace, drug delivery devices that help patients carry out the injection procedure more reliably are emerging. Union Medico's Personal Injector (page 4) is one such device, invented by a multiple sclerosis sufferer to help make IM injections of interferon more tolerable, but also applicable to IM and SC injections of a variety of products.

Other companies contributing to this issue discuss solutions to problems of safety relating to prefilled syringes, a format that is gaining rapid popularity in the US, Europe and throughout the rest of the world.

It is important to mention one other drug delivery approach that has a variety of benefits on compliance and efficacy as well as promoting safer injections. As exemplified here by OctoPlus (page 11) and QLT USA Inc (page 25), controlled-release injection formulation systems allow the frequency of injection to be reduced from once daily to as little as once every six months. The number of times the injection procedure is carried out is decreased, leading to a decrease in the risk of a needle-related injury.

Conclusion

The science and business of drug delivery have many appealing characteristics. But if I had to choose one of them above all others then it would be that successful drug delivery technology development calls for scientists to step out from behind the microscopes through which some prefer to view the world. Rather than zooming in on only one aspect of the task in hand, such as alleviating the symptoms of the disease, those developing a drug delivery system must consider the whole patient – not only as a biological organism, but, for example, as an individual with feelings, fears and habits, and as a consumer with purchasing power and the ability to make (or at least influence) choices.

Over the past decade or so the benefits of the less blinkered, less compartmental approach have begun to gain acceptance across the board in healthcare, but broader thinking like this has been at the heart of drug delivery from the outset.

It is therefore perhaps not surprising that the drug delivery industry has been so keen and adept at meeting the relatively new challenge of addressing the issues surrounding needle safety. To achieve this it has been necessary to take an even wider view – taking into account not only the patient but also every other person who might come into contact with the needle before, during and after it is used. While the topic of Safer Injections is a highly specialised area of drug delivery, it is also one that requires capacious thinking.

Guy Furness
Managing Director, ONdrugDelivery Ltd

UNION MEDICO'S PERSONAL INJECTOR:
PERSONAL BY NAME AND BY NATURE

Union Medico's Personal Injector is a self-injection device that improves the quality and comfort of both intramuscular and subcutaneous injections across the spectrum of therapeutic classes. It is compatible with all marketed syringes. Union Medico founder Michael Perthu invented the device after he was diagnosed with multiple sclerosis in 1998, and along with thousands of other users, he now uses Personal Injector to administer his own regular medication. Here, he gives an insight into how the device was conceived, and the thinking behind its elegant design and function.

"My fingers tingled a little bit before we started the climb. In some ways I sensed that something was approaching. The year before, I had had problems with my sight and went partly blind for a period, but the disease hadn't been diagnosed yet. Now I was hanging on a steep wall of ice, 200m from the top of the mountain, with an ice hatchet in each hand. It was not the most convenient time to get an attack in my arms.

"At this point I still didn't know what was wrong with me. I thought the symptoms might be due to mountain sickness. After we successfully reached the top and returned back down safely, I began to realise that feeling so unwell couldn't be due to mountain sickness.

"Shortly afterwards in 1998, multiple sclerosis (MS) was diagnosed and I started treatment with Interferon Beta. It has allowed me the freedom to carry on almost as I did before I had my diagnosis.

"However, the administration of my medication immediately began presenting problems. To begin with, I had to face the prospect of regular injections for the rest of my life. It was with this in mind that I chose Avonex, a depot intramuscular format, which is taken only once weekly.

"Then it became clear that I was going to have trouble giving myself the IM injections using a standard needle and syringe, not least because the MS affected the function of my hands and arms. Among several improvised methods, I used a vacuum cleaner tube to help me inject. I would hold the tube against my leg, perpendicular to my skin with one end placed on the injection site, and drop a syringe down through the other end and into my muscle.

"Having to get by with such inadequate delivery technology clearly pushed me some

Figure 1: The Personal Injector's attractive look and feel promote compliance

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1 Injection release. The injector has an automatic safety release mechanism, allowing "look-away" injection.

2 Safety lock. Childproof.

3 Syringe gripping jaws. Can be made for all kind of syringes.

4 Syringe holder-slide. Tests results show that the impact speed remains constant after 10 years of normal use.

5 Built-in weight and balance.

6 Light activator. Made out of non-slip material ensuring stability when injecting.

7 Needle protector. Guarantees minimum contact with needle.

8 Stabilizes penetration angle, ensuring uniform angle of injection (also slightly stretches skin at injection point

9 Lights up the area to inject.

10 Lights up the syringe, thus making it clear whether there is air or blood in the liquid.

Figure 2: Design and functionality of the device

of the way towards inventing a device myself. But the final motivation came when I was invited by the Danish MS Society to give a presentation to other sufferers. Talking with them I quickly realised that one of their main concerns about their treatment was a common aversion to the needles they had to use. They were particularly afraid of the longer needle required for IM injections, despite the advantages in terms of reduced dosing frequency of IM formulations compared with subcutaneous products. The very day after this meeting with the MS society, I began the development of the Personal Injector."

A PROVEN TECHNOLOGY

Jump forward seven years to the present day and the Personal Injector is established as a fully functioning injection technology. Although, as described above, it began as an MS patient's personal endeavour, the commercial and regulatory aspects of bringing a novel medical device to the global market have not been compromised.

Protected by worldwide patent applications, the Personal Injector is marketed and used by patients throughout Europe and in South Africa. It has CE mark approval in the EU, 510(k) approval in the US and equivalent medical device approval in Canada. It meets the relevant ISO standards and GMP manufacture is carried out in Denmark.

WHY IS IT "PERSONAL"?

The events leading up to the Personal Injector's conception were included here not purely to add a human touch. The personal opening account clearly goes some way to explain the name of the device, but the thinking behind the Personal Injector's name runs far deeper. The fact that the device was invented by an MS sufferer whose condition on one hand limits his manual dexterity and on the other requires that he gives himself regular injections, is the key to understanding its design, function and efficacy as a first-class drug delivery technology.

The majority of other injection devices, from the earliest needles and syringes to the most advanced auto-injectors on the market today, have been developed by scientists and engineers who assimilate all available information about, for example, the formulation to be delivered, the disease, and patient physiology and anatomy, in order to try to come up with the optimal design. They also of course, increasingly in recent years, pay attention to factors concerning the patient experience, such as safety, comfort, ease of use and avoiding fear of needles. The result – especially in the past decade – has been a trend towards automation, with the aim being that the patient's involvement in the various steps of the procedure should be minimal – often reduced to pushing a button after which the device takes care of everything. The Personal Injector bucks this trend.

MANUAL COMPONENT

The most notable difference between the Personal Injector and other auto-injectors is that rather than trying to be fully automatic, some parts of the procedure are intentionally left in the control of the user. Among these manual elements is the process of depressing the plunger to discharge the dose. An automatic mechanism could blow all of the formulation into the muscle at once, rapidly stretching and tearing the tissue to accommodate the incoming volume of the drug substance. Once the button is pressed, there is no turning back. If the formulation happens to be forced into a particularly sensitive part of the muscle, the mechanism of course cannot sense the pain it is causing and there is neither time nor any way for the user to halt the process. As well as acute pain during the actuation, the resulting tissue damage can cause tenderness at the injection site long after the dose is delivered, together with unsightly blue bruising that takes days to fade.

Contrast this with the user-controlled plunger depression offered by the Personal Injector. The user can deliver the dose as slowly as they want – at whatever rate feels comfortable. As soon as any pain or discomfort even begins, they can slow down or even stop. No automatic device can compete with the user's own sensibility about how the injection process feels.

With routine bodily procedures such as, for example, brushing your teeth, combing your hair or cutting your fingernails, although using devices to help out is necessary and quite

a. **The syringe is placed in the gripping jaws**

b. **The safety lock is turned to the "on" position and held**

c. **The injector is placed gently against the skin at a 90° angle**

Figure 3: Selected steps in the Personal Injector procedure

acceptable, you would not want to hand over any of these activities entirely to a machine. These activities are too personal for that. Union Medico understands that patients regard injections in exactly the same way.

AUTOMATIC COMPONENT

Union Medico has isolated only one specific part of the injection process that truly benefits from automation – namely, needle insertion. With respect to this particular stage of the procedure, the Personal Injector has the same advantages as conventional auto-injectors.

One is reduction of fear of needles. Immediately before an injection, on a primitive level our minds tell us that it would be damaging to plunge a razor sharp piece of metal into our bodies. The Personal Injector's mechanism limits the user's involvement in this part of the process and makes it less daunting, even enabling the user to look away if desired. It serves to disconnect the user from the direct action of pushing the needle into their skin and muscle.

Another advantage of automating the needle insertion process is improvement of the quality of the injection. The user only needs to press a button lightly to activate the device, meaning that they can concentrate on positioning the injector correctly, perpendicular to the skin, and holding it still. Furthermore, the speed, force and the depth of needle insertion are controlled precisely and reproducibly by the device, rather than by the user.

DESIGN FEATURES

The vision with the Personal Injector has been to transform an unpleasant necessity into a good experience. A great deal of effort has therefore gone into the design and functionality of the Injector. Field tests show that the Personal Injector quickly becomes part of the user's everyday surroundings since it provides a sense of quality instead of the dismay normally associated with injecting.

Traditional auto-injectors are usually made from plastic, a material not readily associated with quality, and this material determines their look and feel. In contrast the Personal Injector is made from matt, brushed Aluminium and is available in a number of colours (see figure 1). This and the attractive overall appearance, means that a sense of quality is felt as soon as one sets eyes on the device or picks it up. It is not too heavy, but neither is it flimsy. It feels robust and substantial.

The various design features are shown and explained in figure 2 on page 5. The Personal Injector's excellent functionality is best explained during the course of a description of the steps for using it, as follows.

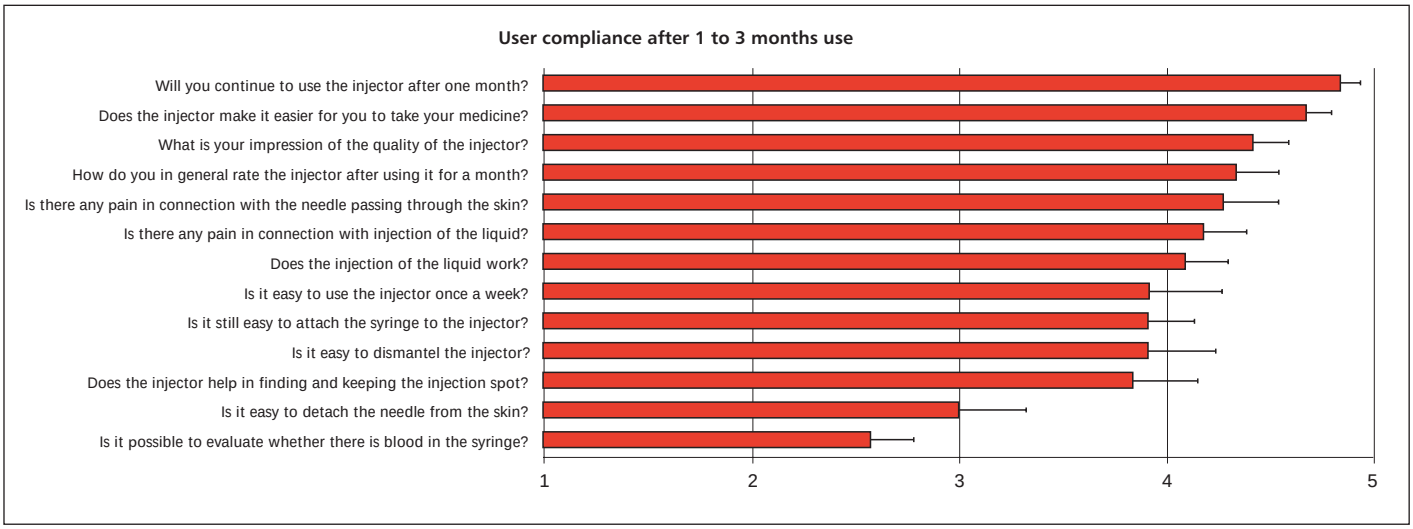

Figure 4: Summary of focus group study results

The user first draws back the syringe holder-slide until a click is heard. If not using a pre-filled product, they fill the syringe. They then place it between the two gripping jaws (figure 3a). Union Medical can provide gripping jaws that are compatible with every syringe available on the market from 1-5 ml, and it takes only a few seconds for the user to change the jaws if they want to change syringe type.

After cleaning the skin at the injection site – the upper thigh, for example, the user prepares the injector by turning the ribbed safety lock clockwise to the "on" position and holding it there using gentle finger pressure (figure 3b).

The user then presses the injector against their skin gently and at a 90º angle (figure 3c). The balance of weight through the device, and its shape, are such that it is easy and natural to do this correctly.

The part of the device that touches the skin (see figure 2, number 6) is the light activator, which is made out of a non-slip material to ensure stability. When sufficient pressure is applied (only gentle pressure is needed) the light activator pushes in and the device gives out a light as a signal that it is ready.

Next, with the index finger the user presses the button at the top of the device, activating the mechanism and causing the syringe holder-slide to descend and the needle to be inserted into the muscle. This action occurs at the same speed as an average manual needle insertion, and is powered by a spring made from highest quality steel. Tests carried out for Union Medico by an accredited contract laboratory found that the speed of the mechanism would remain constant for more than 10 years of normal use.

The light from the lamp also helps the user to see whether there is blood in the syringe, which can happen when an intended intramuscular injection accidentally hits a vein. The user checks for blood by drawing back the plunger very slightly.

Importantly, the Personal Injector has three further advantages at this stage of the injection process. The first is that as well as making it easier to check for the presence of blood, it reduces the risk of hitting a vein in the first place because it gives the user much more control over the process. The shape of the device and the manner in which the weight is balanced allow the user to keep the needle steady, avoiding unnecessary and uncomfortable movement of the needle tip within the muscle.

Secondly, if a vein is hit, there is no need to abort the whole process and discard the syringe unused. Instead the user just stops and resets the device by sliding back the syringe holder-slide, ready for a second attempt.

The third advantage is that the device helps the patient to position the needle tip well, and to hold it steady, for a successful depot injection without hitting a vein.

The next step is for the user to depress the plunger and deliver the dose at whatever speed they feel comfortable. Finally, they withdraw the needle by pulling the syringe holder-slide back up until a click is heard. The empty syringe is easily removed form the gripping jaws and discarded.

APPLICATIONS

The Personal Injector came about because its inventor, with reduced functionality in his hands, needed a better way to give himself IM injections. However, its use is by no means limited to MS sufferers. People with any condition that requires regular injections can benefit from using the device.

The Personal Injector is not limited to the delivery of IM injections. Intramuscular delivery is more prone to complications than SC delivery, but many of the problems of IM injections are common to SC injections also. They include fear of needles, difficulty in positioning the needle correctly and, with conventional auto-injectors, the rapid delivery of the formulation can cause painful SC injections and unsightly blue bruising in the same way it does for IM injection. Another longer-term effect of repeated, rapidly delivered SC injections is that hard scar tissue can form at the injection site, making the surface of the skin lumpy. The Personal Injector solves each and every one of these issues.

FOCUS GROUP STUDY

In 1999, the Personal Injector was tested in a focus group study of MS patients taking Interferon Beta, conducted at Rigshospitalet, the largest MS hospital in Denmark. The results, which are summarised in figure 4, are expressed as answers on a scale of one to five, where five was the most positive.

Particularly noteworthy from the focus group test is that all patients opt to continue using the injector and that the injector makes it easier to take the medicine, serving as testimony to Union Medico's success in realising its design objectives

CONCLUSION

Rather than following with another fully automated injector design, Union Medical is leading the way with an entirely fresh approach. The company has realised that an injection is an intimate and personal process, and that some elements of the procedure are therefore best carried out manually in order to achieve optimal safety, comfort and efficacy.

Without compromising the medical functionality of the device, Union Medico has created a device that is appealing to users and helps make their continuing need for daily or weekly injections tolerable.

SAFER INJECTION DEVICES:
PHARMACEUTICAL INDUSTRY PERSPECTIVE

One of the keys to Becton Dickinson's success in the injection safety market has been its understanding of how the emergence of injection safety as an increasingly important issue is perceived by the various stakeholders – pharma companies, healthcare workers, regulators and patients – and its effect on them. In this article, Karim Benazzouz, European Product Manager/Marketing at BD Medical - Pharmaceutical Systems, explains with a focus on how injection safety impacts on pharma companies.

The spread of blood-borne diseases such as HIV, and hepatitis B and C has highlighted the risks that healthcare workers are taking everyday when using sharps. Safety in this context is best summarised by the following statement: Prevention of unsafe injection practices that can lead to the transmission of blood-borne pathogens from patient to patient, from patient to health personnel or from patient to the community at large.

BD, pioneers in the field of safety-engineered devices for over 20 years, has made significant progress to address the issue of disease transmission through syringe/needle re-use and needle-stick injury, developing an extensive range of non-reusable and protected injection devices.

Healthcare workers, being the first players concerned by contamination problems, are heading most of the initiatives to make it happen. But the final users are not necessarily the purchase decision makers. Employers are.

Pharmaceutical companies which provide injection systems in combination with their drugs are also important players. Some of them are anticipating legislation changes, others are following recommendations issued by physicians and nurses – their customers.

DIFFERENT PLAYERS, DIFFERENT MOTIVATIONS

Healthcare workers' primary interest is to provide the best professional care to their patients, but at the same time to avoid contamination problems to themselves through accidental injuries.

Pharmaceutical companies' drivers are more complex. They are certainly concerned about their customers' safety requirements however additional cost is also a consideration. Unlike for healthcare workers, a pharmaceutical company's decision to provide safety products cannot be justified by the overall savings that are made (by avoiding needle-stick injuries and therefore also avoiding the resulting cost of treating them).

Gaining additional market shares by providing safety solutions is one of the keys to funding such implementations at pharmaceutical company level.

When the devices can be reimbursed through state organisations or insurance companies, another way is to build pharmaco-economic cases highlighting the medical benefits of using safety products.

LEGISLATION

The regulatory stance on using safer devices is progressively shifting from broader recommendations, such as those in place in Japan and South America, towards specific recommendations, like those made in Europe, and ultimately to obligations, as illustrated by US laws. No organisation involved in healthcare can claim today that they are not aware.

In the US, use of safety-engineered devices has been an obligation since April 2001. There are still exceptions, such as needles used for reconstitution or self-injection, but this market is moving towards full conversion.

In Europe, several directives already guide employers regarding the evaluation of risk and the provision of measures to protect their work-

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ers. These directives are now complemented and re-enforced by guidelines specifically recommending the use of safety-engineered devices. This is the case in Germany for example with the TRBA250. It is also the case in the UK with the Blue Book (Chapter 19). And it is probably expected soon in France.

More recently, in Spain, specific legislation was published by the Madrid autonomy in May 2005, and signed by the Spanish Parliament in June 2005. This law lays down the regulations for the implementation of safety medical products incorporating needle protection, and procedures to minimise the risk of biohazards to personnel working in healthcare. The legislation is expected to extend beyond Madrid to the other autonomous regions of Spain in the near future.

These recommendations apply primarily to healthcare employers. Nevertheless, the pharmaceutical industry has an important responsibility in the process. Providing non-safety engineered devices is a risk that should not be taken anymore considering the existing legal environment.

IS THE COST INCREASE REALLY AN ISSUE?

From the employers' point of view, safety-engineered products may appear to be expensive at first glance.

The reality is different and the calculation is simple. Safety engineered devices work and provide effective protection. More than 80% of accidental needle-stick injuries (NSIs) are avoidable. It is widely recognized that on average one accidental needle-stick injury occurs every 2000 injections.

Various statistics are now available with regard to the expenses related to the treatment of those NSIs. These costs vary from US$200 for simply testing in an uncomplicated case where no pathogen is transmitted, to US$1,500 in the case of minor infectious diseases other than HIV or hepatitis, to hundreds of thousands dollars when HIV and/or hepatitis is transmitted. The impact is not only related to direct cost like testing. Indirect factors such as the costs related to lack of productivity, insurance premium increases, lawsuits, etc, are likely to be far higher still.

Building a chart comparing the product related cost increase to the money spent on taking care of accidental needle-stick injuries is fairly explicit: safety engineered devices are clearly cost effective solutions!

For pharmaceutical companies, the reasoning is a bit different. There is going to be a cost increase linked with the supply of safety-engineered drug delivery devices. Importantly, though, its impact can be balanced by the following facts.

Figure 1: BD Preventis™ needleshield system, before and after activation

1. Biotech drugs for the treatment of, for example, highly infectious diseases like HIV, often carry a high price tag. In these cases the cost impact of adding a safety device, as a proportion of the overall price of the product, is lower.
2. Higher reimbursement rates may be requested for newly registered drugs.
3. Additional potential market shares could be gained following the introduction of differentiating devices.
4. A collective shift towards safety by the major pharmaceutical companies in a particular market segment.

WHAT A PHARMACEUTICAL COMPANY SHOULD EXPECT FROM A SAFETY DEVICE SUPPLIER

Excellent knowledge of the drug container

The first objective of any pharmaceutical company is to provide drugs for delivery to patients. Having said that, adding safety features to any drug container must absolutely not impact the drug delivery functions.

Safety systems dedicated to prefillable syringes need to be designed and manufactured incorporating all drug container characteristics. Taking the risk of supplying the container and the safety features from two separate, different sources is a hazardous challenge that may have important financial and health consequences.

Industrial capabilities in high scale manufacturing

Developing concepts and prototypes is one thing but industrial manufacturing with the quality usually required by the pharmaceutical industry is another story. BD being a worldwide injection device manufacturer has developed the specific skills and capabilities to provide the appropriate level of service required.

Safety experience and anteriority

Whenever an innovative solution of any kind is launched, start-up problems often occur and

Figure 2: The BD SafetyGlide™ needle

need to be solved quickly and efficiently. BD developed and sold the first safety syringe in 1988 and has the experience to avoid the pitfalls that any actor in this field has or will have to encounter. The learning curve is quite long!

Ability to understand end-users concerns

One of the advantages of being part of a global company is the opportunity to work with different business units that address different markets with the same products. It is an important point when you realize that protection against accidental needle-stick injuries is a critical problem for nurses. Having direct and privileged access to their concerns and requirements, and being able to translate them into specifications for the pharmaceutical industry, are significant benefits not only in terms of time, money and real competitive advantage.

Figure 4: The BD Integra™ retractable syringe

Ability to meet high level of quality and service expectations

BD has a specific unit to address the needs of the pharmaceutical industry. In other words, there are dedicated people assisting our customers for marketing, development, medical, technical regulatory and quality concerns.

Innovation

When all basic requirements are satisfied, innovation comes. Here again, innovating for a limited market is completely different from innovating in the drug delivery field. Reliability, appropriate skills, ability to follow long and complex projects, and ability to fit with different customers expectations are just a few examples of where BD has demonstrated its skills and ability specifically in the safety field.

BD's safety portfolio

BD is a true one-stop-shop for safety devices. For the pharmaceutical industry market, safety is a cross-technology platform that provides effective solutions for a various range of prefillable syringes and drug delivery devices.

BD Preventis™ needleshield system is our leading product (see figure 1 on previous page). It is an add-on device that fits with BD Hypak™ prefillable syringes with staked needles. It is assembled on the syringes after filling and stoppering. It is an automatic controlled protection device that also fits the nurses' requirements with limited impact on their usual injection technique.

BD Preventis™ looks like a simple device. Yet in reality it represents a huge concentration of technology that really makes the difference. The triggering of the safety mechanism, the activation as well as the de-activation forces, the number of parts, the materials, the process and even the colour were carefully, chosen, characterised and studied to make it a success. At the end of the day, this is what really makes the difference. Having been marketed since 2003 in the US, BD Preventis™ has become a huge commercial success, with more than 150 millions unit sold.

BD SafetyGlide™ (figure 2) and BD Eclipse™ (figure 3) are safety needles that are widely distributed and sold to end users in both private and public healthcare sectors. These are BD's solutions to be used with Luer-Lok™ BD Hypak™ prefillable syringes. BD SafetyGlide™ has a sophisticated assisted safety mechanism while BD Eclipse™ has a pivoting needle shield. Both are effective and easy to use. Vaccine and biotech customers are packaging them with their drugs.

Being a major actor of the safety environment, BD is also offering solutions for customers having liquid drugs in vials. BD Integra™ retractable syringes (figure 4) and BD SafetyGlide™ syringes are offered to such customers. BD Integra™ is the most advanced safety injection technology that BD has developed. The needle retracts backwards into the plunger rod when the mechanism is triggered.

BD SafetyGlide™ syringes belong to the BD SafetyGlide™ family being activated in the same way as the needles. BD insulin and tuberculin syringes are also available as part of the BD SafetyGlide™ range.

Figure 3: The BD Eclipse™ safety needle

As for the safety needles, they need to be packaged together industrially with the drug containers and BD is providing all the appropriate support and advice to handle such operations.

Pursuing the objective of holding a solid position in safety, BD is also working proactively on advanced safety solutions to be used in combination with self-injection and intradermal drug delivery devices.

Last but not least, it is important to mention two of BD's major core competencies both of which apply to the safety field. The first is our proven ability to make our solutions work for the pharmaceutical industry. The second is our track record of being able to transform ideas into successful products.

Art.05/Safety Article/ENG/01 SUR/MED090515

PRODUCT DEVELOPMENT NOURISHED BY DEEP ROOTS IN DELIVERY TECHNOLOGY

OctoPlus develops products in-house, collaborates with partners on the development of their compounds using its proprietary drug delivery technologies, and provides contract pharmaceutical development services to client companies. In this article, Dr Ruud Verrijk, Senior Staff Scientist, and Dr Henrik Luessen, Director Business Development, both of OctoPlus, describe the company's sustained-release injectable delivery technologies OctoDEX, PolyActive and SynBiosys, and outline how their development fits in as an essential part of an integrated business model.

Compiled by ONdrugDelivery on behalf of OctoPlus.

The exceptionally successful – such as celebrated musicians, famous actors, distinguished politicians and pioneering business leaders – often pass on to others wishing to follow in their path an important piece of advice. "Always remember your roots," they urge. And it is not only individuals who can benefit from keeping in mind where they came from. Successful companies, while they constantly evolve, adapt and grow, tend to benefit from keeping in touch with the core elements that first set them on their chosen paths.

For OctoPlus, founding core elements included impeccable science applied in the field of pharmaceutical development and drug delivery by a team of experienced and skilled researchers. When the company was born, just over ten years ago, it focused on the provision of contract development services to pharmaceutical and biotech company clients, and on this basis, with a successful track record, it has built a global reputation for innovation and professionalism.

During its first decade, OctoPlus has developed several proprietary drug delivery technologies, with an emphasis on the controlled release of injectable biopharmaceutical drugs. OctoPlus offers its drug delivery technologies for licensing to third parties on a product-by-product basis. One example is the co-development of a controlled-release alfa interferon, a product named Locteron™, for which OctoPlus entered into a partnership with US-based Biolex in February 2005. Under the terms of the agreement, Locteron™ combines OctoPlus's PolyActive™ technology with Biolex's BLX-883, a recombinant alfa interferon produced in Biolex's patented LEX System™.

Furthermore, like almost all drug delivery companies able to do so, OctoPlus has in recent years shifted up a gear and entered the higher-value realm of pharmaceutical product development in-house, boosted in early 2005 by the completion of a US$ 24 million financing round. Its proprietary product pipeline now includes both Locteron, a controlled-release formulation of human growth hormone, and a novel peptide for chronic ear infection.

CONTROLLED-RELEASE INJECTABLES

The chief application of OctoPlus's three drug delivery technology platforms, which are described in more detail below, is in the controlled delivery of injected products – particularly proteins and peptides but also including single-shot vaccines and lipophilic small molecules.

Although proteins have significant therapeutic potential, and protein and peptide product candidates are being generated with increasing frequency as the role of biotechnology in drug discovery continues to grow, their successful development is often held back by drug delivery problems such as:

– that proteins are susceptible to chemical and conformational instability in both the solid and dissolved state. This may affect the bio-

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- Biodegradable with safe degradation products
- Biocompatible in standard tests:
  - Low cytotoxicity
  - No sensitization
  - No lasting histological, morphological, systemic toxic effects
  - No genotoxicity
  - No carcinogenicity
  - No pyrogenicity
  - No immunogenicity
  - BSE-free
- Protein integrity ensured
- High protein loading
- High encapsulation efficiency
- Stable in storage (2 years)
- Release-profile tunable
- Ease in upscaling
- Inexpensive and high-quality material readily available

Figure 1: Key characteristics of hydrogels for injectable proteins

logical activity of the drugs and increase immunogenicity
– the hydrophilicity and large size of many proteins and peptides limits the possibilities to permeate biological membranes at therapeutically effective amounts and rates
– usually, the half-life of proteins and peptides is short (in the order of minutes)

The result is that by the time such products reach the market, in order to surmount these delivery problems, the products' developers find themselves backed into a corner, having to compromise by accepting less than ideal dosing regimens or administration methods – frequent injections or cumbersome infusion systems being among the common fixes.

The many advantages of gaining control over the release of drugs, particularly injected products, to solve these delivery problems, are discussed often and will be familiar to most readers. They include: achieving the optimal pharmacokinetic profile (for example, preventing high initial plasma concentrations); reducing injection frequency; and improving patient compliance and ultimately the therapy efficacy.

A most promising broad category of controlled delivery systems entrap the active compound within a polymeric matrix that degrades over time to release the drug. In the delivery of labile compounds such a proteins and peptides, these types of systems have the additional advantage of protecting the drug against premature degradation in the body.

The safety benefits that arise from controlled release are also hugely important. In fact, compared with frequent injections, a controlled release formulation enhances safety in two important ways.

Firstly, on a pharmacological level, controlled-release delivery systems increase safety by promoting constant drug levels and eliminating the drastic fluctuations in blood levels that can arise with frequent dosing. The preferably linear release characteristics of such systems prevent the high peak plasma levels that are believed to increase side effects, and prevent the low trough plasma levels that might reduce the efficacy of the treatment. The resulting improved clinical profile has the potential to improve patient compliance and ultimately therapy efficacy.

Secondly, every time a healthcare practitioner or patient goes through the injection procedure they expose themselves and others to the many risks associated with using a needle. It follows that, for example, halving the injection frequency will reduce the risk of injury by the same factor. Furthermore, with fewer injections being given, the number of opportunities to make a dosing error is smaller.

Taken as a whole, the factors described above have driven rapid growth in demand for controlled-release delivery systems, and the number of such systems available to pharma and biotech companies has rocketed in recent years to the extent that the supply hugely outweighs the demand. That is, there are now many more delivery systems out there than there are opportunities to apply them in pharmaceutical development projects.

With so many similar technologies available, it is difficult for pharma and biotech companies to differentiate them in order to find the system best suited for the delivery of their particular compounds.

Various approaches have been explored over the past three decades. Proteins have been formulated in amorphous form or as crystals (for example insulin) to ensure release over a short period of up to two days. Liposomal dispersions release their content over periods of up to three weeks after subcutaneous injection. A third, frequently investigated polymer involved in the design of controlled-release systems for proteins is poly(lactic-co-glycolic acid) (PLGA). However, its intrinsic drawbacks as a protein-releasing matrix are becoming increasingly apparent. Organic solvents have to be used to prepare pharmaceutical dosage forms such as microspheres, and acidification inside the matrix during protein release has been observed. Moreover, it is difficult to manipulate the release of a protein from PLGA matrices, resulting in an initial burst of protein after injection and a poor in vitro – in vivo correlation.

OctoPlus's technologies provide substantial benefits over the strategies mentioned above. Like other systems, they produce formulations comprising microspheres, are most commonly applied in subcutaneous injections and are also used, albeit less frequently, for intramuscular products. However, OctoPlus's technologies are clearly differentiated from others available in this space because, unlike technologies that have come before them, OctoPlus's OctoDEX and PolyActive systems are based on hydrogels.

Hydrogels are three-dimensional hydrophilic, polymeric networks capable of imbibing large amounts of water. The combined properties and characteristics of hydrogels amount to an extremely attractive substance in which to incorporate drug molecules – especially biomolecules – and from which to release them in a controlled manner over a defined timeframe.

The high aqueous content of hydrogels offers a protein-friendly environment, and many of them show excellent biocompatibility. pH drops do not occur during protein release, and the use of organic solvents often can be avoided during the preparation of formulations. The release of proteins can be meticulously controlled by bulk degradation of the hydrogel rather than by surface erosion, as with other systems.

The key characteristics of hydrogels for use in injectable protein formulations are summarised in figure 1.

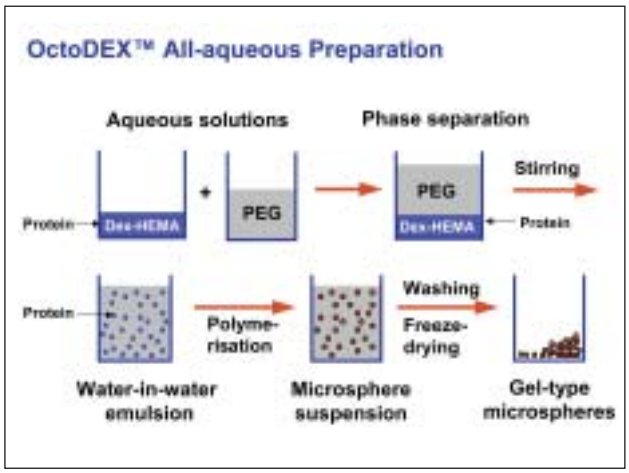

Figure 2: all aqueous preparation of OctoDEX microspheres

OCTODEX™: RELEASE FOR UP TO TWO WEEKS

In terms of its development status, one of the most advanced of OctoPlus's delivery technologies is OctoDEX, a biodegradable microsphere formulation licensed exclusively from Utrecht University, the Netherlands, which enables controlled release of biopharmaceuticals for up to two weeks. OctoDEX formulations can be injected subcutaneously or intramuscularly, through a 25-gauge needle.

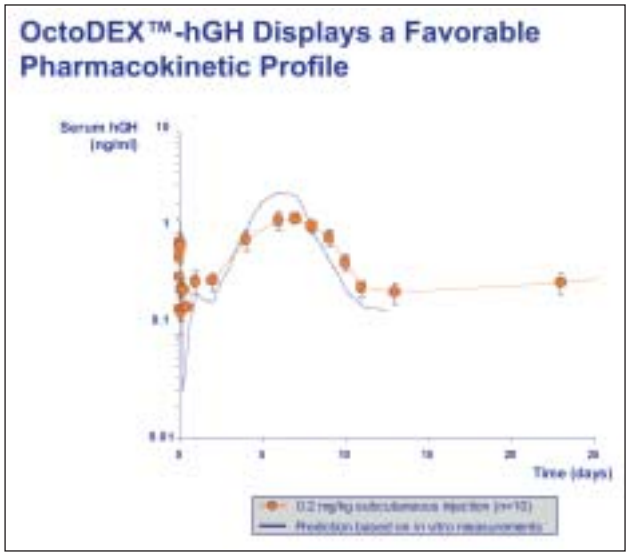

Figure 3: In vivo – in vitro correlation of hGH release from OctoDEX

Configuration	Example of delivery product	Example of active compound
Microspheres	Parenteral delivery systems	Biotherapeutics
Films	Topical delivery systems	Growth factors, anti-infectives
Gels/Wafers	Local drug delivery system	Oncolytics
Rods	Removable delivery systems	Psychotropics, contraceptives
Coatings	Implant coating delivery systems	Anti-proliferative agents

Figure 4: Range of application for PolyActive configurations

The structure and function of OctoDEX microspheres is perhaps best explained by first describing the simple all-aqueous process used to produce them.

The process, which is summarised in figure 2, is based on the phase separation that occurs in a system consisting of an aqueous solution of dextran (conjugated with for example hydroxyethylmethacrylate (HEMA)), and an aqueous solution of poly(ethylene glycol) (PEG). This phase separation is used to create an emulsion of dextran conjugate-enriched droplets in a continuous PEG-enriched phase. Subsequent polymerisation of HEMA groups attached to the dextran chain results in crosslinking of the dextran chains inside the modified dextran droplets, forming microspheres of average particle diameter 2-50μm.

Enrichment of the dextran phase with incorporated protein, allows protein encapsulation efficiencies of more than 90%. Appropriate reaction conditions are chosen so as to reduce oxidative damage of the encapsulated protein.

Another attribute of OctoDEX formulations important in the delivery of proteins is the avoidance of acidification during degradation. The hydrogel network allows small molecules to pass, meaning that, as long as sufficient low-molecular-weight buffer species are present, no pH drop will occur during the release process. This represents a significant advantage over other delivery systems, such as those that use PLGA.

TRUE CONTROL OVER RELEASE PROFILES

Three main variables determine the release kinetics of incorporated proteins from the dextran microspheres under physiological conditions (at 37ºC and pH 7). The first two are the cross-link density (degree of substitution), and initial water content of the hydrogel. The third factor determining the release profile is the nature of the cross-links, which influences the degradation kinetics. Methacrylate forms very stable links, which do not degrade under physiological conditions. HEMA links are degradable and dex-lactate-HEMA break down even more rapidly.

Degradation of the microspheres, rather than diffusion, controls the release of drug molecules from hydrogels. Therefore, careful control of the parameters described above allows release profiles to be tailored to the specific requirement of a given product. In addition to near zero-order release avoiding initial burst, novel modified dextran formulations can be designed to give pulsed and delayed release profiles, creating an attractive system for the delivery of single-shot vaccines.

Indeed, OctoPlus is actively involved at the forefront of vaccine formulation. For example, in September 2005, the company began co-development of a single-shot Japanese encephalitis (JE) vaccine in collaboration with SingVax, a Singaporean vaccine-development company. Existing JE vaccines typically require two or three doses, compared with which, the single-shot vaccine will increase patient compliance and efficacy. Clinical trials are expected to begin in the next two years.

Next to advanced vaccines, larger structures such as liposomes, virus particles (e.g. hepatitis B antigens), viruses and cells can be entrapped in and released from modified dextran microspheres.

IN VIVO DATA

In a mouse model, the in vivo therapeutic performance of one injection of IL-2 in OctoDEX microspheres was compared with five intratumoural injections of free IL-2. For both treatments, the total IL-2 dose was the same. The mice treated with the microspheres showed at least similar survival rates as the mice injected daily with free IL-2. In a dwarf mouse model, similar growth rates were obtained with one injection of microspheres with hGH when compared with daily injections of hGH.

PREDICTABILITY OF PRODUCT POTENTIAL

In 2003, OctoPlus carried out a clinical proof-of-principle study in healthy, male elderly volunteers, showing that the in vitro-in vivo correlation of hGH release from OctoDEX is excellent. After a single subcutaneous dose of 0.2 mg/kg hGH in OctoDEX microspheres, serum hGH and IGF-1 (a marker for hGH bioactivity) levels were measured and compared with a pre-

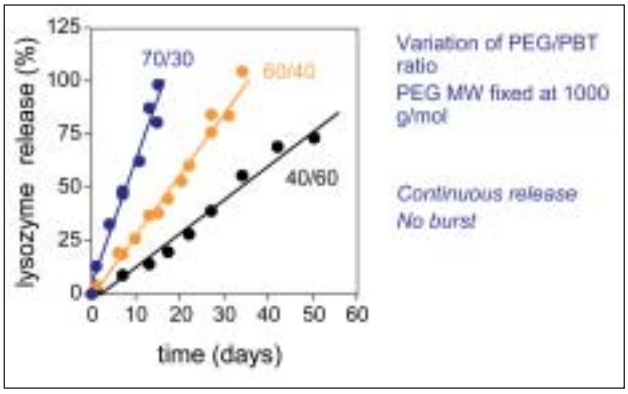

Figure 5: Effect of varying PEG to PBT ratio on release from PolyActive

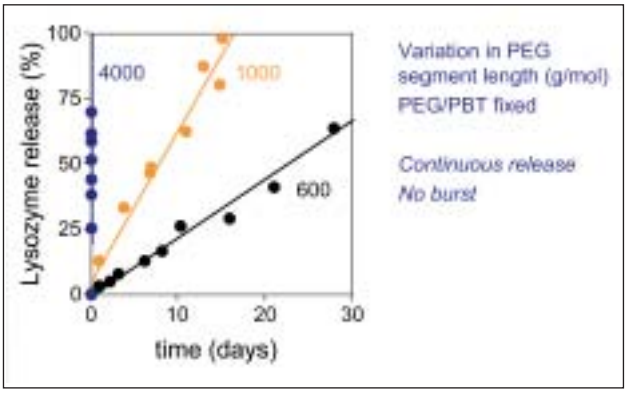

Figure 6: Effect of varying the length of the PEG segment on release from PolyActive

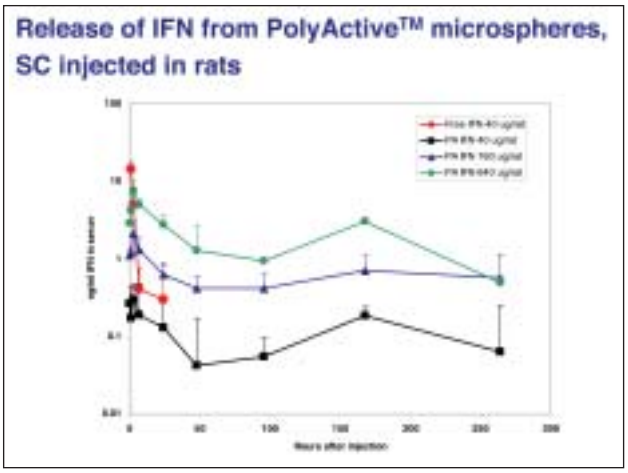

Figure 7: Results from in vivo study of IFN release from PolyActive

dicted hGH serum profile, based on the in vitro release profile of the clinical trial material. The measured hGH levels coincide with the predicted curve (see figure 3).

Maximum growth hormone serum concentrations after administration of OctoDEX-hGH formulation ranged from approximately 1.0 to 2.5 ng/ml. Growth hormone levels started to rise at about 48 h after administration, and the elevated growth hormone levels were no longer appreciable 10-12 days post injection. The growth hormone effect biomarkers IGF-1 and IGFBP-3 followed the growth hormone curve.

COST-EFFECTIVE, ROBUST AND EASILY UPSCALEABLE MANUFACTURING PROCESS

OctoDEX-based drug delivery systems, suitable for preclinical and clinical evaluation, can be produced under cGMP conditions in OctoPlus's pilot plant in Leiden, the Netherlands. A small-scale process is available for feasibility studies and for situations where only small amounts of protein are available. Larger scale process development is ongoing. OctoDEX microspheres are manufactured on a 60 mg scale (lab scale) up to 12 g batch scale, under a validated aseptic microsphere manufacturing process. Up-scaling to >100 g microsphere batches is currently in progress.

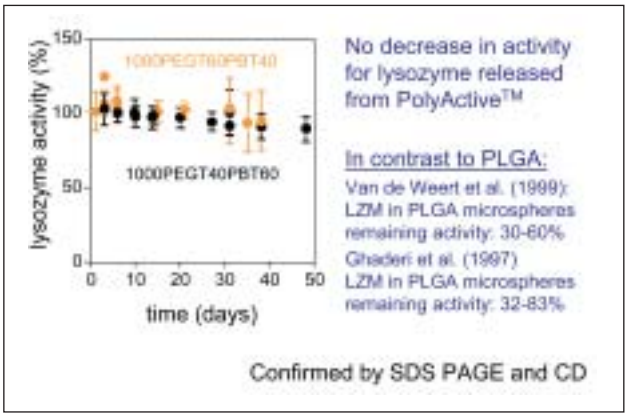

Figure 8: Stability of proteins in formulated in PolyActive

POLYACTIVE™: RELEASE OVER SEVERAL MONTHS

The second of the technologies described here is called PolyActive. The most striking difference between PolyActive and OctoDEX formulations, both of which are hydrogels, is that where OctoDEX can give sustained release for up to two weeks, drugs can be released from PolyActive formulations for several months, even up to one year.

For products where longer release is required, PolyActive therefore offers a solution. However, it is important to note that shorter release profiles are not exclusively the domain of OctoDEX. Some compounds perform well enough in OctoDEX but better when formulated in PolyActive, and in these situations PolyActive offers an appealing alternative.

The poly(ether ester) multiblock copolymer structure of PolyActive comprises two building blocks, one hydrophilic (poly(ethylene glycol) (PEG)) and the other hydrophobic (poly(butylene terephthalate (PBT)). Microspheres are produced using the double emulsion technique (W/O/W). First, an emulsion of protein-containing water droplets in an organic polymer solution is prepared. Subsequently, that W/O emulsion is emulsified in a second, external water phase. The organic solvent then is removed by evaporation, and the protein-loaded microspheres can be collected. Extremely high protein-entrapment efficiencies, close to 100%, can be achieved.

Bioassays at multiple time points throughout the microsphere production process of a PolyActive™ Interferon formulation showed that there was no loss of IFN activity. Nor was there any important oxidation or aggregation compared with controls.

PRECISE CONTROL OVER RELEASE

The ability to vary the amount and the length of each of the two building blocks (PEG and PBT) gives a huge flexibility together with precise control over a range of polymer matrix characteristics such as swelling, degradation, mesh size, and release rate.

Importantly, PolyActive products can be processed into various shapes and configurations. This gives an additional level of control over release profile and enables application in a wide range of products (see figure 4).

Using the release of a model enzyme (lysozyme) as a marker, the effect of varying the ratio of PEG to PBT, with the molecular weight of PEG fixed at 1000 g/mol, is shown in figure 5. Similarly, variation of the length of the PEG segment, at a fixed PEG:PCB ratio, is shown in figure 6. In both studies, continuous release with no burst was seen.

Results of an in vivo study of IFN release are summarised in figure 7. In rats, levels of serum IFN were measured over time following sc injection of different doses of IFN-loaded PolyActive microspheres. This was compared with serum IFN levels following sc injection of free IFN. The results show a dose-dependent linear release from the microspheres *in vivo* during 14 days.

EXCELLENT STABILITY PROFILE

In many protein- and peptide-release systems, aggregation may occur during formulation, storage and release periods. PEG/PBT copolymers cause fewer protein stability problems compared with polylactide-based systems, due to the hydrogel character of the material and since PEG/PBT degradation is slower and generates less acid end-groups.

Figure 8 summarises the results of a study that investigated the stability of proteins formulated in PolyActive, using the enzymatic activity of released lysozyme as a marker. There was no decrease in activity, indicating that this protein was neither damaged during the formulation, nor the storage and release process despite the organic solvent. These results contrast with results from similar studies with PLGA systems, where significant decreases in lysozyme activity were observed.

ROBUST SAFETY DATA AVAILABLE

The use of PolyActive in humans is well established with two implantable orthopaedic medical devices made from PolyActive having gained US and European approval. A Device Master File is available. To date, PolyActive has been used in implants in more than 5000 patients.

Extensive animal safety data is also available. Numerous subcutaneous injections of protein- and peptide-loaded microspheres have

been given to rats. Toxicity, biodegradation and long-term biocompatibility studies have been carried out in, for example rats, rabbits and goats.

Across all of the abovementioned studies of PolyActive in humans and animals, there have been no indications for local or systemic toxicity.

POLYACTIVE MANUFACTURING

As with OctoDEX, OctoPlus produces PolyActive microspheres, suitable for preclinical and clinical evaluation, under cGMP conditions in its own pilot plant in Leiden, the Netherlands. PolyActive polymers are manufactured under a supply agreement on a 10-20 kg scale under GMP conditions.

CONCLUSION

The technologies described here have arisen from OctoPlus' belief that a successful injectable controlled-release technology portfolio must set itself in a different league from the myriad of other systems occupying the market space.

Yet the company is also aware that simply having developed and owning the rights to a first-class technology portfolio is only one part of the formula for success. The real edge is gained by combining such technologies with a company possessing the right characteristics. Among them are: a team of experienced and skilled scientists; an excellent track record in attracting and retaining partners; financial stability; respect from the scientific community; and an excellent reputation within the industry. OctoPlus can confidently tick all of these boxes.

It is important to note that OctoDEX and PolyActive are just two of several proprietary systems developed by OctoPlus. A third, SynBiosys, is another biodegradable polymeric system, under development in collaboration with InnoCore (the Netherlands). SynBiosys is designed for the controlled delivery of small and medium-sized biologically active molecules over two weeks up to several months.

These three proprietary, branded systems – OctoDEX, PolyActive and SynBiosys – give just a glimpse of a far larger number and broader range of formulation approaches, techniques and scientific disciplines with which OctoPlus has become adept during its first decade of existence – particularly in the course of its contract development experience. For example, the company is globally recognised as an established player in the field of liposome formulations for the delivery of drugs, antigens and genetic material. Its other capabilities include: high-end formulation development with lipid particles and micelles; analytical chemistry; and small-scale production of cGMP clinical trial material according to EMEA and FDA requirements.

As OctoPlus's product development activities became worldwide recognised, the company made an important strategic decision that its contract research activity and its novel drug delivery technology businesses should remain absolutely crucial and an integral part of its structure. Other technology companies might turn away from contract research activities, viewing them as the mere stepping-stones they once needed to reach a product-focused business model. In contrast, OctoPlus is able to leverage effectively the synergies between its drug delivery and drug development activities, and recognises that maintaining this strong relationship is one of its strengths. Therefore, it will continue to offer its pharmaceutical development expertise and build new drug delivery partnerships around its own technologies. OctoPlus will always remember its roots.

GERRESHEIMER
pharmaSystems

PREFILLED SYRINGES AND SAFETY OPTIONS

The provision of safety features to comply with recent national and international needle safety laws and guidelines is usually the domain of medical device companies and healthcare institutions. However, in the case of prefilled syringes, the drug and device are intrinsically linked. This calls for the pharmaceutical company that markets the product to consider needle safety also. In this article, Mathias Romacker, Business Development Director, and Marén Krakau, Product Management, both of Buender Glas GmbH, discuss some of the key issues.

THE PRE-FILL CONCEPT

Pre-filling injectable drugs has become a mainstream standard over the course of the last few years. Initially used mainly for heparins and vaccines, this concept can now be found in many other therapeutic classes. Strong usage can be observed in the area of biotech drugs. The advantages are as follows:

- Convenience, easy to use
- Safe dosage form
- Easy drug identification
- Low dead space; less drug waste
- RTF® (Ready-To-Fill) syringes as gold standard
- Wide array of product options/combinations
- Cost-efficient processing
- Contract filling available
- Clear regulatory path
- Basis for other drug delivery platforms like nasal or intradermal

SAFETY LEGISLATION

Laws to prevent sharps injuries and needle-stick injuries first came into effect the US in September 2000. The European Union has introduced guidance on the issue with legislation planned, and many countries have introduced or plan to introduce legislation.

In the US, since 2000, compliance with the new legislation has been good – nearly 100% of, for example, peripheral intravenous catheter use has been converted to safety products, and the conversion from standard hypodermic needles to safety needles started picking up in the last few years.

In Europe, meanwhile, recommendations and guidance on how to prevent sharps injuries has emerged. One example is Germany, where the Berufsgenossenschaft (equivalent to OSHA) states that whenever safety devices are available they have to be utilised. Regulations such as these lack legislative character, meaning that in Europe the conversion to safety devices is lagging behind the US. So far the conversation is running slowly and the accuracy of predictions for an acceleration is difficult to assess.

Including diabetes treatment, more than one billion injections are self administered worldwide per annum. The market segment of self-injection has not yet been regulated in any geographical region despite the fact that some treatments for contagious diseases need to be self-administered.

ACTIVE SAFETY VERSUS PASSIVE SAFETY

Perhaps the best way to explain the terms "active safety" and "passive safety", is to use a motoring analogy. Buckling up with car safety belts is an activity so the safety belt is an active safety feature. In contrast, the presence of

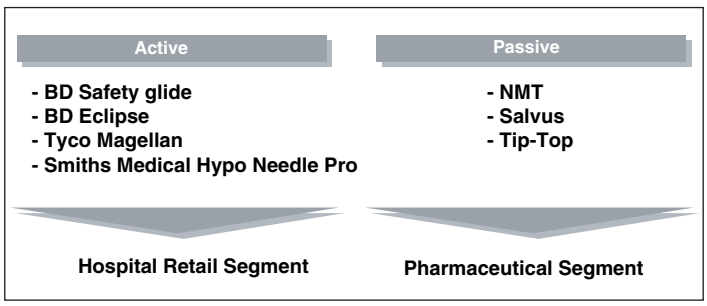

Figure 1: Solutions for prefilled syringes with stand-alone needles

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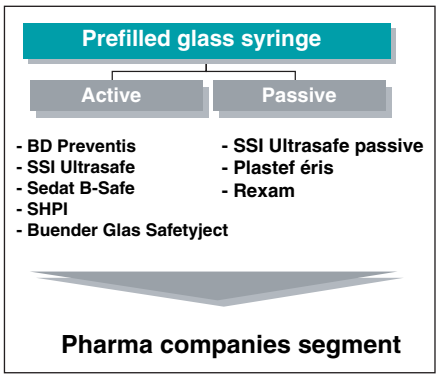

Figure 2: Solutions for prefilled syringes with staked-in needles

airbags whose inflation is triggered in the event of a collision, is a passive safety feature.

In the context of injections, active needlestick prevention requires the activation of a safety mechanism after the injection has been finished, while passive needlestick prevention occurs automatically once the injection has been administered.

For the marketers of injectable drugs in prefilled syringes, three safety solutions are available. First, they can offer a safety solution for staked-in needle syringes. Alternatively, they can switch to a luer/luerlok syringe and provide no needle (effectively passing the responsibility for needle-safety to the end user). The third option is to provide a stand-alone needle alongside the prefilled syringe.

Figure 1 summarises some of the active and passive solutions available for prefilled systems with stand-alone needles. Figure 2 summarises active and passive solutions available for prefilled systems with staked-in needles.

The first available safety systems were active systems – for stand-alone prefilled syringes and for staked-in needle prefilled syringes. Examples of active safety devices for stand-alone needles are BD's Safety-Glide and Eclipse. For staked-in needle prefilled syringes, an example of an active device is Buender Glas's Safetyject system (see figure 3)

Passive safety systems for stand-alone devices are still at the project level. For example, New Medical Technology's stand-alone Safety Prefill Needle Unit is shown in figure 4. However, staked-in needle prefilled syringe systems like Plastef's éris (see figure 5) are already established as a market standard.

Figure 3: Buender Glas Safetyject™ system

AUTO-INJECTORS

With prefilled syringes becoming mainstream they were used as primary packaging and drug delivery containers in conjunction with auto-injectors. The majority of existing needle safety legislation and guidelines are geared towards protecting healthcare professionals from accidental needlestick injury. As such, self-injection is not specifically covered and remains unregulated by the authorities with respect to accidental injury prevention.

However, virtually all disposable auto-injector platforms offer safety. Typically safety is ensured because the needle is hidden before, during and after the automatic injection. An example of such an auto-injector is The Medical House's ASI AutoSafety Injector, shown in figure 6.

Reusable auto-injectors typically do not have such a safety feature, because a prefilled syringe needs to be inserted into the device prior to use and taken out after use. Ypsomed and Safety Syringes Inc (SSI) have addressed the issue by collaborative development. The result is that Ypsomed's re-usable auto-injector can accommodate a prefilled syringe with SSI's UltraSafe Passive Delivery System (see figure 7).

The various examples of auto-injectors given above demonstrate that industry already offers innovate safety solutions for self-injection and is clearly ahead of the game despite the lack of legislation.

OUTLOOK

Prefilled syringes have become an established format for the delivery of product across the spectrum of therapeutic classes over the last decade. Many safety solutions have become available, and conversion to safety devices has been marked where legislation is in force. However for prefilled formats, safety devices often still appear to be niche products for the time being. It is likely though that as the issue of needle safety becomes more widely recognised and regulations strengthen, the benefits of employing needle-safety devices will become apparent. Over time, safety solutions will become mainstream, just as the prefilled syringe has done.

ABOUT BUENDER GLAS

Buender Glas GmbH is the world's second-largest manufacturer of prefilled syringe systems, and also supplies the pharmaceutical industry with glass cartridges, specialty vials, ophthalmic dropper bottles and inhalers. The company has invested heavily in the production of presterilised prefilled RTF® syringes, which compare with Hypak™ SCF syringes. Our RTF® syringes conform to US, European and Japanese pharmacopoeias.

Buender Glas GmbH is part of the Gerresheimer group, headquartered in Dusseldorf, Germany. Buender Glas, together with Polfa in Poland, comprises the Gerresheimer pharmaSystems division of the group.

Figure 4: NMT stand-alone Safety Prefill Needle Unit

Figure 5: Plastef's éris for staked-in needle systems

Figure 6: The Medical House disposable AutoSafety Injector (ASI)

Figure 7: Ypsomed re-useable auto-injector (above) for use with Safety Syringes Inc (SSI) UltraSafe Passive Delivery System

WHAT IS THE BEST INJECTION SAFETY POLICY?

Injections are the most commonly applied medical practice in both prophylactic and curative medical treatment around the world. According to the World Health Organisation (October 1999 report), almost 16 billion injections are given worldwide each year. In this article, Mr Bob Huang, President of Formosa Medical Devices, describes some of the associated safety problems and outlines available solutions.

Unsafe injection practices have encouraged the spread of blood-borne pathogens. Infections of hepatitis B caused by unsafe injection practice reach more than 8-16 million cases reported annually. Similarly, 2-4.5 million cases of hepatitis c, and 75,000-150,000 cases of HIV infection are thought to be caused by unsafe injections, and the overall number of deaths caused by unsafe injection practice is 1.3 million each year.

The direct medical cost of unsafe injection is calculated as around US$535 million annually, and the indirect cost to society is, while certainly many times more, incalculable. The avoidable human tragedy and financial burden caused by unsafe injection practices is escalating and we can no longer afford to ignore such an immense problem.

Unsafe injections can be categorised into three main groups.

1. Re-use of needles and syringes

This problem occurs mainly in Africa, Asia, the former Eastern Block countries of Europe, and other developing countries where needles and syringes are difficult and expensive to obtain, and there is little knowledge about the risks of re-use. The Safe Injection Global Network (SIGN) is a voluntary coalition of stakeholders aiming to achieve safe and appropriate use of injections throughout the world. In a 2003 joint policy statement (WHO/V&B/99.25), WHO, UNICEF and UNFPA urged that "by the end of 2003, all countries should use only auto-disable (AD) syringes for immunization." In 2005, with the problem of needle re-use still growing fast, it is clear that there is a long way to go.

2. Needle-stick injuries

According to Greystone Associates, there are 30 needle stick injuries reported per 100 hospital beds per year, but it is thought that only 40% of such incidents are reported. The direct medical cost for each needle-stick injury is around US$500-3000, excluding the cost of subsequent medical treatment and the cost to society. A study conducted by the US Centers for Disease Control (CDC) showed that the implementation of safety injection devices prevents 84% of needle-stick injuries. Former US President Bill Clinton passed and signed the Needlestick Safety and Prevention Act in November 2000, which requires healthcare employees to provide safety-engineered sharp devices and needle-less systems to employees to reduce the risk of occupational exposure to blood-borne pathogens. Other developed countries are following with legislation or guidelines on safety devices.

3. Inappropriate waste disposal infrastructure

Inappropriate disposal of sharps can cause injuries. It is therefore important to handle the collection and management of sharps waste in order to ensure the safety of those who might subsequently come into contact with it.

Aware that unsafe injection practices are causing death and injury to millions of people worldwide, international organisations, governments and medical device suppliers are working hand-in-hand to curtail the problem. In two areas in particular – educational safety promotion and device support – progress is being made.

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CHARACTERISTICS OF THE BEST SAFETY DEVICES

The best safety devices need to solve the three major problems outlined above meanwhile they must also be accepted by the purchaser and attractive to the user. The characteristics such devices should possess are described below.

Auto-disable/auto-destructive function. After each use, these devices are unavoidably and automatically destroyed and/or cannot be reused. The AD feature should be activated on completion of the delivery of the intended dose.

Safety mechanisms. Such functions can be activated once the device has been used. Safety Mechanism is able to reduced the needle stick injuries to minimum. The safety feature should be an integral part of the device and the safety feature should remain activated during disassembly and disposal.

Safety should be maintained throughout the duration of handling process and no additional equipment should be required when conducting the waste disposal procedure. The size of contaminated waste should be eliminated to the minimum.

Price should be kept in an acceptable range.

The benefits of conventional syringes should be maintained but the addition of AD or safety function to the design should not increase handling complexity.

TYPES OF SAFETY SYRINGE

Safe injection syringes can be divided broadly into three groups in the current market, AD syringes, Safety syringes and Safety AD syringes. Each group is described below.

AD syringes

The function of AD syringes is to prevent re-use. In most devices, and additional metal loop is placed on the plunger, which is similar to the plunger in a conventional syringe. After drawing fluid into the barrel of the syringe, the plunger can only work in one way, the injection direction, making it impossible therefore to withdraw the plunger.

The drawbacks are:

a. Lack of safety function to prevent needle-stick injury.
b. Must dispose into safety box after use.
c. Cannot fully prevent re-use since it is only the plunger that is rendered useless. Most needles with current AD syringes can be re-used by replacing the disabled syringe component with a new syringe.
d. Once the plunger has been pushed forward for whatever reason, it cannot be withdrawn. This mechanism causes problems and inconvenience to operators. For example, they often withdraw a higher dose than needed since the plunger cannot be pushed back and forth for dosage adjustment.

Figure 1: SafePro Safety Syringe after use, with needle contained within syringe barrel

Safety syringes

The purpose of safety syringes is to reduce needle-stick injuries once the safety function is activated. Most safety syringes found in the current market are designed by adding components to a conventional syringe. Most approaches involve attaching an additional protector on the needle, which either click-in or sleeve-in once the injection is finished.

The drawbacks are:

a. This is a passive safety function in that it must be performed by the operator after injection. However, if the operator does not activate the safety function, the device remains a risk.
b. Syringe and needles can still be reused even if the safety function is activated. This is not an effective way in preventing re-use.
c. The additional parts not only cause inconvenience to the operator while drawing up the dose into the syringe, but also during the injection administration procedure.
d. Adding extra parts to the conventional syringes increases the size and weight of waste products.
e. The price is high, sometimes above the acceptable limit..

Safety AD syringes

The combination of both safety and AD functions brings several advantages. After injection the safety function is activated. The needle is withdrawn inside the barrel, and the barrel thus becomes the needle's safety container.

To ensure accuracy on both functions in such safety device, production control and product designs must be well implemented and supervised strictly during manufacturing.

The selling price of Safety AD devices is generally higher than that of conventional syringes, and production speed slower. However, after unceasing hard work, Formosa Medical Devices has overcome these problems of cost and production speed.

Its range of SafePro safety syringes (see figure 1) has been widely used and has received positive feedback from many medical professionals in clinics and hospitals. To learn more about SafePro, please visit www.formosamed.com.tw.

CONCLUSION

A November 2003 WHO publication entitled: "Managing an Injection Safety Policy" stated that a strategy to achieve safe injection practices should contain three main elements, as follows:

1. **Behaviour Change:** among patients and healthcare workers to reduce unnecessary injections and achieve safe practices
2. **Equipment and supplies:** provision of sufficient quantities of new, single-use injection equipment and infection control supplies
3. **Sharp Waste Management:** safe collection and management of sharps waste.

Formosa Medical Devices Inc strongly supports these recommendations. The SafePro Safety AD Syringe has fulfilled the requirements of the Injection Safety Policy. Indeed, we can add the word "safety" to point two above so that it specifies the "provision of sufficient quantities of new, single-use, ***safety*** injection equipment and injection control supplies." This prohibits device re-use, reduces needle stick injury and reduces the workload of sharps waste management. This then truly represents the best way of managing an injection safety policy.

GMP REQUIREMENTS IN THE MANUFACTURE OF PREFILLABLE SYRINGES: ISO 15378

INNOVATION AND STANDARDISATION AS PREREQUISITES FOR SAFER DRUGS

A drug formulation and its contact packaging material must be regarded as one inseparable unit. Consequently, aspects of integrity and safety play an important role, particularly with respect to interactions. In this article, Dr Peter Schröder, Director of GMP and Compliance at MGlas, explains how today, it is one of the non-negotiable requirements that manufacturers of primary packaging materials follow the rules of Good Manufacturing Practices (GMP). To emphasise the special importance of innovative packaging components for parenterals, MGlas has initiated the ISO GMP Standard 15378.

MGLAS IS INNOVATIVE IN:

– contributing to the realization of the most effective and safest drug products for human use
– contributing to processes in compliance with GMP in the manufacture of primary packaging materials made of tubular glass
– meeting patient convenience.

INTRODUCTION

Prefilled syringes belong among the most innovative drug applications. They offer a high level of safety in the form of exact dosage, stability of the glass container against the product, functionality and patient convenience. Safety also means user protection in hospital and homecare applications.

As with all medicinal products, ensuring the safety, effectiveness and acceptance of products presented as prefilled syringes, is paramount. All of these factors can be influenced favourably by selecting the correct primary packaging material, or unfavourably if the packaging material is not selected carefully enough. The quality of the medicinal product must be guaranteed for its entire shelf life.

Unfortunately, the importance of the primary packaging material to the performance of the medicinal product is still underestimated. Regulatory authorities assign the responsibility for selecting the right primary packaging material to the pharmaceutical company. The pharmaceutical company, in turn, transfers parts of this responsibility to the manufacturer of the primary packaging material, particularly those related to production and control in compliance with GMP.

Interdependency and mutual influence of all manufacturers involved in the manufacture of medicinal products must be taken into consideration. The harmonisation of machines and packaging materials plays an essential role.

This is especially true for parenterals, where GMP conformance of processes presents a special challenge: preparation, filling and closing with RABS (restricted access barrier system) or isolator technology.

For primary packaging materials made of tubular glass, one of the prerequisites for achieving a high drug quality is constructive co-operation between those involved in the process. The interdependent relationships are summarised in figure 1 on the following page.

Design and ergonomics of production machines and control systems with regard to clean-room production of primary packaging materials are GMP essentials. Maintaining a laminar airflow serves the controlled removal of particles, unavoidably caused by, for example, a needle-bonding automat (wear debris) or a foil welding apparatus.

The co-operation of machine manufacturers and manufacturers of primary packaging materials has improved in the last few years. MGlas

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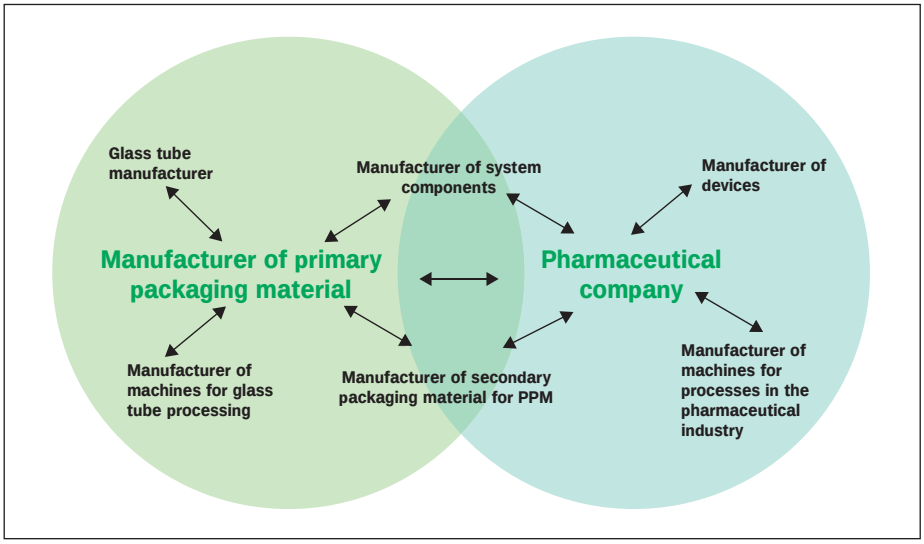

Figure 1: The interdependence of machine and packaging material

holds meetings with machine manufacturers on a regular basis.

INNOVATIVE PACKAGING COMPONENTS

The need for special glass containers for drugs and pharmaceutical diagnostics encouraged MGlas to design non-standard containers – some of them in co-operation with pharmaceutical companies. They are described below:

Figure 2: Needle design (left to right): V Bevel Needle® (MGlas), Spoon Point Plus Needle® (MGlas), Spoon Point Needle® (MGlas), 3 Bevel Needle (Standard). Source: MGlas

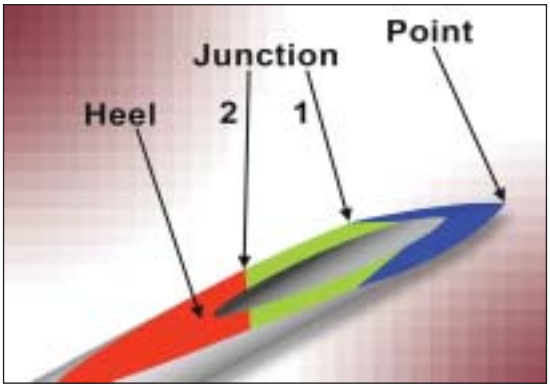

Figure 3: Details of the tip of the V Bevel Needle® (MGlas). Source: MGlas

1. Innovative Needles from MGlas

The needle is the most sensitive part of a pre-filled syringe. In addition to the standard 3-bevel needle, which is well known on the market, MGlas is offering three new needle types, which are the latest innovations in this field: V Bevel Needle® (MGlas), Spoon Point Needle® (MGlas), Spoon Point Plus Needle® (MGlas) (see figure 2). Details of the needle tip of the V Bevel Needle are shown in figure 3.

These needles were designed and developed to increase product safety as well as to enhance patient compliance. Specifically, the innovations aim at decreasing penetration forces and consequently pain during injection. Another, equally important motivation is the prevention of the coring effect (punching out skin during needle penetration as opposed to just cutting a small opening into the skin).

For mounting needles into barrels, MGlas uses state-of-the-art production equipment and technologies. Online test methods include the assessment of bevel areas (MGlas has developed a device for needle bevel control, type KSP), pull-out forces and inspection for clogged needles.

Needle penetration forces of the different needle designs with 3 and 5 bevels have shown individual benefits. These new and innovative needle types easily meet the standard of conventional needles with 3 bevels. The validation of bonding V Bevel Needles® into glass barrels, the preparation (washing, siliconisation, assembly of needle shields), filling and closing of syringes was performed in close cooperation with a participating pharmaceutical partner. The validation results met the specifications.

2. Glass component for a needle-free injection system

MGlas produces the glass capsules for Aradigm's Intraject® needle-free injector. The manufacture of this glass container meets every GMP requirement. This capsule is an excellent example for a highly innovative packaging component for an application system – not least due to its very special strengthening treatment. Furthermore, it meets an important safety requirement: lower risk of contamination during injection (HIV or hepatitis viruses), with added benefits to patients affected by needle-phobia or nickel allergy. In addition, there is no pain during injection.

3. Cartridge with inner bypass from MGlas

The two-chamber cartridges with inner bypass for PENs (see figure 4) are an important example of MGlas' most innovative glass containers. They were developed in collaboration with Pharmacia Stockholm, Sweden (now Pfizer). The cartridge is part of an application system for a growth hormone.

4. Anti-counterfeiting and safety guards

Tamper-evident seals and similar components are essential for identifying tampering, prior usage and drug counterfeiting. The significance of anti-counterfeiting features is increasing.

Prefillable syringes must be designed to permit the assembly of safety guards, and vice versa. Safety guards for application systems are gaining importance in protecting the user against accidental contamination, with HIV or hepatitis viruses, for example. Safety guards and anti-counterfeiting components often complement one another. While the number of pending patents in this field is increasing, only a few needle-protection systems are widely in use. One of the safety systems for prefilled syringes is Plastef's Eris™. Eris™ is already on the market and used with Sanofi-Aventis's prefilled Lovenox® Heparin syringes.

5. Innovative Processes at MGlas

Several years ago, MGlas introduced laser cutting of glass tubes in order to produce the previously mentioned two-chamber cartridges with inner bypass. These glass containers meet the requirements of the Japanese market in every respect. The great advantage of laser cutting is the prevention of glass particles during

the cutting process of glass segments. To the best of our knowledge, MGlas is the only company in the world using lasers for tube cutting in production.

Laser technology is also used at MGlas to drill an accurate hole into the glass capsule for the Intraject® needle-free injection device.

Initial trials to cut glass tubes for 0.5 and 1.0 ml syringes have been performed.

ISO 15378

At present, there are no international regulatory GMP requirements for manufacturers of packaging materials. However, GMP is a binding requirement of the pharmaceutical industry on the production of primary packaging materials. Pharmaceutical companies fulfil their obligation of selecting suitable packaging materials by performing what are effectively GMP audits at their suppliers. This leads to one question: what are "the" GMP rules for manufacturers of primary packaging materials?

To answer that question, MGlas has taken the initiative for all manufacturers of primary packaging materials to achieve an internationally valid GMP certification according to an ISO Standard. The benefits of closing the delta and bringing ISO and GMP closer together are clear to everybody involved (see figure 5).

The proposal for an ISO GMP Standard for primary packaging material was developed together with the DIN (German Institute for Standardisation), NAMed B 3, Berlin, and the Technical Committee ISO/TC 76.

To date, this proposal has acquired the status of a Final Draft International Standard (FDIS), thanks to international experts and the DIN. The standard constitutes the basis for a future GMP certification of production and control at manufacturers of primary packaging material according to internationally valid rules. This fulfils the authorities' requests and requirements on the pharmaceutical industry.

CURRENT SITUATION IN THE PACKAGING INDUSTRY

Standardisation significantly contributes to the pharmaceutical and medical safety of application systems. The standardisation tasks related to primary packaging materials are:

– Standardisation of the proof of quality of a primary packaging material including analytics (EP, USP, ISO)
– Standardisation of dimensions (ISO)
– Standardisation of the quality of attributive aspects (Defect Evaluation Lists (DEL), publisher: Editio Cantor, Aulendorf, Germany)
– Standardisation of production and control of primary packaging material (ISO GMP Standard ISO/FDIS 15378).

For many years, various organisations have been working on achieving the first three tasks listed above, and these standardisation tasks have reached a high level. With the development of ISO 15378, the fourth standardisation task is now making good progress.

Nevertheless, standardisation efforts are never finished. One current example is the blow-back design of injection vials. These blow-back vials are used with a stopper designed for lyophilised products or, for instance, with Teflon-coated stoppers (risk: the Teflon coating may cause a pop-off effect prior to fixation by crimping). Although there are two designs, the European version is preferred to the US version. A Draft Standard is being developed by ISO/TC 76/WG 2 and DIN, Berlin, NAMed B 3. It needs to be emphasized that this design not only influences the glass forming process, but also and foremost drug safety. A safe design for sterility requires perfectly harmonized vials and closures.

This ISO 15378 standardisation task is exclusively applied within in the scope of primary packaging material for medicinal products including: glass containers; plastic parts; rubber parts; foils and laminates; and aluminium containers. The scope of application of the standard does not include diagnostics, cosmetics or foods.

Figure 4: Glass containers for injection (left to right): two-chamber cartridge with inner bypass for PENs (see also 2.), two-chamber cartridge with two outer bypasses, three-chamber syringe with two outer bypasses. Source: MGlas

THE MAIN DOCUMENT

ISO 15378 contains the complete text of ISO 9001:2000. The experts attached particular importance to the definition and explanation of the GMPs in Section 3 "Terms and Definitions", if necessary with supplemental notes. This is the great value of the standard to manufacturers of primary packaging material. They are only faced with requirements that are explained in the standard. Figure 5 outlines important GMPs, which must be considered in the manufacture of primary packaging materials.

In addition, selection and definitions promote better communication between the primary packaging manufacturer and the pharmaceutical company. It was a declared goal that both parties speak the same language, so the primary packaging manufacturer and the pharmaceutical company have the same understanding of, for example, the term "change control" (documented control of planned and unplanned changes).

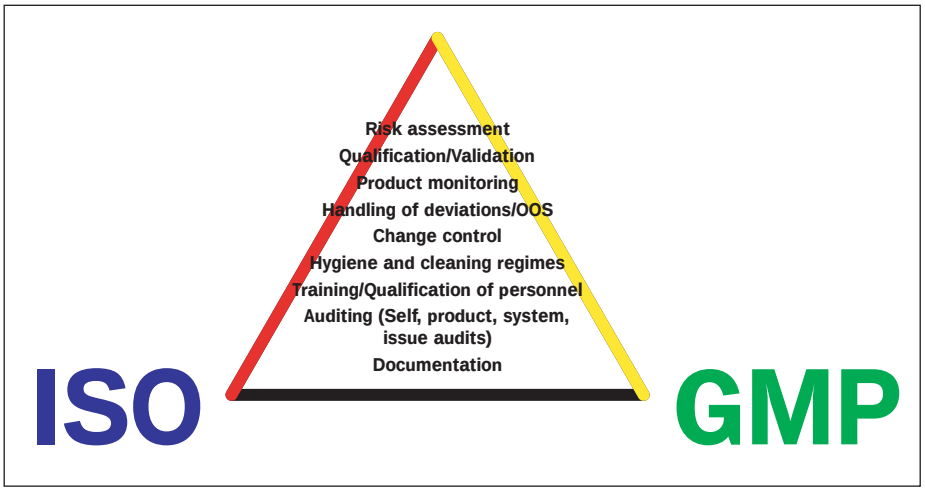

Figure 5: The Integration of GMP to close the gap to ISO 9001:2000. Source: Schröder, 2005

ANNEXES

The existing annexes of ISO 15378 are expressly designed to support the manufacturers of packaging materials in the implementation of the standard, both in the form of requirements / normative (e.g. Annex A: Printing) and in form of recommendations / informative (e.g. Annex B: Verification/Validation and Annex C: Risk Management).

The recommendatory nature is particularly noticeable in Annex B "Guidance on Verification and Validation Requirements for Primary Packaging Materials".

BENEFITS OF ISO 15378

The benefits of ISO 15378 include:

- COMBINATION of quality management according to ISO 9001:2000 with principles of GOOD MANUFACTURING PRACTICES
- Potential overall COST REDUCTION and increased competitiveness
- A common language for manufacturers and pharmaceutical industry, resulting in improved COMMUNICATION and common understanding of GMP-related topics
- STANDARDISATION of production and control of Primary Packaging Material WORLDWIDE
- Definition of MINIMUM REQUIREMENTS to be met by suppliers worldwide
- Platform for production IMPROVEMENT and innovation
- CERTIFICATION requiring GMP
- Efficient MANAGEMENT of external and internal AUDITS
- Superior competitive position for CONFORMING suppliers
- Increased ACCEPTANCE of an INTERNATIONAL Standard compared with National Standards and Guidelines and, consequently, reduction of the risk of increased legislation

CONCLUSION

Innovation and standardisation of contact packaging materials are an important aspect for safe drug usage. The standardisation of pharmaceutical packaging materials and their production contributes to the good performance of a medicinal product over its entire shelf life.

Drug and primary packaging material must be regarded as an inseparable unit. Today, the incorporation of GMP into the production and control of contact packaging materials is absolutely essential. We propose to include primary packaging materials in progressive programmes, as the PDA/FDA focuses more and more on primary packaging materials for parenterals (see Task Force Glass Defects, PDA) for an improvement of a Good Drug Performance.

In the future, the cooperation of manufacturers of primary packaging materials and machine manufacturers will carry a much higher significance than it does today.

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QLT USA, Inc.

INJECTABLE, BIODEGRADABLE IMPLANTS:

THE ATRIGEL® DELIVERY SYSTEM PROMOTES CONVENIENCE, IMPROVES COMPLIANCE AND ENHANCES SAFETY

Safety, patient compliance and ease of administration are important factors in any treatment regimen. Patient compliance in particular becomes more difficult when treatment is required over a long period. QLT USA offers a solution that not only provides a simple vehicle for the administration of a variety of compounds, but also ensures that therapeutic levels of a drug remain in the body for up to six months. In this article, Eric Dadey, Vice-President of Drug Delivery at QLT USA, says that, in addition to convenience and compliance, it is important to remember that there are clear safety benefits from sustained-release injections. For example, reducing the frequency of injection clearly reduces the exposure of patients and healthcare professionals associated to the hazards of syringes and needles.

Compliance, ease of administration and safety are all key features of the ATRIGEL® Delivery System, the sustained-release drug delivery platform owned by QLT, a global biopharmaceutical company specialising in the development of treatments for cancer, eye diseases, and dermatological and urological conditions. The ATRIGEL® system is a US FDA-approved sustained-release delivery platform that provides therapeutic levels of a wide spectrum of drugs, from a few weeks to several months with a single injection.

QLT USA Inc (Fort Collins, Colorado, US), a wholly-owned subsidiary of QLT Inc, (Vancouver, British Columbia, Canada) has developed a liquid, biodegradable drug delivery system (ATRIGEL®) for the sustained-release of small molecules, peptides and proteins. The delivery system consists of biodegradable polymers such as the lactide/glycolide copolymers dissolved in biocompatible solvents. A drug is incorporated into this solution and the resulting mixture is injected parenterally using standard syringes and needles. Upon contact with body fluids, the ATRIGEL® Delivery System solidifies and traps the drug in a solid implant. Drug is released at a predetermined rate as the implant undergoes biodegradation (see figure 1).

Using the ATRIGEL® Delivery System, QLT has delivered a variety of drugs, ranging from small molecules to recombinant biopharmaceuticals with a duration of drug delivery ranging from one week to six months. Currently, QLT has a number of FDA-approved products on the market that utilise the ATRIGEL® Delivery System, including leuprolide acetate for hormone-responsive advanced prostate cancer (ELIGARD® 7.5 mg, ELIGARD® 22.5 mg, ELIGARD® 30 mg and ELIGARD® 45 mg) and the dental pharmaceutical products Atridox® (doxycycline) and Atrisorb-D®, as well as several products in clinical trials.

THE ATRIGEL® DEPOT PROTECTS SENSITIVE BIOPHARMACEUTICALS FROM IN VIVO DEGRADATION AND ENZYMATIC INACTIVATION

The ATRIGEL® Delivery System offers a number of distinct advantages over other parenteral sustained-release delivery systems. For example, microspheres must be manufactured using aseptic processes that may include the use

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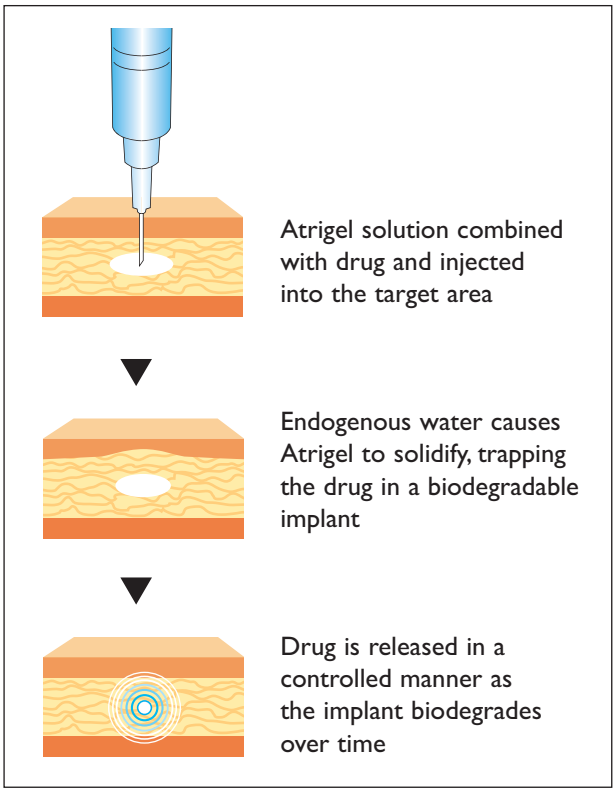

Figure 1: Controlled release from a biodegradable solid implant following liquid injection

of halogenated solvents. Furthermore, the drug to microsphere ratio is controlled by the encapsulation efficiency, a process that can result in the irretrievable loss of 25 to 50% of the active pharmaceutical ingredient (API) during the manufacture of the drug product. In comparison, the ATRIGEL® Delivery System is composed of biocompatible ingredients and is prepared by dissolving the appropriate biodegradable polymer in a biocompatible solvent. In contrast to microspheres, the ATRIGEL® Delivery System can be terminally sterilized using conventional techniques, including gamma irradiation. The unique manufacturing process and proprietary product configuration essentially eliminates the loss of drug during manufacture. Furthermore, the ATRIGEL® Delivery System can deliver large doses of API in small injection volumes as compared with small doses in large injection volumes for microspheres. Most importantly, the ATRIGEL® depot protects sensitive biopharmaceuticals from in vivo degradation and enzymatic inactivation.

The ATRIGEL® technology is a patient-friendly delivery platform when compared with implantable or reservoir devices. The ATRIGEL® drug product is injected parenterally and the resulting implant releases drug over a predetermined interval of time. Typically, the implant biodegrades at the same rate that the drug is released; therefore, the injection site essentially resolves in time for the next injection. In comparison, mechanical implants must be removed surgically and replaced or refilled after the drug reservoir is depleted.

QLT's novel technology is currently being evaluated in combination with a number of therapeutic agents for applications including bone regeneration, and in the treatment of cancer. Wide market acceptance of this approach has been demonstrated through its use in the ELIGARD® product franchise, which recorded sales of US$84 million in 2004 alone.

ELIGARD® – PROVEN IN THE MARKET

ELIGARD® is QLT's palliative treatment for hormone-responsive advanced prostate cancer. All ELIGARD® products use the ATRIGEL® system to deliver leuprolide acetate, a lutenising hormone-releasing hormone (LHRH) agonist, for one, three, four or six months. ELIGARD® is currently, or will be, sold through marketing agreements with Sanofi-Aventis in the US, Tecnofarma in Latin America, Sosei in Japan and Mayne Pharma in Australia.

In February 2005, a six-month Eligard formulation became commercially available in the US. The FDA approval was based on data from an open-label, multicentre clinical trial involving 111 advanced prostate cancer patients. ELIGARD® 45 mg was administered as monotherapy once every six months for 12 months to a patient population that included all stages (Stage A to Stage D) of disease.

The efficacy of ELIGARD® 45mg was confirmed by its ability to suppress and maintain serum testosterone levels below the FDA-defined castrate level over 12 months. In this Phase III study, circulating levels of testosterone were measured below or equal to 50 ng/dL by Day 28 in 108 of the 109 (99.1%) patients.

Oliver Sartor, Director of the Stanley Scott Cancer Center and Chief of the Hematology/Oncology Section at Louisiana State University Health Sciences Center, stated that those patients who would benefit from the six-month formulation of Eligard would include individuals that express a desire for fewer injections, travel a great deal or are away from home for long periods, patients with restrictive work schedules, and those who live far from their physician's office or have transportation difficulties.

A number of pharmaceutical companies are evaluating the ATRIGEL® Delivery System and QLT has several non-exclusive, non-disclosed partnerships for the technology. For example, VasoGenix Pharmaceuticals, announced earlier this year the execution of a worldwide agreement with QLT to develop a sustained-release formulation of Calcitonin Gene Related Peptide (CGRP) using the ATRIGEL® Delivery System. It is anticipated that the Atrigel/CGRP product will provide sustained regulation of important haemodynamic parameters – essential to improving patient outcomes – and significantly reduce the economic burden of cardiovascular disease on the healthcare system. QLT USA will develop the product to which VasoGenix has the option to acquire an exclusive worldwide royalty-bearing license.

ABOUT QLT

QLT is a global biopharmaceutical company that specialises in the development of treatments for cancer, eye diseases and dermatological and urological conditions. Established in 1981, QLT employs about 500 professionals in the fields of research and development, manufacturing, technology and business, and is one of Canada's largest biotechnology companies. QLT, Inc. is based Vancouver, British Colombia, with its subsidiary, QLT USA, located in Fort Collins, Colorado, US.

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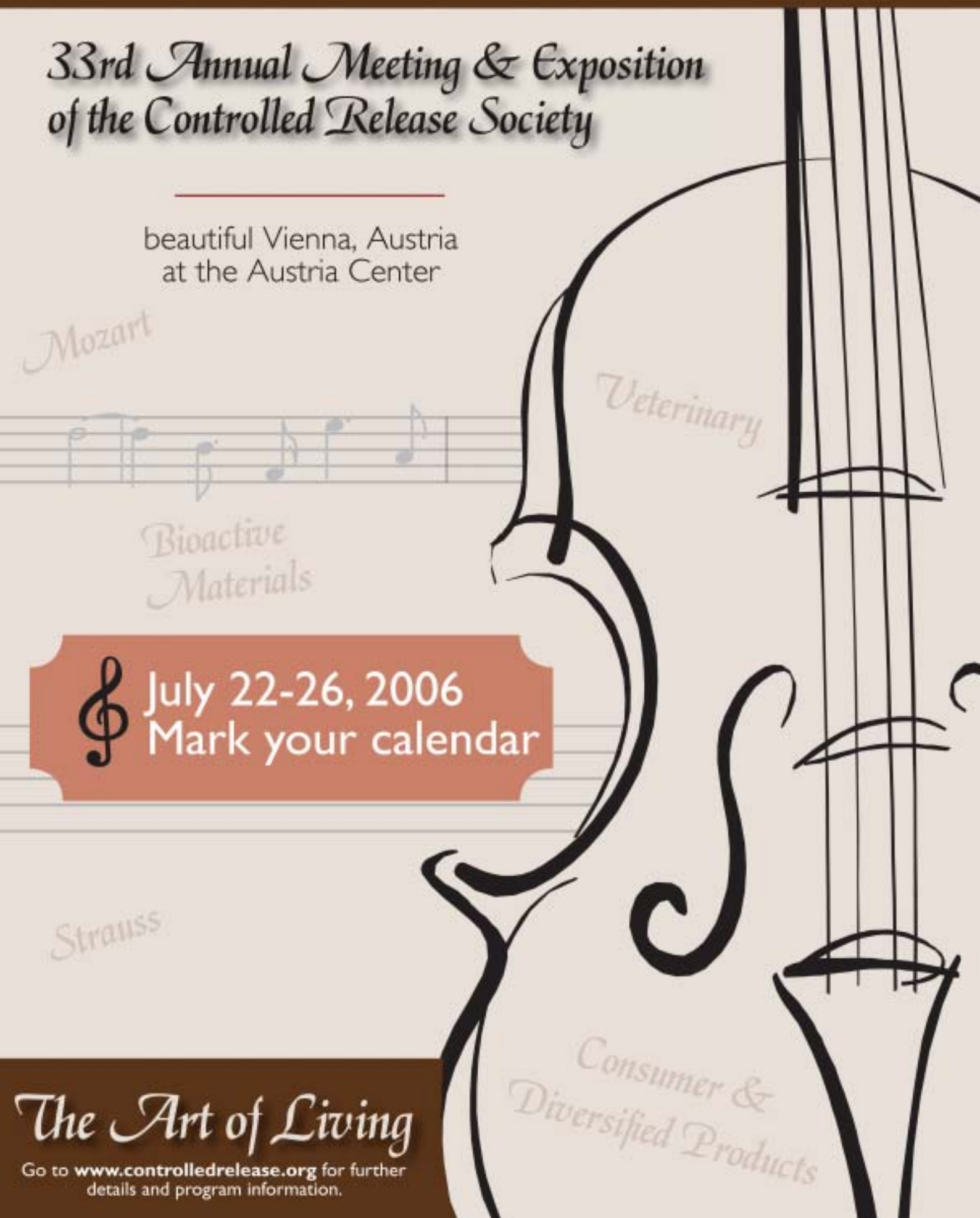

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