DELIVERING INJECTABLES:

DEVICES & DEVICE COMPONENTS

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"Delivering injectables: devices & device components"

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CONTENTS

INTRODUCTION

The majority of pharmaceuticals are delivered orally or by injection. One of the overt differences between these, the two most popular routes of administration, is that injections require a delivery device, whereas oral delivery does not. When considering the development of new injectables, what are the implications of having to involve a delivery device?

GLASS HALF EMPTY

From the less-than-positive point of view, the necessity for a delivery device could be viewed as an added complication for pharmaceutical product development. Whether or not involved directly in developing or manufacturing the device itself, the pharma company needs to ensure that its formulation is compatible with the intended delivery device, and this can raise technical barriers and add cost. In the case of drug-device combinations, the pharma company is involved in the device development and must make sure that the device (as well as the drug) meets the required regulatory standards.

For the patient, the introduction of a device into the process of taking their medicine could be seen as an additional, inconvenient step. Also, there are associations of pain, discomfort, blood and cross infection which could be made with the use of a needle. Further, it is the patient who often ends up bearing the additional cost of designing, gaining approval for and manufacturing the delivery device.

However, it is not all doom and gloom. Not by any means.

GLASS HALF FULL

Injection – intravenous, intramuscular or subcutaneous – is a powerful delivery method. It transports the active pharmaceutical in liquid form directly into the body where (unless specifically designed not to) it immediately begins being distributed throughout the system. Compared with other delivery routes, injections facilitate rapid onset, high bioavailability and precise dosing. Furthermore, the vast majority of pharmaceutical compounds are suitable for delivery by injection and readily formulated as such. In contrast, in oral delivery there are many compounds for which the oral route is not an option.

When viewed in light of these significant advantages, there is a strong and straightforward argument that, even if the device is an added complication, it is very often worthwhile.

Is the use of an injection device merely a trade-off though - added complication, cost and inconvenience being a bearable price to pay in exchange for the therapeutic benefits? Or does the injection device give something more back?

I believe it gives back, in several ways. First, it is important to note that device development is generally far less time consuming, risky and costly compared with pharmaceutical product development, and the regulatory environment is less demanding. With this in mind, we can begin to see how introducing a device into the equation can create a market opportunity.

Product lifecycle management springs to mind. However, in contrast to formulation-based LCM such as modified-release reformulations, where an NDA (and all that this entails) is usually required, device-based LCM often only necessitates the approval of a new device.

Whether part of a lifecycle management strategy for an existing injectable product, or for the first iteration of a new injectable product, the injection device presents other opportunities for product optimisation, and for gaining an edge over competitors. For the injection device is an element of treatment with which the patient becomes deeply personally involved - both physically and emotionally. From the patient's point of view, the device is the most tangible, material aspect of their treatment - far more so than the molecules that make up the formulation. Even though it is these molecules that will actually relieve their symptoms, it is the delivery device that they will consciously see, touch, feel and hear.

Through the device, there is enormous potential to enhance patient perception of the product, and strengthen the brand.

Yet the opportunities presented by the device do not end with mere image and perception. An injection device, like any other delivery system, ensures that the active compound reaches the right place in the body safely, in the right quantity and at the right time. It is an integral factor in a drug's clinical safety and efficacy.

Before the delivery process even begins, a device is sometimes the storage vessel, which has to keep the formulation pure and in tact. This means that it must remain adequately sealed to keep the contents sterile and prevent air entering (see West's article on page 16 for more on secondary seals). It must also be fabricated from materials (glass and polymers) which are stable in contact with the formulation (see M Glas's company profile on page 9).

Safety is also maintained by device features. Clear and easy dosing is enabled by, for example, dose dialling or a simple and easy method for loading the appropriate dose into the device. Security features such as child-proofing and other lockouts (for controlled substances, for example), are possible.

Needle safety is a key feature enabled by injection devices. Auto-injectors such as those under development by The Medical House (page 13), hide the needle, and needle shield systems minimise the risk of needle stick injury. In the context of mass vaccination campaigns in the developing world, auto-disable (AD) syringes eliminate devastating cross-infections from needle re-use (see Emunio's article on page 10).

A comfortable injection experience is facilitated by the device too. Ultra-fine needles and needles with innovative tip designs reduce the discomfort of needle penetration to almost nothing. And auto-injectors enable a process where, for self-injection, the patient simply presses a button and is therefore not directly involved with the needle, meaning minimal anxiety and pain perception (Ypsomed, page 4).

Finally, the device can be ergonomically designed for a pleasant and comfortable look and feel, and specific features can be incorporated to make it possible for patients with limited dexterity, such as the elderly and those with disabling diseases, to manage the device.

SUMMARY

So, compared with a tablet, for example, which goes straight from its packet into the patient with the help of nothing more than a glass of water, the injection device is an extra technology requiring design, development, regulation and manufacture. But rather than being a necessary 'headache' in the development process, the fact that some sort of device is needed to deliver all injections can be viewed as an opportunity. The device adds another dimension to the product, connects with the patient, and opens up many new possible ways to improve the product's value both to patient and industry.

The injectables market has undergone consistent growth for decades. Kalorama calculates that the implantable/injectable drug delivery market generated record revenues of US$9.8 billion worldwide in 2006 and predicts this figure will reach $12.6 billion by 2010. New active compounds and formulations are of course key factors, but it is clear that delivery device innovations are also at the heart of this market's continuing success.

Guy Furness

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MARKET TRENDS FOR SELF-INJECTION TECHNOLOGIES:

PENS AND AUTO-INJECTORS

The market for self-injection devices, both pens and auto-injectors, continues to grow at above average rates, based on patent-protected technical designs customised to patient and pharma partner needs. In this article, Ian Thompson, Manager of Business Development at Ypsomed AG, reviews the development of self-injection technology and examines some of the key features incorporated into modern-day devices, as well as future developments.

The market for self-injection devices – pens and auto-injectors – continues to show above-average growth as a result of several factors. The surge in biotech-based research means that many more protein therapeutics are reaching the market, driving demand for injectable products as a whole. Also, the increased incidence of diseases such as diabetes and the availability of therapies for previously untreatable conditions are expanding the injectables market. The advanced features of modern-day self-injection devices are making them much more acceptable to patients. If patients can self-administer their medications, then not only is it more convenient for them, it also saves on healthcare resources and costs – making self-injection much more cost-effective.

PENS AND AUTO-INJECTORS

Pen injectors are essentially sophisticated cartridge-based syringes. The first pens were introduced for insulin in 1984 and were developed for the reliable and accurate self-administration of the first wave of biotech molecules, mainly insulin and human growth hormone (hGH). Today, insulin still dominates the market for self-injection devices, followed by hGH and newer therapies such as fertility treatments (FSH) and osteoporosis treatments (PTH). During the 1990s the insulin pen market became segmented with the introduction of disposable pens and re-usable pens incorporating improved handling functions and electronics.

These therapies require frequent, often daily, manual injection with weight-based dosing or dose titration and injections are repeated until the cartridge is empty – usually after one to two weeks. The drugs in the multiple-dose cartridges require the use of preservatives, while individual dose volumes are typically 0.5 ml or lower. Pen injector patients are accustomed to injecting themselves manually with 29-31G pen needles and the need for automated needle insertion or injection traditionally has been outweighed by the patient's desire for discreet and easy-to-use devices.

Auto-injectors have been on the market as long as pen injectors but, until the 1990s, their use was restricted to emergency situations such as epinephrine for treating anaphylactic shock and sumatriptan for treating migraine. Re-usable auto-injectors have been used since the 1990s for syringe-based hormone replacement therapies, and are increasingly being used as new waves of biotech molecules become available as pre-filled formulations – for example, ,-interferon for treating multiple sclerosis (MS). The first disposable auto-injector for a therapeutic protein was launched in 2005 by Amgen for their EPO Aranesp.

Auto-injectors, as their name implies, automatically insert the needle and perform the injection – typically spring driven – and are usually designed for use with fillable or pre-filled syringes. A key requirement for auto-injection is the need for liquid-stable formulations in a pre-filled syringe or cartridge-based drug reservoir. Some of these drugs are injected daily, but many long-acting therapeutics are now injected weekly or less frequently, particularly those for treating autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis. Most of these newer drugs do not contain preservative (mono-

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dose formulations) and have comparatively large injection volumes of 0.5-1.0ml.

Figure 1 provides an overview of the major self-injection markets.

FACTORS INFLUENCING SELF-INJECTION DEVICE DEVELOPMENTS

There are a range of patient and technological factors influencing the further development of pens and auto-injectors, which are blurring the lines between the two types of devices:

Firstly, being scared of injections (needle-phobia) has spawned the development of needle hiders and automated needle insertion systems for pens, and auto-injectors for pre-filled syringes. Studies performed with needle-naïve patients confirm that up to half of patients are unwilling or reluctant to inject themselves. As patients gain experience giving injections the proportion of patients with needle phobia is in the range 10-15%. Among insulin-dependent diabetics who inject themselves very frequently the proportion of needle phobic patients is less than 10%.

Secondly, whether a pre-filled syringe or cartridge-based injection is being performed the need for needle safety is essential for injections performed in the clinic or at home. Patients who self-inject are concerned about the risks of needle-stick injuries to friends or family and about the easy and safe disposal of the used product. Whether patients use a syringe or an auto-injector, safety is an important concern. This has led to the development of safety pen needles for pen injectors, safety syringes for use with pre-filled syringes and disposable auto-injectors.

Thirdly, finer needles for pen cartridges and pre-filled syringes are reducing the pain of injection. The introduction of 31G pen needles have however increased the force required to push the drug through the fine cannula - this means that for larger volume pen injections some form of energy assisted injection mechanism can help the patient to perform the injection more easily. Pre-filled syringes are being equipped with finer thin-wall 29G needles, which have the same flow-characteristics as traditional 27G needles.

The fourth factor influencing pen and auto-injector development is that many new biotech drugs are in a freeze-dried state and not available as a liquid in a pre-filled syringe. The dual-chamber cartridge provides a convenient means of self-injecting these drugs. If they are multi-dose formulations, such as hGH, pens have been available for many years. But, many new lyophilised drugs are mono-dose formulations, injected immediately after reconstitution. If the dose needs to be varied, a pen-like dosing device used with a safety pen needle is ideal.

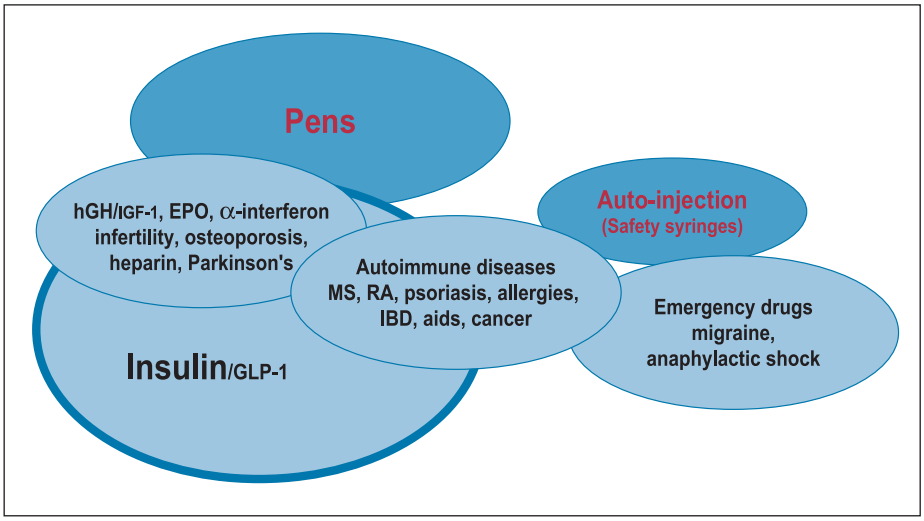

Figure 1: Overview of the main self injection markets by therapeutic category

BROAD RANGE OF CARTRIDGE-BASED SYSTEMS

Varied patient requirements, and the broad range of pen therapies, me that there is a requirement for pens with a range of functionalities. Pen systems can be segmented into the following categories:

1. Re-usable and disposable insulin pens incorporating all the functionality expected by diabetics such as easy dose setting and clear last-dose indication when the cartridge is nearly empty. For re-usable devices simple cartridge exchange is essential. Above all the dose display must be large and easy to read, while the device itself needs to suit the target patient group. Insulin pens are today very much a consumer product where design, look and feel are very important. Accessories and options offered to diabetics such as needle-hiders, auto-inserters and electronic displays are also available for pens in other therapeutic areas. Safety pen needles developed for insulin injections performed in care-giving situations can also be used for other pen therapies.
2. Pens to deal with dosing requirements for non-insulin therapies. Many therapies require weight-based dosing, but once this dose is defined, the patient does not have to change the dose. Dose-memory pens simplify handling so that the patient only needs to set the required dose once. For all subsequent injections the patient only needs to pull and push the dosing knob until the cartridge is empty. Other therapies require very small doses and the pen must incorporate mechanisms to communicate clearly that the dose has been set and injected.
3. Pens used with dual chamber cartridges. The use of dual-chamber cartridges puts special demands on the pen system in terms of intuitive reconstitution, priming and dose-setting steps. It is very important for the patient that these steps are therefore easy to learn and always performed in the correct order.

Which pen device is ultimately selected depends on the dosing demands and patient preferences.

SCALE OF CONVENIENCE FOR PRE-FILLED SYRINGES

In conjunction with efforts to move mono-dose formulations from the vial into the pre-filled syringe, pharma partners are looking for easier ways of giving injections. A simple pre-filled syringe alone can bring much convenience to a self-injection therapy. When used with a passive safety syringe the clinician or patient is provided with needle-safety, and an injection aid, making it easier to perform the injection.

The passive safety syringe devices – with their low activation forces – can also be used in conjunction with new generation re-usable auto-injectors. This has the advantage that the same safety syringe (single stock-keeping unit (SKU)) can be used in both the clinic and home environment with the simple addition of an auto-injector for home care without the cost and risk of packaging every syringe in a disposable auto-injector.

In terms of convenience, the fully disposable auto-injector device is the obvious gold standard for self-injection. Here, the pre-filled syringe is already packaged in the auto-injector, providing both ease-of-use and convenience for the patient. All the patient needs to do is remove the device cap, press the device against the skin and start the injection process.

The device automatically performs the insertion of the needle and the injection. After injection, the needle is automatically covered and made safe, as the device is removed from the

injection site. With disposable auto-injectors a clear indication of the device status before, during and after injection is important; the handling should be intuitive and the device should give visual and audible notification that the injection has been successful.

For devices with spring-driven drug delivery, the interaction of drug reservoir and injection mechanics is critical to assure maximum system reliability.

Ultimately, which device is selected from the pre-filled "scale of convenience" depends on the competitive environment, the proportion of patients self-injecting and their specific needs (see figure 2).

THE PATIENT MUST DRIVE THE DEVELOPMENT PROCESS

It is the patient who drives the continued development of new self-injection devices and this is why device companies are developing standardised device platforms that have been tried and tested with patients to cover their basic needs of *ease of use, safety and reliability*. The diverse range of therapies and needs of pharma partners mean that the device manufacturers must be in a position to provide tested and standardised devices at short notice which can then be customised to the needs of each drug, therapeutic area and patient segment as needed.

Beyond the patients' basic needs there are a range of special needs depending on their age and clinical condition. For example, patients with visual impairment (such as diabetics or the elderly) have special requirements, as do those with age-related or motor disabilities (multiple sclerosis, rheumatoid arthritis, cancer). Care about needles is an issue with HIV/AIDS and Hepatitis C, while 10-15% of the population can be expected to have needle phobia.

This wide range of needs can only be met with customised designs, taking into consideration indication-specific patient characteristics.

Figure 2: The "scale of convenience" created by prefilled syringes, safety delivery systems and auto-injectors

To minimise the risk of poor compliance, the most appropriate device and dedicated ergonomics are selected to make the injection process as easy and intuitive as technically possible.

A range of self-injection devices available from Ypsomed is shown in figure 3.

CONCLUSION

In summary, the market for self-injection devices – pens and auto-injectors – continues to grow at above-average rates, based on patent-protected technical designs customised to patient and pharma companies' specific needs. Novel technical features to provide safe and reliable use have by no means been exhausted, and the choice of the correct device requires careful selection and close collaboration between the patient, the device company and the drug manufacturer.

ABOUT THE AUTHOR:

Ian Thompson is Manager of Business Development, at Ypsomed AG, where he has been working for the last ten years with pharma and biotech partners to develop and bring to market innovative and reliable injection systems for self-administration. Ian has 20 years' experience in the selling and marketing of technical products, the last 14 of which have been spent in the field of medical devices. He has a degree in Biochemistry, a Masters in Biotechnology and an MBA from Henley Management College, UK.

Figure 3: A range of pens to cover various dosing needs and cartridge types

COMPANY PROFILE – MGlas AG

Our customers from the pharmaceutical industry know us as a future-oriented partner. Creativity, dynamics and a "can-do" philosophy at MGlas AG result in market-oriented solutions for primary packaging material as well as primary packaging and injection systems. Our products will continue to set standards. Worldwide.

It is people and their visions that create success stories. MGlas was and still is a pioneer for top-quality products made of tubular glass. What once started as a small family business has grown to be an internationally recognised supplier with more than 400 employees, a focus on personal commitment and team spirit.

COMPETENCE, EXPERIENCE

The willingness to learn and progress is our formula for competence. The search for the best customer-specific solutions made us a recognised manufacturer of innovative and consumer-friendly products.

In addition, we develop and hold own patents, and we work on the respective products until they are ready for production.

Precision is THE characteristic of pharmaceutical primary packaging materials as well as primary packaging and injection systems. In close communication with our customers, we develop and annually manufacture approximately one billion syringes, cartridges, vials, ampoules and special containers, which meet this high standard.

Our production is based on sound knowledge combined with a high degree of automation. Qualified staff as well as validated processes ensure reliable manufacturing. Internal audits keep us primed for your future demands.

Highest customer requirements can call for the exclusion of "cosmetic defects". These demands are defined to achieve the so-called Japan quality and MGlas meets them using opto-electronic surface controls (OE-SC). This system detects the smallest irregularities on the glass surface, such as scratches or coloured spots.

As early as 1992, we were the first in the industry to meet the International Quality Standard ISO 9001 in its valid version. In early 2001, we were again the first to be certified according to ISO 9001:2000. All processes at MGlas comply with the Good Manufacturing Practices for primary packaging material and therefore meet the highest international quality standards as well as specific customer requirements on a "good practice".

GOOD PACKAGING

We completely fulfil the requirements that WHO, FDA and EMEA make on our customers. Challenging GMP audits – especially on international level – are part of our daily business. Regular reviews of our DMFs, performed by external consultants, confirm the efficiency of our measures, particularly regarding the compliance with Good Manufacturing Practices.

MGlas is one of the best in its trade – for a reason: we continuously work on technological progress and on improving existing standards. Our initiative for the development of the GMP Standard for primary packaging materials, ISO 15378, closes the gap between ISO and Good Manufacturing Practices.

As the first manufacturer of primary packaging materials for the pharmaceutical industry, MGlas has been certified based on ISO 15378:2006. In order to pave the way for an international GMP certification, MGlas has presented a first draft of this ISO standard as early as in 1999. Ever since, MGlas has been committed to standardisation work.

As a consequence, MGlas was awarded the DIN Prize 2005. The award-winning contribution convincingly presented the benefits of a committed participation in an international standardisation task.

The new DIN ISO 15378 "Primary packaging materials for medicinal products – Particular requirements for the application of ISO 9001:2000, with reference to GMP", initiated and actively co-designed by MGlas , offers manifold benefits: cost reductions, improved communication, worldwide standardisation of manufacturing, defined minimum requirements and increased acceptance of the International Standard as an industry-specific solution, so additional legal requirements are no longer necessary. Benefits also include the minimisation of rejects, improvement of the environmental protection by recycling, and investment security.

ENVIRONMENT, PROTECTION AND FUTURE

We are all responsible for future generations. This is reason enough to treat natural resources with care. Consequently, we have been recycling all reusable materials for decades. It is obvious that we were also the first to be certified according to DIN EN ISO 14001 Environmental Management and the EU ECO AUDIT scheme.

PARTNERSHIP

Lasting success is mainly based on trust. Our actions are transparent and therefore reliable. Our customers appreciate this openness and involve us in shaping the future.

We have the right answers to your questions.

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Dr Peter Schröder's article, "GMP requirements in the manufacture of prefillable syringes: ISO 15378 innovation and standardisation as prerequisites for safer drugs", published in ONdrugDelivery's 2005 Safer Injections issue, is available at: www.ondrugdelivery.com/publications/MGlas2006.pdf

AUTO-DISABLE (AD) SYRINGES:
FOR IMMUNISATION PURPOSES

Several factors lead to the widespread re-use of syringes and needles in the developing world. They including a lack of awareness regarding the risks associated with syringe re-use and cultural resistance to waste in countries where resources are scarce. Also contributing to needle re-use is the lack of supplies of syringes and needles as well as the absence of infrastructure for the safe collection and destruction of used injection equipment which, unfortunately, allows for scavenging and parallel market development. In this article, Ms Tina Norgard, Co-Founder and Managing Director of Emunio, gives an insight into the current situation and potential solutions.

Almost 20 years has passed since WHO in Geneva encouraged syringe manufacturers to develop an immunisation syringe which could only be used once. It sparked a whole new generation of syringes – auto-disable (AD) syringes – which have a feature that automatically activates upon administration of the intended fixed dose to prevent subsequent re-use of the syringe and the needle.

MOVING IN THE RIGHT DIRECTION

Today, immunisation is a key service in any country's healthcare management schemes and programs. In developing countries, most preventive (EPI) vaccines are given by injection. Safe injection practices have become a critical component of the program to avoid exposing patients, health workers, waste handlers and the community to injuries and infections with blood-borne pathogens. In this respect, WHO standards on injection safety state that safe injections do not harm the recipients, do not expose the healthcare worker to any avoidable risk and do not result in waste that is dangerous to the community. Today at least 25 countries in the African region use auto-disable (AD) injection equipment for all EPI vaccinations – the number has steadily increased since the first introduction in 1989. Because they cannot be re-used, AD syringes present the significant advantage of practically eliminating the risk of patient-to-patient infection with blood-borne pathogens such as hepatitis B and C, and HIV).

Despite a WHO, UNICEF and UNFPA joint statement on AD syringes which also urged that by the end of 2003 all countries should use only AD syringes for immunisation, today in the African Region, AD syringes are almost exclusively used in campaigns in which injectable vaccines are given. In some 20 countries, disposable syringes are still used for routine EPI vaccination, particularly when AD syringes are no longer available. Evaluations carried out in the WHO/Eastern African sub-region indicate that an average of 13% of EPI injections given in health faculties use disposable injection equipment. In spite of the tremendous improvements, there is clearly still a long way to go.

PROMOTING SAFE PRACTICES

In many cases, trained healthcare workers such as physicians, nurses and paramedical staff have not been trained in safe injection practices. Often, they lack the awareness of the risks associated with unsafe practices. In addition, in some communities, untrained laypersons administer injections outside the formal healthcare sector. As a result, unnecessary risks occur. The main risk associated with poor injections practices is blood-borne disease transmission.

Patients and healthcare workers often believe that injections are more effective and act faster than oral medication. In addition, healthcare workers can charge an increased fee for injections. The more injections are given, the more people are exposed to needles and syringes that may be contaminated. In addition, if the use of injections exceeds the availability of injection equipment, re-use of syringes and needles will occur. Therefore, the higher the use of injections, the higher the risk.

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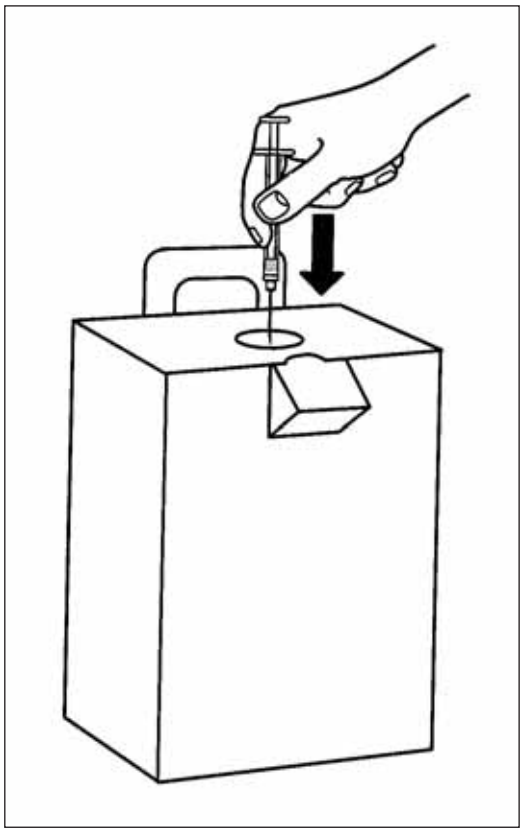

Figure 1: Proper disposal is a key safety factor

Safe injection practices have been evaluated in many countries. The results reveal various areas of risks in injection practices. These results also clearly indicate the areas where improvements are needed. Some of the unsafe practices observed during assessments include:

- Use of non sterile syringes for injection,
- Non retirement of needle from multi doses vial,
- Recapping of syringe needles after injection,
- Non-immediate placement of needles and syringes in safety boxes,
- Inadequate closing/over loading of safety boxes.

To promote safe injection practices, training resources are available from many sides. *Proper Handling and Disposal of Auto-Disable Syringes and Safety Boxes* is an excellent publication by the Children's Vaccine Program at the Program for Appropriate Technology in Health (PATH). WHO has presented numerous publications on the subject, and healthcare providers are encouraged to draw on these resources.

There is much that is being done to reduce the prevalence of unsafe injections in the developing countries. The various activities are gradually leading to reduction in the overuse of injections, prevention of re-use of syringes and needles without adequate sterilisation, as well as improving provision of single injection equipment. In particular, the interest in sharps waste disposal is expected to enhance activities to promote proper disposal of dirty needles (figure 1). An absence of proper disposal expose health workers and communities to the risks of deadly diseases.

QUALIFYING SUPPLIERS

In 2006, almost 20 years after the first AD syringe saw the light of day, an international standard, ISO 7886-3, for AD syringes for fixed dose immunisation was adopted. The preparation of ISO 7886-3 was recognised as a high priority requirement to prevent the reuse of fixed-dose immunisation syringes in developing and transitional countries. The prequalification of AD syringes by WHO leans on this standard in combination with the requirement for a quality management system for manufacturing medical devices, ISO 13485.

When Ministries of Health, donor agencies, UN organisations and others procure AD syringes, WHO in Geneva may be contacted or information can be found at www.who.int about qualified manufacturers and products.

Procuring WHO prequalified products will assure buyers that the product meets ISO 7886-3 and is produced under ISO 13485-certified conditions. In addition to that, the buying agencies are free to specify their additional requirements on environmental impact, suitability for recycling and other aspects they may find of value.

Figure 2 shows Emunio's CADY 0.5ml AD syringe with integrated 23Gx1 needle for immunization purposes. It is suitable for mass immunisation campaigns, and for use in health care clinics. CADY has a built-in mechanism designed to give a single dose of vaccine after which the syringe is permanently disabled. Thus, it prevents reuse of the contaminated syringes and eliminates unauthorized packaging, resale or reuse of the syringe.

It is inexpensive, easy-to-use in a single-hand injection process, environmentally- friendly (PVC free, Latex free). By subsequent disposal, CADY is suitable for use in syringe melters, recycling or for incineration. CADY meets the new ISO 7886-3 standard for AD syringes.

CONCLUSION

The strategies to make injections safe are straightforward. They include change in community behaviour induced through communication activities in a supportive environment. Behavioural change strategies to ensure safe injection practices must involve consumers, patients and healthcare workers.

Nurses and other health professionals can systematically implement and promote the practice of injection safety and proper waste management procedures in all immunisation programmes. Also, adequate injection equipment must be provided in sufficient quantities and a reliable waste disposal infrastructure must be made available. Many success stories suggest that this is an achievable goal. Adequate provision of injection equipment and associated commodities is key, and can not be emphasised enough.

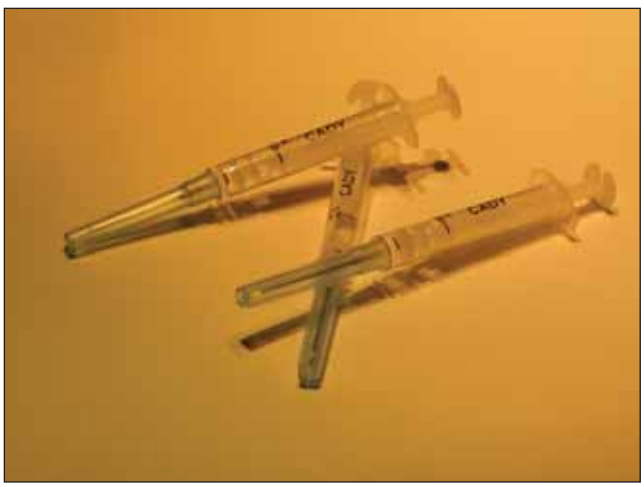

Figure 2: Emunio's 0.5ml AD syringe, CADY

LONG BEACH
CALIFORNIA

Photos courtesy of the Long Beach Area Convention & Visitors Bureau

34th Annual Meeting & Exposition of the Controlled Release Society

July 7–11, 2007
Long Beach Convention Center
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  Bill and Melinda Gates Foundation, U.S.A.
- Joseph M. DeSimone
  University of North Carolina, U.S.A.
- Marie-Paule Kieny
  World Health Organization, Switzerland
- Teruo Okano
  Tokyo Women's Medical College, Japan
- Patrick Soon-Shiong
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- David A. Tirrell
  California Institute of Technology, U.S.A.

Mini-symposia Topics

- Liposomes: Alive & Kicking
- Recent Delivery in Diabetes
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COMPANY PROFILE – THE MEDICAL HOUSE

The Medical House (TMH) is a UK-based company that designs, develops and manufactures delivery systems which enable simple, safe and comfortable self-injection, even by those patients who have an aversion to needle-based delivery. Working closely with its partners, TMH has developed a range of bespoke needle-based disposable autoinjectors for the delivery of injectable products.

The ASI (left) and the Compact ASI (right)

TMH's ASI provides the platform for bespoke systems to meet a wide range of injection needs, including provision of solutions to specific challenges.

ASI offers:

- **Simple, automated injection process requiring only two user steps**
  - needle insertion, injection, and automatic needle retraction
  - used needle and syringe captured safely inside the used auto-injector after delivery
- **Needle hidden from the patient at all times**
  - before, during & after delivery
  - addressing patients' needle aversions
- **Compatibility with common pre-fillable glass syringes**
  - facilitating rapid, cost-effective commercialisation programmes
- **Minimal number of device components**
  - providing an inherently reliable, cost-effective and versatile system
- **Enhanced capability to deliver viscous (e.g. sustained release) formulations**
  - incorporating TMH's proprietary system to protect against risk of syringe damage from elevated injection forces
  - allowing use of narrow gauge needles
- **Compact ASI option**
  - convenient and discreet

ASI Benefits

The ASI system creates competitive advantages for TMH's partners by:

- **Minimising dependence on clinical expertise**
  - enabling patients to manage their own therapy
  - reducing costs of healthcare provision
- **Overcoming patients' needle aversion**
  - improving compliance with optimal therapies
- **Eliminating the incidence of needlestick injuries**
  - minimising the risk of disease transmission
- **Facilitating rapid response in emergencies**
  - responding to large-scale injection needs
- **Versatility**
  - range of injection volumes
  - full or part delivery
  - therapeutic options
  - subcutaneous, intramuscular injection
  - emergency, elective therapies

Please contact TMH to discuss your interests and requirements

To discuss your specific requirements, interests and opportunities, or to discuss potential collaboration, please contact TMH directly using the details provided below:

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COMPANY **Profile**

You can't be a leader without thinking ahead.

Continuous New Product Development

Time and again, the world's leading pharmaceutical manufacturers choose the UltraSafe® brand for their prefilled syringe presentations. Since the first pharmaceutical launch of the UltraSafe® needle guard in 2000, followed by our UltraSafe Passive® delivery system in 2002, we have continued on our path of innovation. Our latest devices highlight tamper evident features to combat drug counterfeiting, while others are suited for use with an autoinjector, serving the growing needs of the self-administration market. We will not stop there.

The Choice of Pharmaceutical Leaders

Today, we anticipate the needs of our partners and increase the capacity to do more each and every day. We have become an intuitive and dependable partner to over a dozen leading-edge pharmaceutical companies who will supply over 20 injectable drug products to the market in the very near future.

Newly Expanded Operations

Our recent expansion into a larger and more advanced facility adds another location to our network for device manufacturing and assembly. Our state-of-the-art facility takes automated assembly of our devices to an unprecedented level and allows us to develop a comprehensive business continuity plan for each pharmaceutical partner. Moreover, our ever-growing network of automation builders and packaging experts still ensures you the fastest time to market with your blockbuster drug.

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Our commitment to improving drug delivery for prefilled syringes is proven – and remains our core competency. Our partners' products that are already available on the market demonstrate our leadership position. The UltraSafe Passive® delivery system is the most widely used and accepted device of it's kind on the market today.

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SafetySyringes, Inc.™

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THE INCREASING VALUE OF SECONDARY SEALS FOR INJECTABLE DRUG VIALS

In this article, Carol Mooney, Marketing Manager, West Pharmaceutical Services, and Douglas Stockdale, Chief Executive Officer and Chief Technology Officer, Stockdale Associates, explore the increasing importance of pharmaceutical vial (secondary closures) seals, as related to product and, ultimately, patient safety. The authors examine the many uses of secondary seals, present industry best practices via case study analyses and address issues related to product and patient safety. Also covered are secondary seal considerations when developing a packaging program and new technologies applied to secondary seals that can help manufacturers, distributors and healthcare professionals identify, authenticate and use drugs safely.

Identifying effective and innovative delivery systems and components for injectable drugs – whether a serum, lyophilised or dry-powder drug – is a challenge for pharmaceutical packaging engineers. Selecting an appropriate secondary seal is just as critical to product success as selecting an appropriate vial and stopper. End users of drug products also need increasing assurance that the product has not been tampered with nor adulterated and that it was made by the original drug manufacturing company.

Secondary seals, seals that do not contact the packaged drug, have an important function in helping to maintain an integral sterile seal, thus securing the drug supply chain and ensuring patient safety. Secondary seals are the first line of protection followed by primary closures, packaging components such as vials and elastomeric stoppers that directly contact the packaged drug product.

Seals ensure the safety and efficacious delivery of injectable drugs. By incorporating overt, covert and forensic technologies, seals protect against counterfeiting and also provide vital information that can help identify drugs as genuine, provide instructions for properly storing drugs as well as cautionary statements and dosing information that can help prevent dosing errors.

SECONDARY SEAL ATTRIBUTES

Until the late 1970s, secondary seals were either two or three-part aluminium shells. In the late 1970s, in response to haemophiliacs who had been cutting themselves on three-piece aluminium seals while trying to gain access to a drug that would stop a bleeding episode, West Pharmaceutical Services, in conjunction with Baxter Healthcare, developed the aluminium shell and plastic tear-off (flip-off) button. At this time, it was also determined that providing instructions embossed on the seal improved user compliance.

Today, most secondary seals applied to injectable drug vials generally consist of an aluminium shell and an attached plastic button that is assembled to the shell, usually in a heat staking process. When the button is removed, the injection site of the stopper is revealed. In the manufacturing process, the seal is applied after the vial has been filled and stoppered.

A capping machine rolls or crimps the skirt of the aluminium shell under the flange of the vial, serving two purposes. First, it holds the stopper firmly in place. Secondly, it creates a tight seal for the vial and elastomeric stopper interface that helps prevent contaminants from entering the vial.

The plastic button provides important protection for the drug package by protecting the stopper injection site to ensure that the elastomeric stopper is not accessed until the time the drug is to be administered. The aluminium shell has a hole in the top that is revealed when the button is removed. The hole allows the person administering the drug to access the contents of the vial by inserting a syringe or IV spike through the stopper. The plastic button also ensures that contaminants do not settle on the injection site during shipping and storage.

The plastic button also provides evidence of tampering. When the button is removed, a portion of the aluminium shell tears away and stays attached to the plastic. Buttons that have been removed cannot be reattached properly to the aluminium shell and the shell will remain in

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place, keeping the stopper secure in the vial.

The plastic button can be imprinted and moulded with conspicuous cautions, warnings and instructions useful during manufacturing, storage and at the point of use. The importance of this feature during manufacturing cannot be understated. Drug vials are frequently labelled after they are filled and a manufacturer may ship the filled vials to another plant for labelling. Information printed on the plastic button or seal, such as bar codes, can help identify products during manufacturing so they are processed in the correct labelling and final packaging line.

PROMOTING PATIENT SAFETY: INFORMATION AT THE POINT OF USE

Printing cautionary and warning statements on plastic buttons and aluminium shells can help reduce medication errors and can promote proper handling and storage of drug products to help assure drug efficacy.

For some drug products, cautionary statements printed on the button and seal are required. For example, the warning statement, "Must Be Diluted" is required on buttons and aluminium shells used to secure vials of potassium chloride for injection. Cautionary statements such as "Paralyzing Agent" are frequently used for neuromuscular blocking agents, a class for drugs used during surgical procedures. Other statements may include warnings such as "Must Be Refrigerated" or "Store Frozen." These statements may be imprinted on both the plastic button and aluminium shell or, if a clear plastic button is used, on the shell only.

PROMOTING PATIENT SAFETY: UNIQUE PACKAGE IDENTIFICATION

Applying the unique characteristics of a vial's contents to the plastic button and aluminium shell can help reduce medication errors and prevent drug mix-ups in the clinical setting. Application can be accomplished by printing directly to the button and shell and by moulding type and other characters into the button, as well as by embossing type into the shell.

The button and shell provides two layers of identification. The overt messages on the plastic button are the first check on a product's identity. Because the button covers the top of the aluminium shell, messages printed on this surface provide a covert layer for additional information. Examples of the type of information that can be applied to the button and shell include:

- The strength of the packaged drug
- Storage instructions
- Dosing instructions
- The manufacturer's name and logo
- The drug product's brand name and logo
- Manufacturing lot and date information

In addition to printed, moulded and embossed information, drug manufacturers frequently select unique colour combinations for the button and shell to help identify their products. The use of unique colour schemes can help differentiate drugs during the manufacturing process, which can help prevent improper labelling.

Some manufacturers also print bar codes and use lasers to etch coding onto the button and shell during the filling process. The coding can also be used to track vials through the manufacturing process.

USING OVERSEALS TO HELP COMBAT DRUG COUNTERFEITING

Drug counterfeiting is becoming a major threat to the drug supply chain and ultimately a threat to consumers. Once a problem limited to under-developed nations, drug counterfeits are now found in the United States, Europe and Japan. Counterfeiting is defined as the intentional dilution, mislabelling or adulteration of prescription drugs.

The importance of using the overseal to help protect against counterfeiting can be seen in an examination of the drugs included in the National Specified List of Susceptible Products released by the National Association of Boards of Pharmacy® (www.napb.net) in December 2004. The National Association of Boards of Pharmacy is the only professional association that represents the state boards of pharmacy in all 50 United States, the District of Columbia, Guam, Puerto Rico, the Virgin Islands, New Zealand, eight Canadian provinces, two Australian states and South Africa.

Of the 32 drugs on the list, 17 are injectables packaged in vials. Of the 17 injectables, seven are currently packaged with the overseal used as one layer of anti-counterfeit protection. The manufacturers of four additional injectables are considering adopting such measures.

The proliferation of counterfeit drugs can be seen in the number of cases tracked by the US FDA, which has grown from five in 1998 to 58 in 2004. The FDA's counterfeit investigations include all dosage forms. Table 1 provides examples of recent injectable drug counterfeiting cases.

Custom-designed packaging components introduced by the manufacturers of two drugs that have been counterfeited – Epogen® and Procrit® – demonstrate how overseals can help protect drug products and identify them as genuine.

Pharmaceutical Sourcing Group Americas (PSGA), manufacturer of Procrit, adopted a colour coding and covert printing scheme to help protect against counterfeiting. The colours of the seals and buttons match colour coding on the label, which helps identify the drug as genuine. Further, printing on the button identifies the product as single- or multi-dose. Printing on the seal identifies the brand name and dosage strength. The printing remains hidden until the plastic button is removed.

Amgen is using a custom button as an anti-counterfeiting measure for its drug Epogen. The buttons are moulded with the Epogen logo and dosing and strength information. Amgen also uses different colour seals to differentiate single- and multi-doses of Epogen.

Pfizer also introduced a printed plastic button for vials of Diflucan®, which was counterfeited in Japan. The printing includes Japanese characters and the strength of the medication.

Specialised printing and colour coded overseals are also used to differentiate drug products that can be confused with others having similar names.

Drug	Indication	Company	Annual sales (US$ millions)
Aranesp®	Anaemia	Amgen	416
Combivir®	HIV	GSK	882
Diflucan®	Antifungal	Pfizer	1,112
Epogen®	Anaemia	Amgen	2,261
Levaquin®	Bacterial infections	PSGA	-
Neupogen®	Neutropenia, Acute myelogia	Amgen	1,300
Nutropin AQ®		Genentech	-
Procrit®	Anaemia	PSGA	4,269
Remicade®	Chrohn's disease/RA Centocor	540	
Retrovir®	HIV	GSK	337
Risperdal®	Dementia	Ortho McNeil	2,146
Serostim®	AIDS	Serono	89
Zyprexa®	Schizophrenia	Lilly	3,689

Table 1: Examples of recent injectable drug counterfeiting cases

ADVANCED TECHNOLOGIES FOR SECURING THE DRUG SUPPLY CHAIN

Other technologies are being incorporated into secondary seals as measures for protecting against drug counterfeiting, providing manufacturers with track-and-trace capabilities and providing covert authentication capabilities from manufacturing to end use.

In a February 2004 report issued by the FDA's Counterfeit Drug Task Force, radio frequency identification (RFID) technology was cited for its potential to provide a methodology to track and trace the movement of every package of drugs from manufacturing to administration. According to the FDA report, reliable RFID technology will make copying medications either extremely difficult or unprofitable. The FDA report strongly suggested that pharmaceutical manufacturers incorporate RFID technologies as appropriate by 2007.

Product authentication data embedded into an RFID tag cannot be altered thus the electronic profile provides a higher degree of security than paper documents that accompany the drug products throughout the supply chain because documents can be altered, forged or counterfeited themselves.

Secondary seals with RFID tags moulded into the plastic button are now starting to come into the market. RFID tags have the potential to provide pharmaceutical manufacturers with the ability to improve inventory management, assign an item-level serial number to each drug vial that passes through a filling line and enable rapid product authentication in the field.

Moulding the tag into the plastic button rather than placing it within the label also overcomes a problem inherent in RFID technology. Namely, a tag in close proximity to a liquid, such as a serum drug, reduces the reliability of the information to be decoded by an RFID reader because the liquid interferes with the radio wave transmitted by the tag.

Other item-level technologies that can be incorporated into the overseal to thwart drug counterfeiting include printing with spectroscopic inks and applying high-quality, full-colour graphics. Information in the form of bar codes, for example, can be printed on buttons in spectroscopic inks that can be seen only under special lighting conditions. The bar coding can be read with a scanner.

High-quality graphics can help identify and authenticate drugs as genuine. Because of the sophistication of the printing and moulding process, this technology may be difficult for drug counterfeiters to duplicate.

THE VALUE OF SECONDARY SEALS FOR INJECTABLE DRUG VIALS

Pharmaceutical overseals serve as the first line of protection for serum, lyophilised and dry-powder drugs packaged in vials. The seals provide protection by:

- Preventing particles from entering the vial and contaminating the drug
- Maintaining the stopper firmly in place
- Protecting the injection site on the stopper
- Providing evidence of tampering
- Incorporating overt, covert and forensic technologies that can help protect against counterfeits; providing track-and-trace functionality from manufacturing to end use; aiding in product authentication; and providing written instructions for storage and usage.

In performing any or all of these functions, the seal serves the most important of purposes: to aid in the safe and efficacious delivery of drug products.

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