

# PREFILLED SYRINGES

## THE TREND FOR GROWTH STRENGTHENS



ONdrugDELIVERY  
niche information & intelligence

[www.ondrugdelivery.com](http://www.ondrugdelivery.com)



## “Prefilled syringes: the trend for growth strengthens”

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: nasal drug delivery; oral drug delivery; delivering injectables; novel biomaterials for drug delivery; safer injections; nanotechnology in drug delivery; transdermal delivery; and pulmonary delivery, among other topics. To find out more about receiving or participating with any of these issues, please contact ONdrugDelivery Ltd.

### Contact:

Guy Furness, Publisher  
T: +44 1273 831 370  
E: info@ondrugdelivery.com



*“Prefilled syringes: the trend for growth strengthens”*

Published by ONdrugDelivery Ltd, Cedar Cottage, Newtimber Place Lane, Newtimber, West Sussex, BN6 9BU, United Kingdom. Registered in England: No 05314696. Copyright © 2006 ONdrugDelivery Ltd\*

The views and opinions expressed in this issue are those of the authors. Due care has been used in producing this publication, but the publisher makes no claim that it is free of error. Nor does the publisher accept liability for the consequences of any decision or action taken (or not taken) as a result of any information contained in this publication.

\* except for the article “Reducing time to market: successful drug manufacturing” © 2006 Vetter Pharma-Fertigung GmbH & Co. KG.

Front cover image, *Validated washing process for aseptically prefilled application systems*, reproduced with kind permission from Vetter Pharma-Fertigung. The image also appears on page 16 of this issue in Vetter’s article entitled: “Reducing Time to market: successful drug manufacturing”.

# CONTENTS

## Introductory comment

Guy Furness

3

## Trends and requirements on prefillable syringes: past, present and future developments

Dr Thomas P Schoenknecht  
(Buender Glas GmbH)

4-8

## Meticulous attention to detail: the key in prefilled syringe production

Horst Koller, Walter Schiess (Schott AG)

10-12

## Reducing time-to-market: successful drug manufacturing

Dr Juergen Koch  
(Vetter Pharma-Fertigung GmbH & Co. KG)

14-17

## Packaging in prefilled syringe systems: selection and evaluation

Frances L DeGrazio  
(West Pharmaceutical Services, Inc.)

20-22

## Current market and key trends of devices used in self-injection

Joël Cotten (BD Medical - Pharmaceutical Systems)

25

## Company Profile:

The Medical House plc

29

## Company Profile:

Ypsomed AG

30

# INTRODUCTION



Some of the cornerstones upon which the prefilled syringes sector's growth has been built are:

- the continuing growth of the injectables market, underpinned by the growing number of biotech product launches
- the growing emphasis on safety, particularly sharps safety
- the increasing realisation that a delivery system's convenience, speed of use and ease of use benefit treatment outcomes
- the rising numbers of high-cost drugs reaching the market, which make it important to reduce or eliminate overfill and other sources of wastage.

These and other drivers have been discussed previously in various publications (including in ONdrugDelivery's 2005 issue, *Prefilled syringes: innovations that meet the growing demand*), and are touched upon in several of the articles that follow here.

Growth drivers, although the prerequisite for success, cannot bring about success on their own. Organisations must come forward to develop technologies and products to meet the need. This is what I would like to discuss here. What characteristics of the companies involved in prefilled syringe production, and of their products and technologies, have led to their success?

First, it is important to qualify that prefilled syringe sales are indeed continuing to grow. Evidence from recent announcements made by the major prefilled syringe producers suggests so. Gerresheimer pharmaSystems' (Buender Glas's) financial results release for the first quarter of 2006 states: "The positive development in the RTF-syringe segment continued with considerably higher sales in Q1/2006 as opposed to Q1/2005." Similarly BD, in its 2005 annual report, highlights the contribution of prefilled syringes. It said that a 6% increase in its US revenues was generated "primarily from strong sales of safety-engineered devices and prefillable syringes". Likewise, Schott's 2004/5 annual report says: "The strongly growing sterile syringes business sector was extended this year."

Independent market analyses paint an equally positive picture. Frost and Sullivan's 2005 report, *The US Pharmaceutical Packaging Market*, says that the US pharmaceutical packaging market is set to

grow at a compound annual rate of 3.3% between 2004 and 2011. "A major portion (16.8%) of this revenue is set to come from the fastest growing prefilled syringes sector," it adds. Another 2005 publication from Frost and Sullivan, *The European Prefilled Syringes Market*, estimates that "the European market for prefilled syringes is worth \$300 million and is growing at 8-10 % per annum".

So how have prefilled syringes achieved this? Looking in from outside, almost every aspect of the prefilled syringes sector appears balanced and well grounded. I believe this is the key.

For example, in terms of their technological complexity, prefilled syringes are positioned midway along the spectrum of delivery systems. They fall between high-technology devices like aqueous droplet inhalers or needle-free jet injectors, and simple, "low-tech" systems such as traditional syringe and vials, for example, or oral capsules and blister packs. Prefilled syringes are neither extremely high-tech, high-value products, nor are they mere commodities.

## RISK AND REWARD

Similarly, from the point of view of the risk to pharmaceutical and biotech companies, prefilled syringes fall into the low- to medium-risk category among the available delivery options for a given product.

Switching to a prefilled syringe format is not a totally risk-free process of course. Stability of the drug within the device (since a prefilled syringe is both container and delivery device), for example, is a source of risk. Lubrication of the plunger within the barrel is another. A prefilled syringe might be stored for some time before it is used and it is essential that the plunger moves freely when required to do so, and does not become stuck to the barrel during storage. Proper processes must be in place to minimise the chances of these problems hindering a product's approval.

However, these risks are minimal and easily identifiable compared with, for example, the "knows" and "unknowns" involved in opting to develop, say, the first systemic inhalable format of a previously injection-only product.

The same balance is seen when considering the reward side of the risk and reward equation. The claims made by prefilled syringe companies about how prefilled syringes can improve and add value to pharmaceutical products are not

wild or staggering.

They are not going lead to a transformation of medicine as we know it in the same way that, for instance, intelligent biomechanical implants and other micro- and nanotechnologies might. Instead, with prefilled syringes, we encounter measured, solid improvements over previous, conventional systems.

There are many examples, but one which typifies the type of benefit I am referring to is that prefilled syringes contain the precise amount of drug that is to be injected. In contrast, vials and ampoules have to contain more liquid than the actual dose in order for the correct amount to be withdrawn, so the excess formulation is wasted. Especially with expensive biotech products, elimination of wastage allows the manufacturer to make significant cost savings. Prefilled syringes reduce wastage of pharmaceutical product. This kind of ostensibly unremarkable advance does not typically make the front covers of eminent journals, but the millions of dollars that can be saved certainly causes drug manufacturers and drug purchasers to sit up and take notice.

The restrained nature of the prefilled syringes sector is even borne out in the way it presents itself to the pharmaceutical industry. As evidenced by the articles contained within this issue from prefilled syringe producers, component manufacturers and fillers, the focus for success – instead of being on lofty claims or a constant push for ambitious innovations – appears to be on perfecting and excelling in their stated capabilities. Prefilled syringe companies do not inhabit a fantasy world of ingenious, revolutionary technologies that might just, if they're lucky, achieve astounding success one day. Rather, meticulously planned and monitored manufacturing and filling processes generate real products today. Sterility, failsafe processes, quality checks, back-up lines and timeliness are strong themes, and they crop up in several of the articles published here.

Again and again, we gain a sense of moderation and stability. Even the very growth which we are attributing to the prefilled syringe sector's poise – with an annual rate in the high single digits – seems considered and deliberate rather than a runaway boom happening at breakneck speed.

Guy Furness, Publisher

## TRENDS AND REQUIREMENTS ON PREFILLABLE SYRINGES: PAST, PRESENT AND FUTURE DEVELOPMENTS

More than 25 years ago it was difficult to promote and market prefilled syringes. Single- and multi-dose vials and even ampoules were the standard and the prefilled syringe was virtually an unknown product, used only for a narrow range of therapeutic classes. The syringe configurations available at that time were known in processing as slow, costly and labour intensive so marketing advantages like convenience, safety, dose accuracy needed to be promoted constantly. The innovative breakthrough of the invention of the so-called all-glass syringe signalled the start of this drug delivery system's continuing story of success, writes Dr Thomas Schoenknecht, Director of Product Development/Product Management at Buender Glas.

Prefilled syringes as we know them were initially introduced in Europe in the 1980s. At that time syringes were predominantly cartridge-based. The innovation of a syringe made completely out of a glass tube with a needle glued into it opened new ways for an effective processing in filling operations. With this type of syringe, mass-market drugs such as anti-coagulants (heparins) and vaccines could be addressed on the market. As those therapeutic classes showed strong organic growth over the years, so did the numbers of prefilled syringes used.

Although the names of the major players involved in manufacturing prefilled syringes have changed as result of the various mergers and acquisitions that have taken place, essentially the same companies are still involved as back then. Among the main heparin marketers were Sanofi and Rhône-Poulenc (both now Sanofi-Aventis), Pharmacia (now Pfizer) and Roche. Examples of large vaccine manufacturers were Institut Merieux (now Sanofi-Pasteur), SmithKline (now GlaxoSmithKline) and Behringwerke (now Chiron Vaccines/Novartis Vaccines).

New indications for those first therapeutic classes were launched, heparins were brought into the US, drug prices were fairly high, and so the franchises grew substantially year after year.

Those growing numbers made it attractive for the producers of prefilled syringes to invest into and optimise their production. Machine makers were motivated to explore opportunities to improve

the processing of prefilled syringes, enhance productivity and introduce cost efficiency. This again raised the profile of the prefilled syringe and awareness of these products in the marketplace.

### MAJOR ADVANCES IN PREFILLED SYRINGE PROCESSING

During the 1980s, an increasing number of pharmaceutical companies began filling prefilled syringes in-house. How did this become possible?

In the early days of prefilled syringes, prefilled syringe manufacturers would supply so-called "bulk syringes". Various processes, such as syringe-barrel washing, siliconisation of the barrel and, if applicable, the needle also (to smooth the surfaces for easier administration, and to prevent the non-specific binding of the formulation with the device), and sterilisation, had to be carried out after manufacture but before filling. This was done either by the pharmaceutical company or a contract filler.

In order to make prefilled syringes accessible to a wider range of pharmaceutical customers, pre-siliconised, pre-sterilised syringes were developed. They were presented in a tub and were ready to be filled. Buender Glas supported this trend by launching its RTF (Ready-To-Be-Filled) Syringes.

The US market with a shorter history of prefilled syringes, was particularly keen on the advantages this format gave, to the extent that it is now exclusively an RTF syringe market.

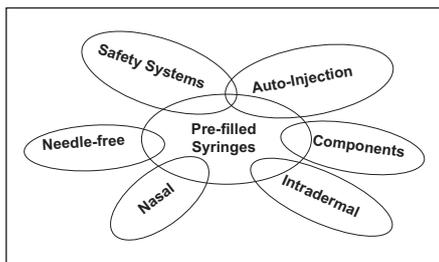


Dr Thomas P. Schoenknecht  
Director, Product Development/  
Product Management

T: +49 52 23 16 42 42  
F: +49 52 23 16 43 16  
E: t.schoenknecht@gerrsheimer.com

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

[www.buenderglas.com](http://www.buenderglas.com)



**Figure 1: Prefilled syringes: the basis for a variety of delivery technologies**

With a growing number of prefilled syringe processing lines established in pharmaceutical companies and a wide array of contract fillers being available, prefilled syringes have become the gold standard for many additional applications.

Today the prefilled syringe as a drug delivery container (system) is the basis for other drug delivery platforms (see figure 1).

Currently there are different types of prefilled syringes available, as shown in figure 2. The drug delivery system based on this container consists of the syringe itself, together with a needle shield in the case of staked-in needle syringes, or a tip cap for the Luer/luer lock syringes, and a plunger stopper made from modern innovative rubber formulation, such as those available from companies such as West Pharmaceutical Services, Helvoet Pharma and Stelmi. Finally, the system itself requires a plunger rod.

Sophisticated contract fillers like Vetter Pharma, Federa/Cardinal Health and Baxter Pharmaceutical Solutions made such prefilled syringe configurations an easily available option for pharmaceutical companies that would initially shy away from investing in filling those kinds of syringes themselves.

Nowadays the latest processing equipment can fill up to 24,000 syringes per hour.

Beside the standard components forming a drug delivery system as described in figure 3, other accessories for syringes such as backstops could be combined with the syringe system. Backstops function as finger flange extenders, offering better handling of the syringe during injection and eliminating inadvertent plunger stopper removal (see figure 4). Nowadays, such systems are available from all syringe producers such as Buender Glas.

For closing the syringe, rubber formulations covering the requirements of all relevant pharmacopoeas (USP, EP and JP) are available from the different producers of pharmaceutical rubbers.

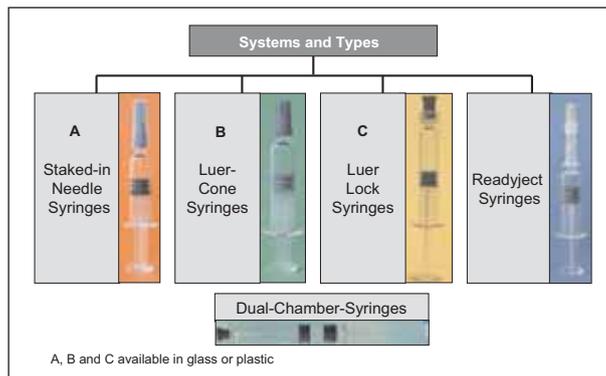
In the case of plunger stoppers these units are available in standard configurations, gamma-sterilised in double bags,

which can be used in normal filling line environments.

In recent years, more isolator and RABS technology has been installed in the market, meaning that stoppers have to be transferred into these production environments in a more sophisticated manner. Buender Glas, together with French isolation technology specialists Geringe La Calhene, has developed a system based on the worldwide-recognised Geringe La Calhene DPTE Isolator transfer port technology (see figure 5).

The system contains a DPTE 105 port unit together with a PE bag system. The transfer port system is available with all stopper sizes and for all rubber formulations required from the major rubber suppliers. All of them have modern latex-free formulations available which will be used for tip caps or needle shields as well as for stoppers.

Needle shields are also available in new innovative materials such as thermoplastic elastomers (TPEs). Buender Glas has developed a new rigid needle shield (RNS), made from TPE



**Figure 2: Prefilled syringes: a variety of options**

with a PE housing, which is produced in a co-injection process, generating a device which is produced completely under particle-reduced production conditions.

Together with thinner needles such as 1/2-inch 29-gauge needles, a pain perception reducing drug delivery system is available in pre-sterilised ready-to-use (RTF) or bulk version (see figure 6 on the next page).

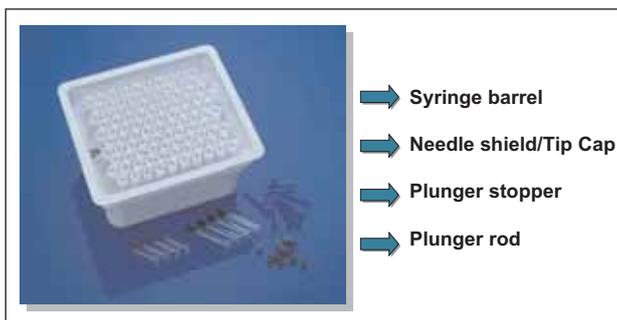
The TPE-based RNS is fully steam or gamma sterilisable and can be used with standard bulk syringe configurations or is available within the

RTF-based drug delivery system platform of Buender Glas.

Beside the goal of minimising pain perception on the patient side, tamper evidence and anti-counterfeiting is becoming more important and is of great interest for the pharmaceutical market. Gerresheimer pharma Systems is offering a new innovative design for such a tamper-evident Luer-lock closure (TELC).

The device consists of a Luer-lock adapter made from polycarbonate and a closure unit made from TPE. The whole device is produced in a co-injection mode, thereby avoiding further particle contamination of the whole syringe system, which can occur with other tamper evident or rigid tip cap-based solutions.

In addition to the TPE-based device, TELC is also available in a configuration described in more detail in figure 7 on next page. Here a rubber insert has to be assembled after the co-injection production process of the TELC itself. The main advantage of this configuration is given in the broad range of different rubber closure formulations available. These can be incorporated into the TELC enabling an easy transition from one Luer or Luer-lock syringe configuration with a given rubber formulation for the Tip Cap, to the tamper evident version of the TELC using the same rubber closure.



**Figure 3: Basic components of a prefilled syringe system**



**Figure 4: Back Stop as flange extender for better handling and eliminating inadvertent plunger stopper removal**



**Figure 5: Stopper in transfer port configuration covering the needs of RABS and isolator technology**



**Figure 6: New needle design together with innovative materials (TPE) open ways to reduce pain perception**

The whole system is fully steam or gamma sterilisable, and can be used either on standard bulk syringe units as innovative closure system or can be used ETO-sterilised, together with the RTF syringe configurations available at Buender Glas.

## NEW REQUIREMENTS

Pharmaceutical companies are considering the pre-filled syringe as the most appropriate way of presenting an increasingly wide range of injectable products. This is underlined by the fact that the prefillable syringes market is growing at more than 10% annually. As the scope of the syringe application broadens, pre-filled syringes will be expected to meet a growing number of requirements, which will be discussed in the following sections.

## DILUENT SYRINGES

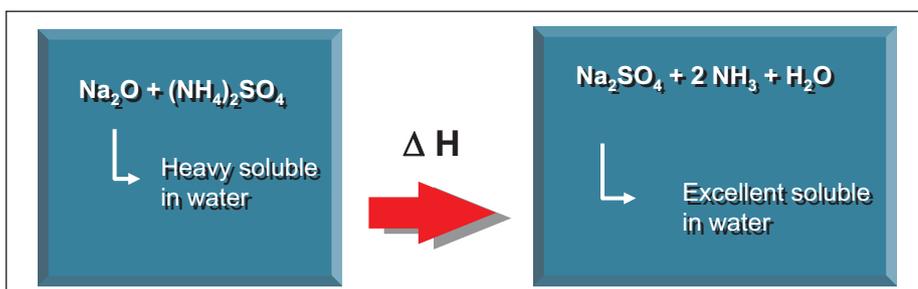
The number of drugs that are only stable as a lyophilised powder, and must therefore remain in this form until just before administration, is increasing, especially for biotech drugs. For sophisticated drug delivery, pre-filled diluent syringes have become an option. The volumes of most diluent syringes used range from 0.5-5 ml.

A challenge with diluent or saline syringes used in this application field is an undesirable

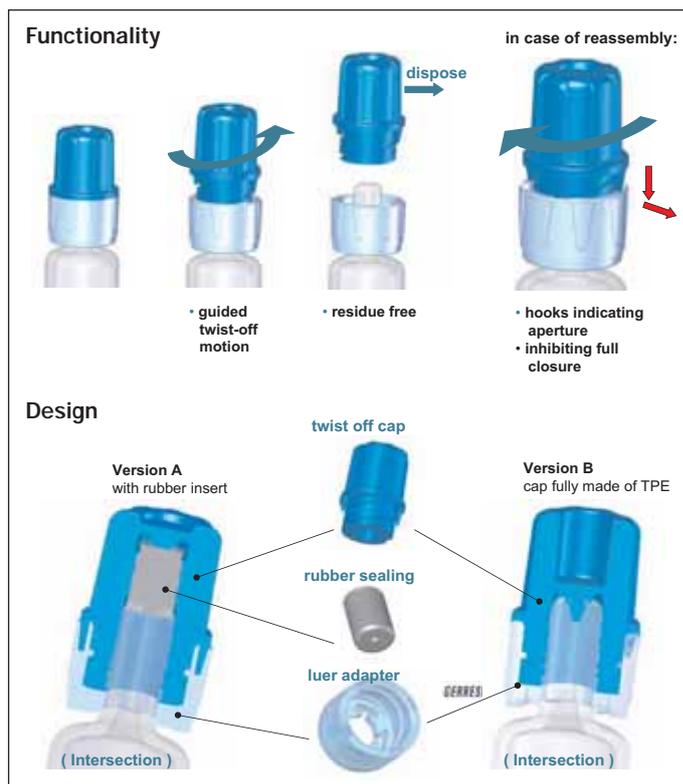
change in the pH value of the diluents stored in the syringes with time. This problem has been observed for several solvent syringes and, especially for WFI syringes, the USP defined upper limit of pH 7 has to be observed.

The shift in pH occurs because the glass used for the syringes is a USP type I glass which contains borosilicate. Syringes are formed by heating the glass thereby sodium oxide is transferred to the surface of the glass syringe. As sodium oxide is characterised by a very limited solubility, the remaining oxide cannot be removed during the cleaning process of the syringe using WFI. However, over time the ions on the inside of the syringe are released into the non-buffered solution – for example, the WFI. This eventually results in an increase in the concentration of hydroxide ions, yielding a change in the pH value.

To overcome this issue Buender Glas has developed an ammonium sulphate pre-treatment process. Ammonium sulphate is sprayed into the glass barrel before the tempering process of the formed syringe is started. The heat energy induces a chemical reaction whereby the heavy, soluble sodium oxide is transferred into the high-



**Figure 8: Reaction scheme for ammonium-sulfate treatment**



**Figure 7: Tamper-evident Luer-Lock closure TELC**

ly soluble sodium sulphate plus water and ammonia. The reaction is summarised in figure 8.

A study comparing the pH-increase in non-treated and treated syringes filled with double distilled water clearly showed a tremendous pH-stabilisation of the treated syringes. After heating the syringes to 121°C for one hour, the pH of the water in the non-treated syringe increased from 5.5 to 6.6 while the pH of the WFI in the treated syringe configuration only increased from 5.5 to 5.9.

## SILICONE-SENSITIVE DRUGS

Many of the recently developed drugs – especially in the area of biotech – have shown an increased sensitivity towards free silicone. However, siliconisation of the inside of the glass barrel and the plunger stopper is essential for the functionality of the syringe.

Buender Glas has established a process that allows silicone to be “baked” on to the inside of the syringe, preventing the formulation of free silicone in the drug containing solution.

The process, which is applicable to most pre-filled syringe types, including RTF syringes, is based on spraying an emulsion of medical grade silicone oil into the glass barrel. During the following heat treatment, low chain-length fractions of the silicone oil evaporate and a given fraction of the silicone oil with longer chain length forms hydrogen bonds as well as covalent bonds with the glass. This process is available in standard siliconisation grades as well as



Figure 9: Pin used for forming the cone bore

in individual customer-specific versions in order to cover specific requirements.

### HEAVY METAL REDUCTION

Over the last few years it has become increasingly clear that biotech drugs are sensitive to heavy-metal contamination in glass syringes. An analysis of reported negative interactions indicated one specific metal ion, Tungsten, as a critical one. Although not an integral component of the glass composition of the syringe, Tungsten is used during the forming process of the syringe by a pin, which is required to form the cone bore and thereby withstand the melted glass during the forming process of the syringe cone.

The use of the pin, in this case a Tungsten pin, is illustrated in figure 9. The Tungsten pin is used to form the opening bore of the syringe cone by moving into the bore when the forming tools form the cone characteristics. Due to the temperature of the viscous glass, with time the tungsten pin becomes smaller as it releases ions into the viscous glass. These Tungsten ions can create the known side reactions with the drug.

This problem can be overcome by using Tungsten-free pins, which requires a specific handling on the glass forming lines. Using established technology, tungsten-related problems with drug solutions can be solved. At Buender Glas, all syringe formats in the product portfolio can be formed using the tungsten-free technology if requested by the customer.

### SELF-INJECTED DRUGS

A growing number of injectable products can be self-administered at home. Often auto-injectors will be used. At present, a stand-alone syringe is usually inserted into a re-usable auto-injector, but for the future a trend for disposable devices is expected.

As the prefilled syringe is emptied using power from a spring rather than a manual process, the silicisation of the glass barrel is of major significance. It has to be complete to

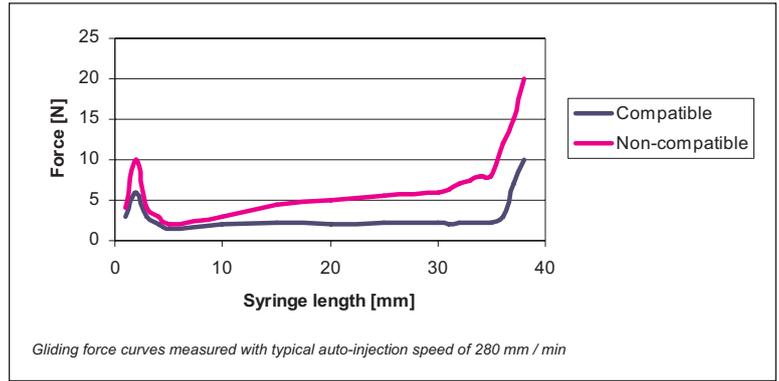


Figure 10: Gliding forces in 1 ml, long syringes

ensure delivery of the entire dose. This can be achieved by a homogeneous surface coating yielding a uniform silicone distribution over the whole glass barrel, thereby generating a stable constant gliding force along the whole syringe length.

A second point, which has to be considered carefully, is the potential side-reaction of the drug active substance with the silicone in the syringe. As a result, quite often the lowest possible silicone concentration is allowed only and the whole system, consisting of the auto-injector (spring constant) and syringe, has to be finetuned to yield the optimal solution. The factors that must be balanced are: the auto-injector characteristics; syringe characteristics such as break-out force; gliding force; silicone distribution; and the silicone requirements of the drug itself.

In figure 10, a gliding-force diagram measured on a 1 ml long, 1/2-inch needle syringe is shown, demonstrating in blue the curve measured on a syringe with optimal silicone characteristics, compared with the red curve, which shows a non-optimal silicone distribution.

### PACKAGING REQUIREMENTS

In recent years, new technologies such as E-Beam sterilisation of sterile syringe packaging units, and further requirements on particle contamination limits of the clean rooms by the packaging configuration, were clearly specified by the end users of the syringes. Buender Glas was able to follow these requirements from the outset.

As a result, sterile ready to use (RTF) syringes are delivered to the customers only in cardboard-free packaging containers made from Acrylux, which can be opened without a knife or any other sharp opening device which can create particles. For the same reasons, a double bag is required around the tub that contains the syringe. Such a packaging configuration is also a standard at Buender Glas.

In addition to the packaging configuration improvements triggered by particle reduction requirements, a specific sterilisation technique

for the syringe presentation itself requires a change in the standard packaging unit. For the past five years, E-Beam sterilization has been applied increasingly in combination with isolator equipment used for syringe filling. In such a filling line, tubs with syringes were moved on their way to the filling line through a curtain of fast electrons, high enough in energy to sterilize the outside of the tub containing the syringes and to create ozone inside the tub.

This ozone formation has to be minimised as ozone is a highly reactive radical, which can interact with the drug to be filled in the syringe immediately after moving through the E-Beam curtain.

The reduction of the ozone formation is practically achieved by inserting a specific inner lid made from Dupont's Tyvek®, which is placed on top of the syringes. This lid absorbs the energy from the electrons as they moving through the outer closing of the tub. Such configurations are available for all typical sterile syringe configurations at Buender Glas.

### THIN NEEDLES

The increasing demand from end-users for technologies that provide convenient injections is one of the major factors driving the prefilled syringe market. This demand for convenience gives companies within the sector an excellent opportunity to differentiate themselves.

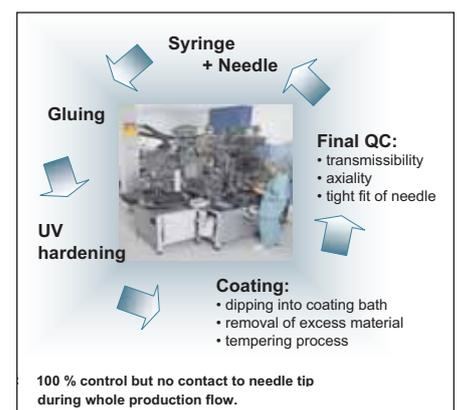


Figure 11: Packaging improvements

Uppermost in the thoughts of many patients receiving injections are pain and discomfort. To overcome this negative image, syringes are placed, for example, into an auto-injector in order to hide the needle visually for the consumer as they get their shot.

Similarly, increasing the numbers of bevels on a needle tip has also been used as a marketing argument to create a more positive atmosphere for injections. Needle tips with five bevels instead of the normal three bevels are available from all needle producers and also used for the production of sterile RTF syringes.

Another way of reducing the fear of injections is to use thinner needles, which reduce the pain perception compared with the normal standard-diameter needles. Such needle types were introduced two years ago for subcutaneous injections – for example, in combination with a 1/2-inch needle. A thin-walled 29-gauge needle with an inner bore diameter close to that of a standard 27-gauge needle was the first to reach the market in combination with a prefilled syringe in a sterilised format, together with a RNS made from TPE.

In line with this market trend, Buender Glas is offering a 29-gauge needle with a standard needle shield and also in combination with a

TPE-based RNS. The company is of the opinion that a thinner needle will reduce the individual subjective pain perception. However, other important needle characteristics also have to be considered in order to minimise pain perception.

Firstly, there are the basic needle-quality characteristics, such as the requirement for a hook-free needle tip and smooth surfaces. These are achieved through a validated, reliable production process. Then there are several more subtle factors such as the number of bevels, angle of bevels and the bevel length. The third set of characteristics – in Buender Glas's experience, the most important – comprise the type of needle coating and the method of assembling, which we have identified in specific tests performed externally at independent laboratories.

At Buender Glas we have a production philosophy for staked-in needle syringes where the needle tip, which is the most critical part on a needle, is not affected/treated during the whole assembling process (see figure 11 on page 7). Furthermore, a specific coating process for the needle is an option which can be used at Buender Glas to produce even with standard needle configurations drug delivery systems where optimal patient convenience during injection is achieved.

## OUTLOOK

In the years ahead, offering the benefits of prefilled syringes will become a must for many injectable drug manufacturers. Easier and more cost-effective processing, a clear regulatory path, and new innovative creations around it will drive growth. The market will expand still further as prefilled syringe technology and know-how is applied in the development of prefilled devices for other routes of administration including nasal applicators, needle-free devices and intradermal injectors. The future and growth has just begun.

Buender Glas, being an established player in the field with a proven successful track record, is in a position of strength to capitalise on the opportunities that lie ahead. Innovative concepts will be realised and launched, and strategic co-operations and partnerships will provide the platforms for continuous worldwide growth. Buender Glas seeks to be the pharmaceutical industry's partner of choice for the development of prefilled syringe systems and is willing and capable to assist them on the way to develop the optimal drug delivery device for a given therapeutic class and application.

*For more information, please visit our web page at: [www.buenderglas.com](http://www.buenderglas.com).*



# BRAILLE REQUIREMENTS FOR MEDICINAL PRODUCTS

## One Year On – Where are we Now?

27 September – 28 September 2006  
The De Vere Cavendish Hotel, London  
Conference No. M9-6106

A limited number of promotional opportunities are available at this event.  
*For more information contact: [Judith.Black@management-forum.co.uk](mailto:Judith.Black@management-forum.co.uk)*

For Brochure  
visit our website:

[http://www.management-forum.co.uk/html/  
con\\_semin\\_section/con\\_display\\_event.asp?id=293](http://www.management-forum.co.uk/html/con_semin_section/con_display_event.asp?id=293)

MANAGEMENT  
FORUM

**Innovation  
&  
Commercialization**

# Asia Pacific Drug Delivery Global Summit 2006

October 17<sup>th</sup> & 18<sup>th</sup>, 2006  
Shanghai, China

**Key Players:**

- LG LIFE SCIENCES
- ETHYPHARM
- DEUTSCHE BANK
- PHARMAVENTURES
- ROCHE PHARMA PARTNERING
- MEDICAL QUALITY INTERNATIONAL
- EURAND
- 3M DRUG DELIVERY SYSTEMS
- NEKTAR THERAPEUTICS
- TAIWAN LIPOSOME COMPANY
- EPIC THERAPEUTICS
- BAXTER HEALTHCARE
- PSIMEDICA, A PSIVIDA GROUP COMPANY
- NOVO NORDISK A/S
- BAYER HEALTHCARE
- UNIVERSITY OF TOKYO

**Key Issues:**

- Significant Success In Pain-Free Technology
- How To Attract Venture Capital
- What Are The Big Pharmas Looking For
- How To Form Successful Alliances And Management Benchmark
- Opportunities And Challenges Facing The Drug Delivery Industry As A Whole
- How To Transform From Drug Delivery Company To Specialty Pharma Companies
- How To Increase Patient Compliance--Consumer-Driven Drug Delivery
- How To Avoid Pitfalls And Make Valuable Contracts
- Most Promising Novel Delivery Systems For Nanoparticles, Proteins, Peptides And Poorly Soluble Molecules
- Innovative Technologies Of Oral Delivery, Pulmonary & Nasal Delivery, Transdermal Delivery And Needle-Free Delivery
- What Are The Competitive Edges For Drug Delivery Companies And Pharmaceutical Companies Respectively

[www.globaleaders.com](http://www.globaleaders.com)



*Organized by*



*Media Partners*



## METICULOUS ATTENTION TO DETAIL THE KEY IN PREFILLED SYRINGE PRODUCTION

Prefilled syringes are used by doctors, nurses and patients alike. While using them to administer a medicine in a couple of seconds, they will rarely spend any time thinking about the amount of know-how and developmental work that actually goes into these small packaging units, which are really much more than just drug containers. In this article, Horst Koller, Head of Scientific & Regulatory Advisory, and Walter Schiess, Product Manager, both of SCHOTT forma vitrum, give an insight into some of the many factors that are addressed during prefilled syringe development and production.

In recent years, the market for parenteral packaging has seen prefilled syringes experience a substantial increase in demand. Simplicity of administration, safety for the patient and cost savings are the main growth drivers. Prefillable syringes enable quick and easy drug delivery, especially in cases of emergency. Compared with other pharmaceutical containers, they present fewer opportunities for mix-up or contamination, and they reduce the overall cost of administration. At the same time, prefillable syringes have become much safer and easier to use in recent years, which supports the general trend to self-medication.

### A SYRINGE IS A HIGHLY COMPLEX SYSTEM

A syringe is a highly complex system that must be able to satisfy even the most challenging requirements. After all, not only must it perform functionally, it must also protect the medication itself from impurities such as contamination and, above all, ensure the safety of the patient. Figure 1 maps out the requirements and relates them to different components of the prefilled syringe itself.

To meet these requirements, SCHOTT forma vitrum develops and manufactures its syringes based on the most stringent of international regulations and ISO standards. A multitude of tests are performed on the characteristics of the material and how well they function. This is done in accordance with the European, US and Japanese pharmacopoeias.

### GLASS OR PLASTIC, COATED OR UNCOATED

SCHOTT forma vitrum is able to custom-design pharmaceutical containers according to the spe-

cific requirements of the medication and its particular application. The company has long and proven experience with parenteral packaging, expertise with different materials, and access to a broad range of resources and in-house technologies from activities both within and outside the field of pharmaceutical packaging. It is therefore able to offer customised packaging solutions in terms of material, design, siliconisation, cosmetic quality, accessories, packing and sterilisation. Innumerable different combinations of product features are possible. The syringe barrel is a good example. It can be made of glass or plastic, coated or uncoated, with free silicone oil, baked silicone or any new lubricant.

### SCHOTT CUSTOM DESIGNS PHARMACEUTICAL CONTAINERS

SCHOTT forma vitrum offers prefillable syringes in two materials: highly resistant borosilicate glass, and Topas® cyclic-olefin copolymer (COC). Glass has excellent barrier characteristics, especially when it comes to vapour and oxygen diffusion, and chemical and heat resistance. However, glass is not always the best solution; in addition to being fragile, its alkaline surface can lead to side reactions. In such cases, the glass-like clarity and inert, low adsorption qualities of COC can make it a viable alternative.

If required, the barrier properties of the container could even be improved by adding a layer of coating onto the glass or COC polymer. In any case, both the composition of the medication and the intended application are carefully considered following consultation with the customer. Only then can a decision be made with



Horst Koller  
Head of Scientific & Regulatory  
Advisory, SCHOTT forma vitrum

T: +41 71 274 16 00  
T: +41 71 274 16 56 (direct)  
F: +41 71 274 16 98  
E: horst.koller@schott.com



Walter Schiess  
Product Manager,  
SCHOTT forma vitrum

T: +41 71 274 16 00  
T: +41 71 274 16 07 (direct)  
F: +41 71 274 16 12  
E: walter.schiess@schott.com

SCHOTT AG  
St. Josefenstr. 20  
CH-9001  
St Gallen  
Switzerland

[www.schott.com/  
pharmaceutical\\_systems](http://www.schott.com/pharmaceutical_systems)

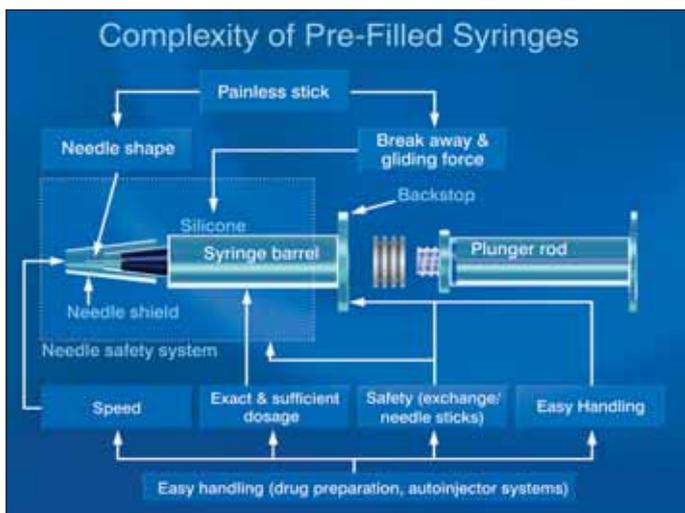


Figure 1: The complexity of prefilled syringe production



Figure 2: Syringes are washed with water for injection

respect to the type of packaging that offers the best solution for the customer.

SCHOTT manufactures syringes in glass (forma 3s® sterile syringe set) in sizes from 0.5-3 ml and up to 10 ml for its TopPac® line made of a COC polymer. Other lengths and flanges or modified shoulder shapes are available upon request. With regard to polymers, basically all shapes or sizes are possible, as long as they can be produced using the injection moulding technique. Customers can also choose between luer-cone, luer-lock and staked needles.

For COC, the luer-lock syringe is currently available as a standard version. Other specifications can be selected with respect to shape, packaging and closure systems. A tamper-evident cap is also available, for example. SCHOTT forma vitrum markets its syringes as complete sets including all of the required rubber components.

### THE SMALLEST DETAILS ARE HIGHLY IMPORTANT

With syringes, even the smallest details are highly important. SCHOTT forma vitrum con-



Figure 3: Syringe production in St Gallen, Switzerland

ducts a variety of tests to demonstrate to its customers that its products deliver both functionality and integrity. The piston and the tip cap are two good examples. On one hand, a closure's dimensions must be such that they ensure the appropriate leak tightness. On the other hand, the piston must provide adhesion and sliding forces for the entire three-year lifetime of the product so that it can still be moved without difficulty and the tip cap can be removed. In other words, it is a question of the right balance between dimensions and functionality.

To achieve this, SCHOTT forma vitrum has even developed its own tests. The TipCap leakage test, for example, examines leak tightness yet ensures ease of use so that the tip cap can still be removed using only a reasonable amount of force. The so-called tip cap removal torque confirms whether this is the case. The respective ISO norms also include tests that the piston is subjected to, such as the axial compression and piston vacuum that ensure the leak tightness of the proximal side. These various inspections are important because, although the norms include certain points of reference, different materials simply behave differently under different conditions.

Integrity of the container is not the only aspect that requires testing. Ease of use is also looked at carefully. Furthermore, ensuring purity during the manufacturing process is of particular importance with prefilled syringes. Standard inspections are performed, for example, on endotoxins, microbial impurities, and particles in the regions of 10 µm and 25 µm (a human hair is approximately 50 µm in diameter) that are invisible to the human eye, but also to rule out visible particles.

SCHOTT forma vitrum performs the tests that were established by pharmaceutical authorities in Europe, the US and Japan, and guarantees that the critical values they describe are adhered to or even bettered. The company manufactures its syringes made of glass and poly-

mers under clean room conditions. Production is strictly controlled and also validated to ensure it is within the specified limits for particles and micro-organisms. Syringes being washed with water for injection (WFI) are photographed in figure 2.

After all, it is imperative to make sure that the products to be delivered to the customer, following external sterilisation, are in fact truly sterile products. All types of sterilisation technique, such as ethylene oxide (ETO) or gamma sterilisation, are validated according to the required international norms.

“Sterile” is an absolute term. However, the assurance that any given item is sterile is a probability function. The Sterility Assurance Level (SAL) of a product is defined as the probability of any given unit being non-sterile after exposure to a validated sterilisation process. The standard SAL is defined as 10<sup>-6</sup>, that is, one surviving micro-organism per one million products.

In order to guarantee customers a product shelf life of three years, for example, worst-case scenarios are developed with regard to sterilisation and the rubber materials used for the pistons and the tip caps. In order to evaluate whether products could possibly age prematurely, test runs are performed by storing products for three months at a temperature of 40°C, in accordance with ICH regulations. This roughly equates to one year of storage at room temperature (ASTM 1980F). The containers for immediate use in packaging are also tested in real time.

This abundance of inspections performed on a regular basis is designed to achieve one goal: delivering to pharmacists a high-tech container that cannot affect a medication adversely. Together with the product, SCHOTT forma vitrum also supplies its customers with important data and information that can be confirmed by customer tests if required.

## CONTINUOUS INNOVATION

In addition to validating existing products, new types of packaging are constantly being developed. Innovative, highly sensitive and often very expensive active agents such as biotech or protein solutions, for example, are often a challenge, even for pharmaceutical packaging experts. In these cases, SCHOTT forma vitrum sets the standards not only with its proven expertise and its broad possibilities using glass and polymers, but also as an expert in the field of surface coatings. The proprietary SCHOTT PI-Coating® technique can be used for the application of specific layers to pharmaceutical glass and polymer containers to achieve, for example, improved chemical stability and inertness, less adsorption of biomolecules, improved barrier properties and prolonged shelf life of drugs in polymer containers.

Safety of patients is the ultimate goal behind all of these activities and developments. This means continual improvements must be pursued at every possible level. At SCHOTT forma vitrum, this all begins with state-of-the-art technology, certified clean-room facilities and strictly controlled processes to ensure a



Figure 4: Glass and polymer syringes by SCHOTT forma vitrum

consistently high quality. Clean-room syringe production work underway at the St Gallen, Switzerland facility is shown in figure 3 on the previous page. All products are manufactured according to Good Manufacturing Practices (GMP), and inspected and tested against current pharmacopeias and ISO standards.

The close contact with the relevant authorities and institutions enables the company to keep abreast of changes in regulations.

By finding the right packaging solution in terms of compatibility, safety, protection and functional performance, SCHOTT forma vitrum supports the pharmaceutical industry in providing the best medication to the patient.

## ABOUT SCHOTT FORMA VITRUM:

SCHOTT forma vitrum is one of the world's leading suppliers of parenteral packaging products for the pharmaceutical industry. More than 500 production lines at ten different manufacturing sites located all over the world manufacture more than six billion syringes, vials, ampoules, cartridges and specialty articles made of glass tubing or polymers each year. Excellent raw materials, the most modern manufacturing techniques and technologies, as well as continued research and development efforts have resulted in innovative product solutions. Backup capabilities at various production sites all over the globe offer flexibility, reliability and safety to the pharmaceutical industry. Prefilled syringes will clearly develop into a high growth market for SCHOTT forma vitrum in the future.

11TH ANNUAL

STRATEGIC RESEARCH  
INSTITUTE  
Providing The Knowledge And Expert Networks You Need

# Drug Delivery Technologies & Deal-Making

The Conference Standard for the Drug Delivery, Pharma/Biotech, and Specialty Pharmaceuticals Executive

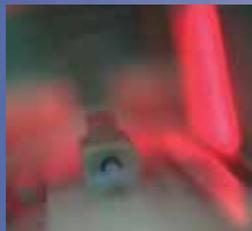
## 2006 KEYNOTE PANELS:

- New Partnerships and Investment In Today's Deal-Making Environment
- Pharma's View on Drug Delivery
- Parameters of Performance - Driving Drug Delivery Value and Valuation
- Developing Products: How Do Emerging Drug Delivery Companies Support the Cost?
- Specialty Pharma Pipeline - Build or Buy?

To Register Call 212-967-0095/1-800-599-4950 or Visit [www.srinstitute.com/cs375](http://www.srinstitute.com/cs375)  
Please Mention Priority Code: DAD003620



## Our Experience in Your Hands...



With a proven track record and more than 50 years' experience in the medical device arena, Owen Mumford is a specialist in the design, development & manufacture of customised automatic injection systems for self-administration of parenteral drugs. Designed to meet the individual needs of our pharmaceutical & biotech partners, and those of varying user groups, these systems facilitate ease of use and improve safety and patient compliance.

Our product portfolio includes single dose & multi dose reusable & disposable auto injectors & pen systems, which are suitable for a wide range of primary containers, including plastic syringes and pre-filled glass syringes and cartridges.

**With the Owen Mumford commitment, we offer a total OEM service:**

- Research & Development
- Market Knowledge
- Full support with focus groups & user evaluations
- IP licensing - from a large patent portfolio
- Product Design
- Prototype Manufacture & Testing
- Production Tooling
- Injection Moulding
- Component Printing
- Clean-room Manufacture
- Device Assembly - including assembly with the syringe/cartridge
- Packaging
- Regulatory Support
- After Sales Support



**SIMPLEJECT™**  
Auto-injector System  
**WINNER OF 5**  
**INTERNATIONAL**  
**DESIGN AWARDS...**



Corporate Head Office:  
Owen Mumford Ltd, Brook Hill, Woodstock,  
Oxford OX20 1TU, United Kingdom  
Subsidiaries in the USA, Germany & France -  
for more contact details please visit our website  
[www.omdrugdelivery.com](http://www.omdrugdelivery.com)

If you are looking for a delivery system or would like to find out more about Owen Mumford, contact the OEM Drug Delivery Team on: +44 (0)1993 812 021 or email: [drugdelivery@owenmumford.co.uk](mailto:drugdelivery@owenmumford.co.uk)



# REDUCING TIME-TO-MARKET: SUCCESSFUL DRUG MANUFACTURING

The time that it takes to get a drug to market nowadays is increasing and so are the problems that these long timelines are presenting to pharmaceutical and biotechnology companies. Outsourcing represents a strategy that, when properly used, can cut time-to-market dramatically. In this article, Dr Juergen Koch, Managing Director at Vetter Pharma-Fertigung GmbH & Co. KG, explains how Vetter works to help its clients' products reach the market in the shortest possible time.

Most industries would certainly agree with Benjamin Franklin's famous saying "time is money". For the pharmaceutical industry, however, time can mean a lot of money indeed: developing, testing, manufacturing and receiving approval for a new and potentially life-saving drug can take up to 12 years of very intensive work, with investments that can cost up to \$1 million a day. Whether the drug will be a hit is, of course, unknown. The challenges are exacerbated by two additional factors: the growing stringency of official evaluation and approval processes, and the fact that patents on drugs are of limited duration, leaving only a small window for the developing company to actually earn back investments before the patents lapse.

One option for reducing time-to-market rests in outsourcing, whereby the contract manufacturer must be examined very carefully. Here follow some key considerations:

- It should be able to provide full service, from pre-project consultation to packaging, as this offers the best opportunities to speed up the entire production and packaging process.
- An experienced contract manufacturer will have standardised protocols that will need only a little tweaking for each new drug. This can shorten the validation process considerably and speed up the approval process with the relevant regulatory agencies.
- A good working relationship between the contract manufacturer and regulators, with a sound track record, can also make a positive contribution to the approval process.
- And finally, the contract manufacturer must

have the infrastructure and capacity available in terms of both technology and personnel, especially if a request comes at short notice. A complete backup system should also be in place to avoid loss of production.

## THE KEY: PLANNING AND ORGANISATION

Reduction in time-to-market can be accomplished in any phase of a drug's development, but in the later phases reductions can be planned with a far better chance of success. Vetter Pharma-Fertigung GmbH & Co. KG, a leading independent specialist in the production of aseptically prefilled application systems, gears its operations toward fast response times.

One recent project, for example, involved a customer that needed to fill a liquid parenteral drug with a best possible time-to-market. The transfer took place in January 2005, filling occurred in April and the regulatory filing process (i.e. submission with six-month data) including validation and packaging, was completed by November. Three key factors that made this possible: conscientious planning, integrated process management and sufficient capacity available on time.

## ENSURING COMMUNICATION

The company's development service is at the core of all of its projects. The same team that does all the development and clinical manufacturing is also involved in the transfer to the commercial manufacturing process. This ensures that intimate knowledge of the drug



Dr Juergen Koch  
Managing Director

T: +49 751 3700 0  
F: +49 751 3700 4000  
E: [info@vetter-pharma.com](mailto:info@vetter-pharma.com)

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

[www.vetter-pharma.com](http://www.vetter-pharma.com)

and filling process is carried over in order to help with any problems that might later arise. It also avoids the need to spend time on knowledge transfer.

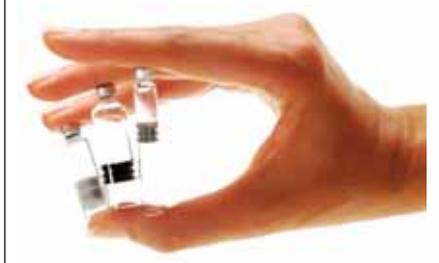
The development service and representatives of commercial manufacturing evaluate all customer inquiries, including reviewing the product specifications and manufacturing requirements, as well as the available technical options. The time factor is dependent on whether Vetter applies a process that has already been validated, or whether it designs, implements and validates a brand new one.



**1a: The dual-chamber syringe Vetter Lyo-Ject® – recipient of the Worldstar Packaging Competition Award 1998, 1st prize at the Eurostar Packaging Competition 1998, and winner of the 20th German Packaging Competition 1997**



**1b: 1 ml single-chamber syringe with V-OVS®. The originality seal V-OVS® guarantees the evidence of integrity of syringes from filling to administration**



**1c: Single chamber cartridges (0.5-3.0 ml)**

**Figure 1: Systems processed at Vetter**

## FIRST STEPS

Once the green light has been given for the project, a specialised Vetter team establishes communication with a team from the client's side. Each team has a dedicated project manager to ensure faster and smoother communications. An intensive consulting and planning stage follows to determine the production process that will move the product from development to market production with no major delays. The necessary work steps are then defined and formulated as a checklist, including milestones to measure project progress.

## A BLUEPRINT FOR EFFICIENT DEVELOPMENT

The primary packaging system also needs to be selected at this point. The solution should be one with which the manufacturer is very familiar, since important parts of the process can be applied as templates. The checklist will include all the equipment that needs to be ordered in time for the commercial production phase. In the project mentioned above, specification of the primary packaging and procurement of components began on the same day, as did the transfer of chemical analyses and, of course, process documentation.

## THE PROCESS

Well-designed, integrated project management synchronises all processes so that they dovetail at the earliest possible moment. The complex filling of a lyophilised parenteral formulation can illustrate this. Vetter has its own patented dual-chamber syringe, Lyo-Ject® (see figure 1a), which requires double filling: with the substance to be lyophilised and with the solvent following the lyophilisation process. (A single chamber syringe, and single chamber cartridges, manufactured by Vetter, are pictured in figures 1b and 1c, respectively)

After selecting the system, the development team reviews the entire filling process – the filling machine, format parts, and so on – so that it can begin informing the company's own suppliers who then, in turn, can deliver the necessary parts in due time. The development team also studies the particularities of the drug and the packing materials to ascertain, among other things, compatibility with regard to light-sensi-



**Figure 2: Inner view of Vetter's state-of-the-art laboratory freeze-dryer**

tivity, filling and pumps. The checklist is the reference point that indicates who must perform which task, and by when.

## CONTROLLING PROCESS QUALITY

Once the preliminary planning stage has been concluded and a detailed process roadmap has been drawn up, the actual testing and filling can begin. The first step is a small-scale feasibility fill, which is done by hand and entirely under laboratory conditions. This supplies a quick indication as to whether lyophilisation is even an option. Each lyophilisation run generates a protocol with a report that describes moisture content, reconstitution behaviour, chemical stability, turbidity, appearance, mechanical stability of the lyo-cake, and application functionality. The specifications of the product are also determined, including whether it should be packed as a single dose or multi-dose, as well as fill volumes and storage conditions. Interaction between the product and the silicon and elastomers is also examined, allowing the customer to make a final decision on the primary packaging. For the first feasibility studies, the galenic formulation candidates need to be selected. The basis for developing a safe and efficient lyo-cycle is the physical-chemical data package. At this stage, the charac-



**Figure 3: Validated cleaning processes. The washing process enables high quality in the manufacturing of aseptically prefilled application systems**

terisation of the sensitive active pharmaceutical ingredient plays a role (for example, shear sensitivity and pH-shift). One rule of thumb is that the more information generated by the feasibility fill, the less time required for adjustments during the commercial manufacturing stage. It is quicker to do adjustments, changes or corrections in the lab than on the filling line.

### PARALLEL JOBS

Completion of the feasibility phase provides the development service with one or two galenic formulations to work with. The first milestones must be achieved very carefully to avoid product-related incidents, such as product stability issues causing launch delay. The lyo-cycle must then be run several times, simulating large-scale conditions in order to fine-tune the process and determine ideal freezing, and primary and secondary drying conditions. This also allows the

lab technicians to monitor such crucial factors as freezing rates, heating ramp and radiation effects, the impact of the pumping system, etc. Vetter's laboratory freeze-dryer is shown in figure 2. Each lyophilisation run is documented and the resulting samples are stored for informal stability testing, usually at 2-8°C, room temperature, 40°C/75% relative humidity. In-house capacity (storage analytics) of the CMO can further speed up this process.

### THE SCALE-UP PROCESS

Though determining the best cycle and formulation together with the customer takes about three months, this doesn't mean that the rest of the team has to sit on its hands. While the development service is working on the formulation and designing the best filling process, the rest of the team can set to work preparing the scale-up process. The production equipment must be procured and set up,

specification and qualification factors need to be met and the cleaning process validated (see figure 3). As well, raw materials and packaging materials must be selected, ordered and prepared. To ensure final success, backup supplies must be in place. All of this presupposes a high degree of organisation and co-ordination.

### TESTING THE FINISHED PRODUCT

Whether the results of the feasibility study are applicable to bulk filling must also be tested and validated prior to commercial manufacturing. During up-scaling, a number of steps have to be carefully evaluated and calibrated as needed – for example, the thawing procedure of the bulk product, and the definition of bulk handling and mixing properties. Filtration is another important aspect that requires expert attention including: the type of tubing to be used; tubing diameter; and maximum allowed filtration pressure, amongst other factors.

The filling profile is then checked with regard to the type of pumping system and aseptic handling. Once everything is functioning properly, the lyo cycle can be put through its tests by performing different runs on minimum and maximum scale, including extensive moisture mapping to verify homogeneity throughout the batch. At this point, the actual filling equipment has been installed and is ready to be tested on scale-up batches.

### THE FINAL STEPS

Production of clinical batches (see figure 4) begins as soon as the scale-up batches are confirmed as having been successful. In order to generate precise indicators for the master batch record, a minimum of three batches must be run using a minimum of 10% of the future commercial batch size. These batches can be used for registration purposes. The crucial factors in determining the success of the batches are good manufacturing practice (GMP), the possibility of human use, and release of the batches by quality control and the qualified person.

The up-scaling runs produce material for stability batches, which can also be used for clinical studies after the stability tests have produced positive results. In the aseptic filling process, each step in a project is geared towards greater safety and speed in the final stages. Figure 5 depicts syringes leaving the filling machine. Prior to commercially manufacturing the drug, however, a detailed risk analysis must be carried out in all steps of the process, followed by validation, which must be conducted on at least one full batch for the European and US markets.

All critical parameters are examined and tested, such as holding times, mixing properties and



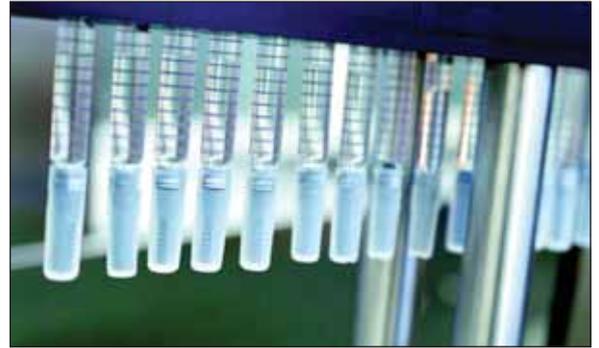
**Figure 4: Aseptic filling of syringes within the framework of clinical study**

full-day production (robust processing). Simulating worst-case conditions is one way to cover all of these bases. Another is to validate an optional minimum and maximum batch size to build flexibility into the commercial production

process. Validation also extends to various shipping aspects, including the container, the packaging and the means of transportation. A validation protocol and a report are generated in the process, to be used for all future commercial batches. The customer, with support from Vetter, submits these documents to the regulatory authorities. If the batches still have sufficient shelf life, they can be used for the product's market launch. The end of the validation process signals commercial manufacturing.

**REDUCING TIME-TO-MARKET: SUMMARY**

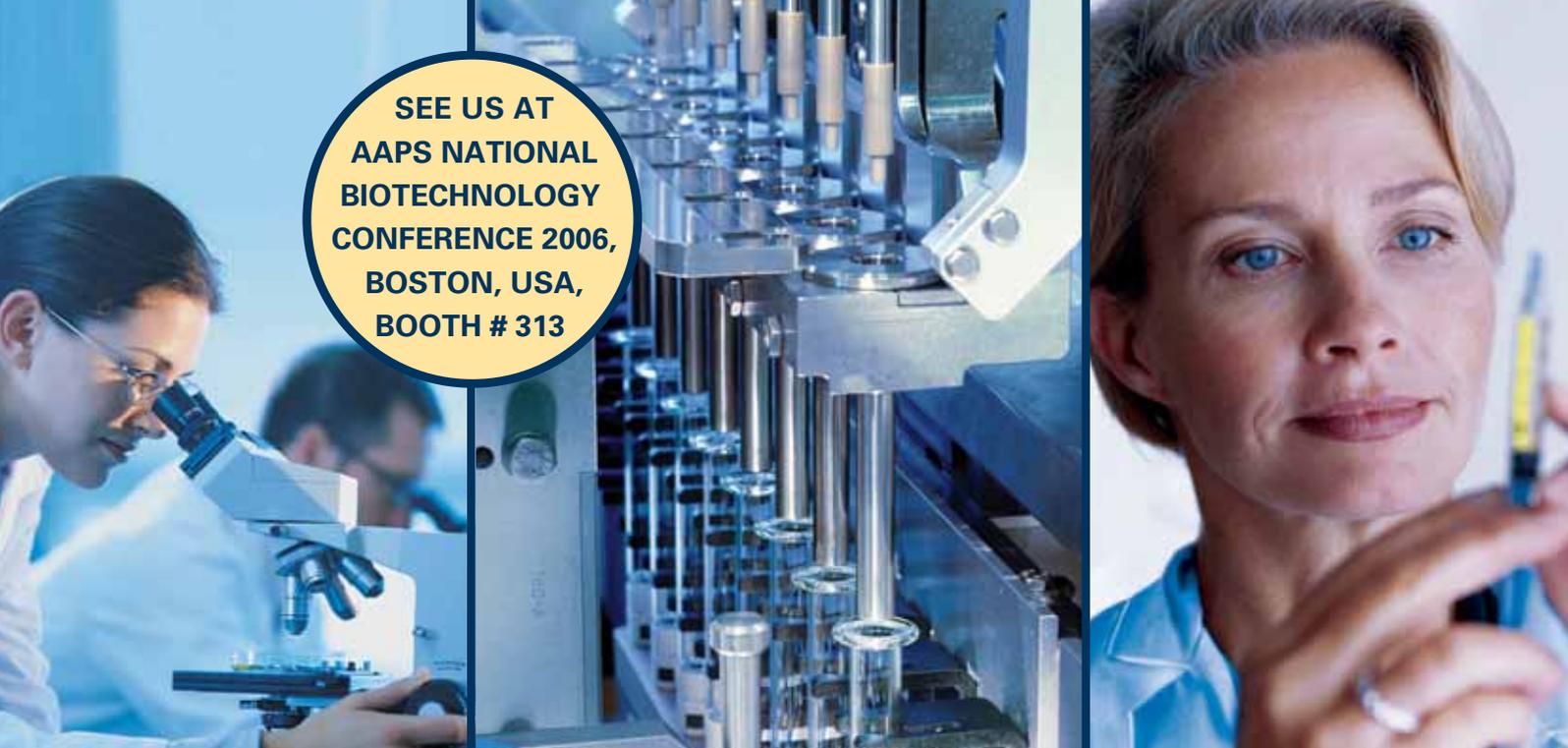
When it comes to reducing time-to-market for their new drugs, pharmaceutical companies should focus their attention on the last phase of development, namely packaging and all that it entails. The processes involved in this phase are precisely planned, and valuable time can be saved at this stage. If, as is often the case, the company is not doing the packaging itself, it is important to find a contract manufacturer with the know-how, expertise, and infrastructure to do the work efficiently.



**Figure 5: Aseptically prefilled syringes leave the filling machine**

Experienced teams, integrated process management and active communication between all units and team members are crucial. Most important, however, is assiduous planning in the earliest stages to ensure that all steps in the process are properly choreographed to save as much time as possible. It is vital that the contract manufacturer has a good track record with regulatory agencies such as the FDA, EMEA and others. Finally, as an outsourcing partner, the company should be highly trustworthy and financially stable. In a word, it should be a global leader in its field.

*Copyright © 2006 Vetter Pharma-Fertigung GmbH & Co. KG*



SEE US AT  
AAPS NATIONAL  
BIOTECHNOLOGY  
CONFERENCE 2006,  
BOSTON, USA,  
BOOTH # 313

## Vetter Produces Quality by Design. Day by Day.

### Vetter Development Service

- Development of Primary Packaging Materials
- Process Development
- Regulatory Affairs Service
- Clinical Manufacturing
- Pharmaceutical Analysis
- Transfer to Vetter Commercial Manufacturing

### Vetter Commercial Manufacturing

- Fill & Finish Services
- Packaging Services
- Pharmaceutical Analysis
- Regulatory Affairs Service

#### Dosage Forms:

Syringes, Cartridges and Vials

### Vetter Solutions

- Dual-Chamber Technology, i. e., freeze-dried/solvent, liquid/liquid
- Anti-Counterfeiting Solutions
- Tamper-Evident Closure Systems

**Vetter is an independent international specialist in the production of aseptically pre-filled application systems.**

**Vetter provides support for its clients from the initial phases of development and regulatory approval process through to the successful product launch and commercial manufacturing.**

**Vetter is renowned for its quality, innovation and loyalty as a strategic partner for its pharmaceutical and biotech clients.**

For US inquiries please call +1-215-321-6930.

For EU inquiries please call +49-751-3700-0.

[www.vetter-pharma.com](http://www.vetter-pharma.com)



Pharma solutions for tomorrow, today.



Discover the latest scientific and technological developments at SMI's...

# Drug Delivery Global Summit

20th & 21st September 2006, Central London

Hear international case studies and expert perspectives from leaders in the field, including:

- **David Stern**, Executive Vice President, Metabolic & Endocrinology, **Serono**
- **Dr Eric Tomlinson**, President & Chief Executive Officer, **Altea Therapeutics**
- **Dr Martin Woodle**, President & Chief Scientific Officer, **Intradigm Corporation**
- **Steven White**, Senior Director, Product Development, **Epic Therapeutics, Baxter Healthcare**
- **Dr Tom Tice**, Executive Vice President & Chief Scientific Officer, **Brookwood Pharmaceuticals**
- **Dr Mason Diamond**, Vice President, Clinical & Regulatory Affairs, **TyRx Pharma**
- **Dr Luk Chui Li**, Director, Global Drug Delivery, **Abbott**
- **Dr Jörg Rosenberg**, Associate Director, Pharmaceutical Development, SOLIQS, **Abbott**
- **Dr Ola Nerbrink**, Principal Scientist, Device Chemistry & Biology, **Novo Nordisk**
- **Dr David Brayden**, Chairman, **UK-Ireland Chapter, Controlled Release Society**

Key issues that will be addressed at the conference include:

- **NOVEL DRUG DELIVERY SYSTEMS:** Hear about the latest developments in drug delivery design and how to comply with Good Manufacturing Practice
- **NANOTECHNOLOGY:** Discover how advances in nanotechnology can advance the drug delivery industry through novel design and application
- **TARGETED DRUG DELIVERY:** Consider how targeting drug action can revolutionise medical treatment and understand the latest developments that can make this a reality
- **CONTROLLED RELEASE:** Appreciate the science and technology behind long-acting parenterals and the design, development and manufacturing considerations for implants and injectable formulations
- **CHALLENGES IN DRUG SOLUBILITY AND ADSORPTION BARRIERS:** Recognise the pitfalls associated with hydrophobic drugs, their delivery and action
- **NETWORKING OPPORTUNITIES:** Meet the key industry leaders, make valuable contacts and learn from their experience and expertise

## PLUS THREE ASSOCIATED HALF-DAY EXECUTIVE BRIEFINGS

**A** **Current Trends in Global Pharmaceutical Alliances: Doing the Deal (PM)**  
19th September 2006, Central London In association with: PharmaVentures

**B** **The Effective Transdermal Delivery of Protein Drugs, Vaccine Antigens and Highly Water-Soluble Low Molecular Weight Drugs (AM)**  
22nd September 2006, Central London In association with: Altea Therapeutics

**C** **Liposomes as Carriers for Vaccines and Nucleic Acids (PM)**  
22nd September 2006, Central London In association with: Polymun Scientific

Sponsored by



Supported by

**Drug Delivery Insight**



Pharma Times



THOMSON PHARMA<sup>SM</sup>

Special Price for  
Academic Researchers

Register online at  
[www.smi-online.co.uk/drugdeliv.asp](http://www.smi-online.co.uk/drugdeliv.asp)

Alternatively fax your registration to +44 (0) 870 9090 712 or call +44 (0) 870 9090 711

GROUP DISCOUNTS AVAILABLE

## PACKAGING IN PREFILLED SYRINGE SYSTEMS: SELECTION AND EVALUATION

Selecting components for a prefilled syringe system is an important consideration for pharmaceutical manufacturers. Here, Ms Frances DeGrazio, Vice-President, Quality Assurance & Regulatory Affairs Americas at West Pharmaceutical Services, describes some of the regulations surrounding container closures for prefilled syringes, and how West's processes and testing protocols ensure that the high standards are maintained.

A syringe system generally consists of a barrel manufactured from glass or plastic, a needle with an elastomeric needle shield or a luer lock/luer cone, and a rod with an elastomeric plunger on the tip (see figure 1). The plunger contacts the drug during administration. In a prefilled syringe system, the plunger may also contact the drug during storage, which may last up to two years.

Manufacturers must understand the requirements for prefilled syringe systems included in the FDA's Guidance for Industry, "Container Closure Systems for Packaging Human Drugs and Biologics" and conduct the extractables/leachables testing that the guidance recommends.

### UNDERSTANDING THE CONTAINER CLOSURE GUIDANCE

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

Packaging suitability is based on four attributes: protection, safety, compatibility and performance (function and/or drug delivery). For injectable dosage forms, the guidance specifies the procedures to test the interaction

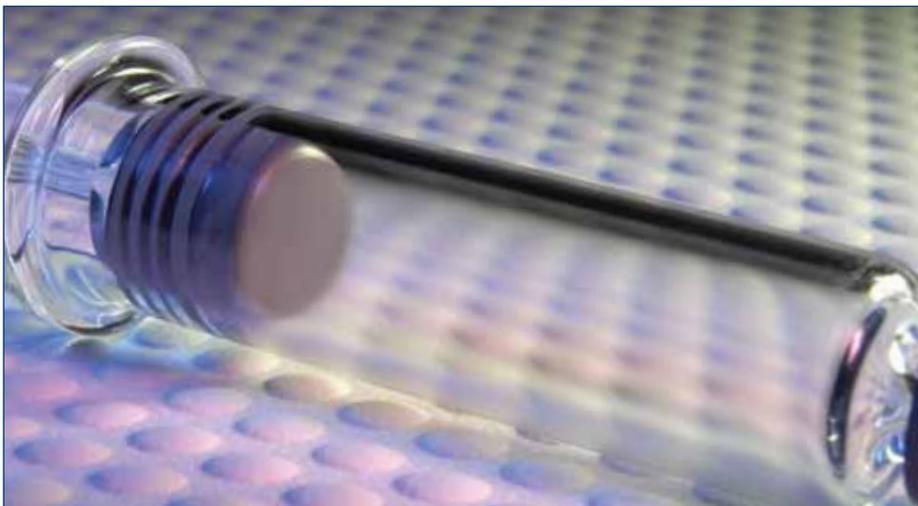


Figure 1: A syringe system generally consists of a barrel manufactured from glass or plastic, a needle with an elastomeric needle shield or a luer lock/luer cone and a rod with an elastomeric plunger on the tip.



Frances L DeGrazio  
Vice-President, Quality Assurance  
& Regulatory Affairs Americas

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

West Pharmaceutical Services, Inc.  
101 Gordon Drive  
Lionville  
PA 19341  
USA

[www.westpharma.com](http://www.westpharma.com)

between the drug and its packaging components. Associated components, such as those used only at the time a dosage is administered and secondary packaging materials, are also included in the review.

## EXTRACTABLE AND LEACHABLES IN PRIMARY CONTAINER CLOSURE SYSTEMS

Factors that must be considered in evaluating container closure systems include the materials used to construct the components, surface treatments applied to the components, processing aids, the dosage form's active ingredients and excipients, sterilisation, and other related processing and storage conditions.

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

Leachables are substances identified in a defined laboratory regimen by simulating use conditions. Typically, leachables are a subset of extractables.

## EXTRACTABLE AND LEACHABLES TESTING CRITERIA

Extractables/leachables testing determines:

- that the materials of the container closure system components are safe for their intended use.
- that the container closure system components do not interact with the drug to cause unacceptable changes in the quality of either the drug or the packaging components.
- that the container closure system provides the dosage form with adequate protection, including seal integrity and the ability to reseal where applicable.
- that the container closure system functions in the manner for which it was designed.

## TESTING PROCESSES

Extractable screening during safety studies is an important step when choosing the appropriate plunger for a prefilled syringe (see figure 2). Test methods must be specific to the drug product or placebo in order to evaluate interferences, linearity and other critical factors accurately.

Pre-screening procedures should begin with a basic evaluation of syringe plunger options. The protocol can involve multiple temperatures and conditions for acceleration. Identification of



Figure 2: Extractable screening during safety studies is an important step when choosing the appropriate closure for a prefilled syringe or drug vial.

extractables can be achieved through analytical testing, such as liquid chromatography/mass spectrophotometry (LC/MS), gas chromatography spectroscopy/mass spectrophotometry (GC/MS), inductively coupled plasma (ICP) and infrared (IR).

The laboratory would identify a potential extractables list for the specific plunger rubber formulation. The laboratory will engage in methods development and conduct an assessment to determine the potential for analytical interference, the limits of quantification (LOQ) and typical percentage of recovery of spiked extractables in non-degraded and degraded drug product or placebo.

If there is significant interference during method feasibility testing, such as HPLC column deterioration, retention time shortening and poor recovery after multiple injections for leachables, the laboratory then deter-

mines that these leachables cannot be detected by that particular method.

Sometimes methods development studies are expanded to improve sample preparation before analysis with a particular instrument. In one case, client samples required dilution with an equal volume of tetrahydrofuran (THF) to enhance the solubility of the leachables. Samples were then centrifuged at a preset time and speed to allow presence of a clear THF top layer. The laboratory then analysed this layer to allow for proper detection of compounds at required concentrations. It was also determined that the clean-up step between sample injections should be made with acetonitrile to maintain column performance.

Methods validation for detection of leachables in placebo or drug product is based on recommended industry practices and International Conference for Harmonisation (ICH) guidelines. A validation plan for each identified test method should be developed and approved by the client.

## RISK MITIGATION STRATEGIES

Syringe plungers with a fluorocarbon barrier film can help reduce the risk of product loss caused by interaction of the drug and the plunger and the loss of the drug through adsorption and absorption (see figure 3).

**A barrier film can:**

- protect the shelf life of packaged drugs
- enhance drug/plunger compatibility
- have exceptional lubricity for enhanced machineability and processing

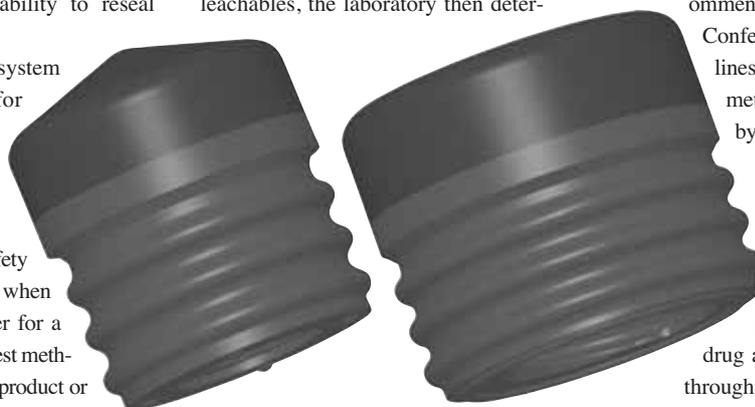


Figure 3: Syringe plungers with a fluorocarbon barrier film can help reduce the risk of product loss caused by interaction of the drug and the plunger and the loss of the drug through adsorption and absorption.



**Figure 4: New state-of-the-art polyisoprene needle shield formulas, using dried natural rubber-free nitrosamine, are MBT-free and ensure good compatibility between the elastomeric component and the drug product.**

A fluorocarbon film provides an effective barrier against organic and inorganic extractables to minimise interaction between the drug and the plunger and maintain the plunger's seal integrity. The fluorocarbon film reduces absorption and adsorption of the drug product, and the low surface energy of the film provides lubricity without the need for silicone oil.

In the past, natural rubber- and polyisoprene-based needle shields and tip caps were subject to

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

cracking through exposure to light and/or fresh air. This cracking resulted either in cosmetic defects or even worse in seal integrity issues. New state-of-the-art polyisoprene needle shield/tip cap formulas, using dried natural rubber free nitrosamine, are MBT-free and ensure good compatibility between the elastomeric component and the drug product (see figure 4). These polyisoprene formulas minimise the risk of coring through the needle and are significantly less sensitive to environmental conditions.

**THE ADVANTAGES OF  
READY-TO-STERILISE COMPONENTS**

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

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

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

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

**CONCLUSION**

The FDA guidance, “Container Closure Systems for Packaging Human Drugs and Biologics”, defines criteria for extractable and leachable testing of packaging components. Pharmaceutical companies may have to initiate testing that will require time and money that must be built into the qualification and stability studies early in the product development cycle.

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

Pharmaceutical manufacturers may reduce risks associated with the container closure system by selecting syringe plungers with fluorocarbon barrier film, state-of-the-art polyisoprene-based needle shield/tip cap formulas and by specifying ready-to-sterilise components.



Connecting People, Science & Regulation

Save  
the Date

# The Universe of Pre-Filled Syringes & Injection Devices

October 23-25, 2006 • Bethesda, Maryland, USA



**Mark your calendar!** Following two very successful meetings on pre-filled syringes, PDA is pleased to bring to you *The Universe of Pre-Filled Syringes & Injection Devices* again this year. Leading experts in drug and syringe manufacturing, regulation, product development and packaging will come together to share recent strides in this rapidly evolving technology.

**For more information visit:  
[www.pda.org/prefilled](http://www.pda.org/prefilled)**

11th Annual

# Drug Delivery Partnerships™

*The Event that Gets You One Step Closer to the Deal*

## SAVE THE DATE!

**11th Annual Drug Delivery Partnerships**

**January 22-24 2007**

**Red Rock Station Hotel & Casino, Las Vegas, NV**

Save the date for the industry's largest comprehensive drug delivery and specialty pharma event driving product development through alliances and partnerships with leading perspectives on:

- Building partnerships, creating value and managing successful alliances with pharma, biotech, generics, OTC companies and more
- Innovative technology that fuels deals: Differentiating your products in a crowded marketplace
- Trends, risks and strategies for accelerating growth in specialty pharma companies
- Challenges and progress in transitioning from drug delivery to specialty pharma
- Responding to and capitalizing on the generic drug market
- New approaches for biotech delivery and combination products
- And much more

**Visit us at [www.drugdeliverypartnerships.com](http://www.drugdeliverypartnerships.com)  
and sign up for updates on DDP 2007**

# CURRENT MARKET AND KEY TRENDS OF DEVICES USED IN SELF-INJECTION

In this article, Mr Joël Cotten, European Product Manager at BD Medical – Pharmaceutical Systems, gives a view of the more established sections of the injectables market. Using examples from the field of self-injection devices, he highlights the reasons for their success, and some of the obstacles that needle-free injection has faced, with the lack of a standardised container foremost among them.

There are many ways to categorise the types of devices used in self injection. Many authors are speaking of pens, auto-injectors, syringe injectors, needle free devices or other pumps for insulin. We propose to define the devices for self-injection in terms of the type of primary containers they use:

- The single- or double-chamber cartridges, which are used in pens.
- The prefillable staked needle syringes, which are used in auto-injectors, but can be used alone by patients.
- Other primary containers that could be rigid, such as vials used in needle free devices, or collapsible, which may be used in products such as the BD™ Micro-infusor. These other primary containers are used in non-classified self-injectors.

The current market of cartridges, prefillable syringes and other containers for self injection is growing at rate close to 14% in terms of numbers of units. Each sub-market follows different trends. Part of the non-classified self-injectors, needle-free injectors have had some difficulty following the market growth. This is probably because of a lack of a convenient and universal primary container, which is present in other sub-markets. For example, the BD Hypak™ syringe is used for auto-injectors, and standard 1.5 ml or 3 ml cartridges are used in pens.

## ... PENS AND CARTRIDGES

Most pens and cartridges are used to administer insulin. The devices allow for multiple injections with variable dosing that can be adjusted

by the patient. The leading pens are re-usable, allowing the patient to reload the pen with a new cartridge (1.5 ml or 3 ml) for additional treatment. Two important trends are apparent in the cartridge and pen markets today.

- A 3 ml cartridge appears to be the leading volume used by the pharmaceutical companies. With the market evolving to disposable pens, the larger-volume cartridge allows for a greater number of injections.
- Patients are pushing for increased convenience and smaller needles. For example, 31-gauge thin wall pen needles like the BD Micro-Fine™ and BD Ultra-Fine™ are increasingly popular (see figure 1).

Thanks to the proven success of pens in the diabetes market, a number of additional therapeutic classes are presenting their products in a self-injection device. The treatment of women's infertility, osteoporosis, and growth hormone deficiency are some of the markets using pens such as that shown in figure 2.

The convenience of cartridges and pens means that they will soon be used for the treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, and Hepatitis C.

Although liquid drugs are easy to fill in a cartridge, new developments from the biotechnology industry have created drugs that are not stable in a liquid format for a long period of time. These drugs require a dual chamber cartridge to keep the drug separate from the diluent. The leading company in this industry to support this technology is Vetter. It offers a selection of cartridges that



Mr Joël Cotten  
European Product Manager

T: +33 0 4 76 68 36 64  
F: +33 0 4 76 68 35 05  
E: Joel\_cotten@europe.bd.com

Worldwide Headquarters  
BD Medical - Pharmaceutical  
Systems  
11, rue Aristide Bergès  
38800 Le Pont de Claix  
France

US Headquarters  
1, Becton Drive  
Franklin Lakes, NJ 07417 - 1886  
USA  
T: 1 800 225 3310

From outside the US:  
T +1 201 847 4017  
F: +33 201 847 4847

[www.bdpharma.com](http://www.bdpharma.com)



Figure 2: BD™ self-injection pen

can be used by re-usable pens or disposable liquid dry injectors such as the BD™ LDI (see figure 3).

### ... PREFILLABLE SYRINGES AND AUTO-INJECTORS

Historically, prefillable syringes were not frequently used in self-injection. Their focus was to help the professional healthcare workers in the fields of the vaccination and heparin therapy. In the late 1990s, the emergence of biotech drugs to treat multiple sclerosis, rheumatoid arthritis, and anaemia, created a need for devices to help patients inject themselves. These drugs also came with decreased frequency of injections relative to insulin – ranging from daily to once every two weeks.

The upshot is that demand for disposable auto-injectors filled with a prefillable syringe, such as BD's Hypak Physiolis™ syringe (see figure 4), has increased.

### ... NON-CLASSIFIED SELF-INJECTORS USING COLLAPSIBLE AND RIGID PRIMARY CONTAINERS

The size of the self-injection market has stimulated development of other non-classified self-injectors beside pens, cartridges, prefillable syringes and auto-injectors. Some of these new self-injectors were initially developed using proprietary primary containers, such as the insulin pump.

Another technology that emerged from the treatment of diabetes is the needle-free injection (NFI) using a rigid container able to accept high pressure during the injection of the drug.



Figure 1: Thin wall BD pen needles

Although the NFI technology is exciting because of the absence of the needle, companies have yet to be successful with the development and launch of a product on a large-volume basis. A limited market of drugs can utilize this technology because of its current high production cost. In addition, pain is still questionable when NFI are non-correctly performed.

Recently, needle-free injector companies have begun initiatives to compete with auto-injectors for injecting mono and fixed doses. However, the lack of a universal primary container has impeded the ability of needle-free injectors to present an alternative to the disposable BD Hypak™ auto-injectors that are in the market.

Nonetheless, leading devices such as the pens and auto-injectors mentioned earlier, are not answering all of the market's needs, so additional technologies have come to the market.

For example, focusing on the subcutaneous delivery of small volumes, pens and auto-



Figure 3: The BD™ LDI



Figure 4: BD Hypak Physiolis™ syringe

injectors are ignoring demand for: injections of volumes above 1ml; injections of viscous drugs; and injections that need to last more than 20 seconds.

The innovative BD™ Microinfusor is answering these demands and is one the first devices to facilitate injections with needles as small diameter as 30 to 34 gauge. The BD™



Figure 5: The BD™ Microinfusor

Microinfusor, which is shown in figure 5, would appear to be a strong challenger in the established self injection market.

*Art.06/Self-Injection article/ENG/01  
BD, BD Logo and all other trademarks are the property of Becton Dickinson and Company.*



- Specialist freelance drug delivery writing
- Themed sponsored publications
- Business intelligence consulting
- Weekly news briefing
- Market reports

To find out more about ONdrugDelivery's niche business information and intelligence services, contact Guy Furness, company founder and managing director.

Tel: +44 1273 831 370.  
Email: [guy.furness@ondrugdelivery.com](mailto:guy.furness@ondrugdelivery.com)

[www.ondrugdelivery.com](http://www.ondrugdelivery.com)

# BD Medical - Pharmaceutical Systems



Helping all people  
live healthy lives

## Because Drug Delivery is a matter of confidence

**BD Medical** - Pharmaceutical Systems is dedicated to developing prefilled drug delivery systems, designed to fit the needs of the pharmaceutical industry. **BD Medical** - Pharmaceutical Systems provides the expertise and experience that the pharmaceutical industry requires in a packaging partner.

We deliver cost-effective alternatives to conventional drug delivery methods which differentiate pharmaceutical products and contribute to the optimization of drug therapy.

All our prefilled devices are designed to meet healthcare professionals' demands for safety and convenience as well as fulfilling patients' needs for comfort.

With a broad range of innovative devices and services, we provide pharmaceutical companies with support and resources to help them achieve their goals. With our worldwide presence and our pharmaceutical packaging process know-how, we are able to propose suitable solutions for all regional market and parenteral drug delivery needs.



**BD Medical**  
Pharmaceutical Systems  
Worldwide Headquarters  
11, rue Aristide Bergès  
38800 Le Pont de Claix  
France  
Tel: 33.4.76.68.36.36  
Fax: 33.4.76.68.35.05  
U.S. Headquarters  
1, Becton Drive  
Franklin Lakes, NJ 07417-1886 USA  
Tel U.S.: (1) 800 225 3310  
Outside of U.S.: (1) 201 847 4017  
Fax: (1) 201 847 4847  
[www.bdpharma.com](http://www.bdpharma.com)

## COMPANY PROFILE – THE MEDICAL HOUSE

The Medical House (TMH), based in the UK, 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 injection. Working closely with its partners, TMH has developed a range of needle-based disposable auto-injectors and needle-free jet injectors for the delivery of injectable products.



### THE ASI AUTOSAFETY INJECTOR

The ASI disposable auto-injector system is specifically designed to incorporate pre-filled glass syringes. Figure 1a shows the device and figure 1b is a cut-away diagram. Utilising TMH's patented, proprietary auto-injector technology, the ASI provides a simple, cost-effective and versatile means of creating competitive advantage for TMH's pharmaceutical and biotech company partners, including Martindale Products, a division of Cardinal Health, and a number of other industrial collaborators. In addition, TMH is currently working with a European government agency to develop a disposable auto-injector for a specific emergency application.

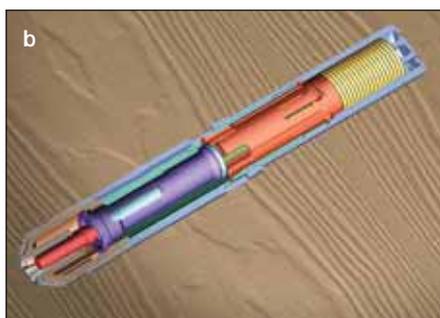


Figure 1: The ASI AutoSafety Injector (a) external appearance and (b) cut-away view showing the inside of the device.

The ASI offers:

- **Simple, completely automated injection process which involves only two user steps**
  - process includes 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 and after delivery
  - addressing patients' aversions
- **Compatibility with a number of the most common prefillable glass syringes**
  - facilitating rapid, cost-effective commercialisation programmes
- **Minimal number of device components**
  - providing an inherently reliable, economic and versatile system
- **Enhanced capability to deliver viscous (e.g. sustained release) formulations**
  - incorporating narrow-gauge needles
  - short injection duration
  - proprietary system to protect against risk of syringe damage from injection forces
- **Integrated, automated reconstitution of dry (e.g. lyophilised) components**

### COMPETITIVE ADVANTAGE

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

- **Minimising dependence on clinical expertise**
  - enabling patients to manage their therapy
  - reducing costs of healthcare provision
- **Overcoming patients' needle aversions**
  - improving compliance with optimal therapies
- **eliminating the incidence of needlestick injuries and risk of disease transmission**
- **Facilitating rapid response in emergencies**
- **Responding to large-scale injection needs**

### INJECTABLE CHALLENGES

TMH's delivery technologies provide bespoke systems to meet a wide range of requirements associated with injectable products, including solutions to specific challenges such as:

- **Presentation**
  - pre-filled syringe, vial, cartridge
- **Injection volume**
  - fixed, variable, part-volume delivery
- **Therapeutic**
  - subcutaneous, intramuscular and intradermal injection
  - emergency, elective
- **Formulations**
  - liquid, lyophilised, powdered, viscous

### 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 above.

David Urquhart  
Managing Director  
durquhart@themedicalhouse.com

Laura Hetherington  
Marketing & Product Support  
lhetherington@themedicalhouse.com

The Medical House PLC  
199 Newhall Road  
Sheffield  
S9 2QJ  
UK

T: +44 (0) 114 261 9011  
F: +44 (0) 114 243 1597

[www.tmh-drugdelivery.com](http://www.tmh-drugdelivery.com)

## COMPANY PROFILE – YPSOMED

Ypsomed is the largest independent developer and manufacturer of custom-made injection systems for self-administration, and has more than 20 years' experience in the development and manufacture of injection pens and pen needles. Pens form the core of its product range, spanning a wide spectrum from simple disposable pens to those with variable dosing and electronic display right up to highly complex injectors with multifunctional electronics. It also manufactures compatible pen needles with a unique click-on function for its own and all other widely available pens.

The demand for new customised injection devices continues to grow as injectable biotech drugs are developed in existing and new therapeutic areas where sophisticated injection devices improve patient compliance and the success of the therapy. Some drugs require frequent, variable dose injections while others require less frequent, fixed dose injections. Larger injection volumes, the need for fixed doses and the often high viscosity of drugs are increasing the demand for auto-injection devices.

Ypsomed's core technology is constantly expanding to cover new therapy and patient needs. Its range includes disposable and re-usable auto-injector platforms for the treatment of autoimmune diseases and for new cancer therapies. A broad-based technology platform and around 100 patents means that Ypsomed can meet virtually all partner needs in the growing market for self-injection systems.

Ypsomed was created in 2003 from one of the two divisions formerly owned by the well-known Disetronic Group. It employs over 1,100 people at several production sites



Ypsomed disposable auto-injector

**YPSOMED**  
SELFCARE SOLUTIONS

in Switzerland and throughout a European sales and distribution network.

All products are developed and manufactured in Switzerland, where internal capabilities include R&D, tool-making, injection moulding, clean-room production and assembly facilities. It has production sites in Burgdorf, Grenchen and Solothurn. Ypsomed provides not only the marketing and technological expertise, but also the production expertise according to the latest regulatory requirements for both low and high-volume production. Ypsomed manufactures in FDA-registered facilities, is inspected regularly, and supplies devices approved for all leading markets including the US, Europe and Japan.

Ypsomed's safe, reliable solutions have earned the company credibility with its many partners and countless patients. The long-standing quality of its products and its responsible conduct form the cornerstones of the company's excellent reputation. It has well-established partnerships of many years with numerous leading pharmaceutical and biotech manufacturers such as Sanofi-Aventis, Genentech, Lilly, Pfizer, Roche and Serono.



**Ian Thompson's article, "New-generation auto-injectors: taking self injection beyond prefilled syringes", published in ONdrugDelivery's 2005 Prefilled Syringes issue, is available at:**

[www.ondrugdelivery.com/publications/ypsomed\\_2005.pdf](http://www.ondrugdelivery.com/publications/ypsomed_2005.pdf)

**Ian Thompson**  
Manager Business Development

T: +41 34 424 32 23  
F: +41 34 424 31 51  
M: +41 79 778 28 72  
E: [ian.thompson@ypsomed.com](mailto:ian.thompson@ypsomed.com)

**Ypsomed AG**  
Brunnmattstrasse 6  
CH-3401 Burgdorf  
Switzerland

[www.ypsomed.com](http://www.ypsomed.com)

*the power of*  
**CONCENTRATION**

**THE POWER OF A SINGULAR FOCUS**

**We focus on one thing— and that's the development of self-injection devices.** We have one vision— and that's to be specialists in our field. It is our purpose to use our expertise, dedicated resources, and experience to provide our customers the ultimate device solutions.

**YPSOMED**  
SELFCARE SOLUTIONS

e-mail us at [info@ypsomed.com](mailto:info@ypsomed.com)  
on the web at [www.ypsomed.com](http://www.ypsomed.com)

©2005 Ypsomed AG



2000



UltraSafe®  
Manual Needle Guard

2001



UltraSafe Passive®  
X50/X100L

2002



UltraSafe Passive®  
Tamper Evident

2003



UltraSafe Passive®  
Luer Lock X150G2L

2004



UltraSafe Passive®  
Autoinjector

2005

**Time and Again the World's Leading Pharmaceutical Companies Choose UltraSafe®.**

Six of the top ten pharmaceutical companies have chosen the UltraSafe® family of products and have proven them safe and effective with well over 100 million used worldwide. UltraSafe® products combine the features of FDA, NIOSH and GERES while offering the ultimate in compliance and protection. Plus they're easily integrated into existing production lines, enabling the fastest possible time to market. And as our product line evolves, it will continue to provide compelling competitive advantages that can make a real difference on your bottom line. The time is right to make UltraSafe Passive® your preferred choice. Contact us today at **760 918 9908** or [www.safetysyringes.com](http://www.safetysyringes.com).

 **SafetySyringes, Inc.™**

We live up to our name everyday

©2006 Safety Syringes, Inc. All rights reserved. UltraSafe and UltraSafe Passive are trademarks of Safety Syringes, Inc.

In sterile contract manufacturing,  
expertise, efficiency, and dedication  
equal success.



## Sterile Fill/Finish

Cardinal Health is a full-service contract manufacturer of biotech and sterile pharmaceutical products. Our expertise covers all key areas of sterile product development and manufacturing, including:

- Lyophilization
- Prefilled syringes
- Blow/Fill/Seal
- Vials

We are exclusively client-based and dedicated to the success of our customers. Our multiple state-of-the-art manufacturing facilities combined with our experience provide flexible capacity and efficiency.

**For all your sterile manufacturing needs,  
from clinical to full-scale production,  
call us at 1.732.537.6200 to discuss how  
we can partner with you.**



**CardinalHealth**

Working together. For life.®

[www.cardinal.com/pts](http://www.cardinal.com/pts)

1.732.537.6200 U.S.

[pts@cardinal.com](mailto:pts@cardinal.com) e-mail