PREFILLED SYRINGES:

THE FUTURE OF INJECTION SAFETY STARTS HERE

ONdrugDelivery
ISSUE No 30
JANUARY 2012
ISSN 2049-145X

OUTSTANDING ISSUE SPONSOR

MedPro™

ONdrugDELIVERY
niche information & intelligence

www.ondrugdelivery.com

BD
Helping all people live healthy lives

DUOJECT MEDICAL SYSTEMS

GERRESHEIMER

novozymes®
Rethink Tomorrow

Nuova Ompi
glass division

team technik
PRODUCTION TECHNOLOGY

TERUMO®

West®
Delivering Innovative Solutions

YPSOMED
SELFCARE SOLUTIONS

ONdrugDelivery Issue No 30, January 2012

"Prefilled Syringes: the Future of Injection Safety Starts Here"

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

EDITORIAL CALENDAR 2012:

Mar	Oral Drug Delivery
Apr	Pulmonary & Nasal Delivery (OINDP)
May	Injectable Drug Delivery : Formulations Focus
Jun	Injectable Drug Delivery : Devices Focus
Jul	Oral Drug Delivery
Aug	CDMOs & CROs Offering Drug Delivery Solutions & Services
Sep	Drug Delivery in Diabetes
Oct	Prefilled Syringes
Nov	Pulmonary & Nasal Delivery (OINDP)
Dec	Delivering Biotherapeutics

SUBSCRIPTIONS:
To arrange your **FREE** subscription (pdf or print) to ONdrugDelivery, contact: Guy Furness, Publisher
T: +44 (0) 1273 78 24 24
E: guy.furness@ondrugdelivery.com

SPONSORSHIP/ADVERTISING:
Contact: Guy Furness, Publisher
T: +44 (0) 1273 78 24 24
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:
Frederick Furness Publishing
48, Albany Villas, Hove, East Sussex, BN3 2RW
United Kingdom

PRODUCTION/DESIGN:
Mark Frost
www.frostmark.co.uk

ONdrugDelivery is published by Frederick Furness Publishing.
(ISSN 2049-145X print / ISSN 2049-1468 pdf)

CONTENTS

Turning Prefilled Upside Down

The most practical solution doesn't always require new parts, just a new way of putting it together...

- Standard Container
- True Passive Safety
- Cost Effective

MedPro™

www.medprosafety.com

*Not available for sale within the United States.
This device has not yet been approved or cleared by the U.S. Food and Drug Administration.

TURNING PREFILLED UPSIDE DOWN

In this article, Garyen Denning, Executive Vice-President of MedPro Safety Products, outlines how prefilled drug delivery is addressing longstanding challenges, but not needlestick safety. He explains the importance of offering passive, automatic needlestick protection and describes how the company's technology provides for a cost-effective drug delivery solution using an innovative prefilled device.

Prefilled drug delivery is an elegant solution to three big problems impacting pharmaceutical companies, patients, pharmacists and healthcare workers:

- Giving the wrong dose
- Medication errors
- Contamination

An estimated 2.7 billion prefilled syringes are used annually.[1] But as elegant and popular as prefilled solutions are, it gets ugly where accidental needlesticks are concerned.

We surveyed 262 healthcare professionals at the 2011 Association for Professionals in Infection Control and Epidemiology (APIC) conference in Baltimore, MD, US. It showed that:

- 68% do not believe that syringe needlestick injuries have been eliminated at their institutions, despite the existence of FDA, Centers for Disease Control & Prevention (CDC), and Occupational Safety and Health Administration (OSHA) requirements being in force in the US for more than a decade
- 43% do not believe existing safety features designed to prevent needlesticks are always activated after use and prior to disposal at their institutions, and less than 40% check for activation
- 43% are not happy with or are ambivalent about the current syringes used at their institutions.

Currently, the injectable drug market has many prefilled syringes. But we are aware of none that offer a fully automatic safety mechanism.

TURNING PREFILLED UPSIDE DOWN

To overcome this, we believe that the most practical solution does not always require new parts, just a new way of putting them together. This is the idea behind MedPro Safety Products' newest drug delivery platform.

By inverting the typical prefilled syringe and plunger rod format, the MedPro system allows for a standard cartridge as the primary container and integrates it with passive safety that remains outside of the fluid pathway. These two existing technologies, the prefilled cartridge and the MedPro fully automatic safety

Figure 1: MedPro Passive Safety Injection System.

Mr Garyen Denning
Executive Vice-President
T: +1 859 225 5375
F: +1 859 225 5347
E: gdenning@medprosafety.com

MedPro Safety Products, Inc
145 Rose Street
Lexington, KY 40507
United States

www.medprosafety.com

Figure 2: True Passive, Automatic Needlestick Protection.

shield, have been combined in a simple and elegant manner (see Figure 1).

The cartridge is inserted into the injection device. When the cartridge is pressed, just like a normal plunger rod, the medicine is delivered and a fully automatic needlestick protection activates. It does not require end-of-stroke activation like devices currently available on the market.

The passive activation of the safety shield also cannot be circumvented. If the patient unexpectedly moves away, the nurse has the comfort of knowing they both are automatically protected from a contaminated needle.

MedPro is currently working with pharmaceutical companies to utilise MedPro's prefilled cartridge for their injectables, and will work with those companies on the regulatory approvals that will be required.

UNDERSTAND THE USER

An integral part of MedPro's product design process is the strong voice of the customer. User focus groups and one-on-one interviews allow us to better understand customers' injection practices. What we've discovered is that current safety solutions do not guarantee safety activation. Current products activate at the end of the injection, and often require additional force to retract a needle. It's not uncommon to find they have not been activated after the injection is complete.

This is backed up by other evidence. A 2010 survey of US clinicians found a significant percentage of respondents admitting to injection practices deemed to be unsafe.[2] There are 385,000 needlestick injuries per year among US hospital workers despite laws requiring safety mechanisms on needles.[3] An audit of sharps containers at three Canadian hospitals found that the safety features on 13% of the syringes (a brand featuring "automated retraction") had not been activated.[4]

This is a key point of differentiation for MedPro technology, and follows on our design of a successful line of phlebotomy products. We focus on automatic, in-use deployment of passive safety (see Figure 2).

The cartridge, especially when packed in a "drug cube" of multiple cartridges, has a footprint advantage over normal prefilled syringes, which are commonly packaged in a blister pack with an attached plunger rod. This is especially true for temperature-sensitive drugs, where refrigeration and cold-chain space is at a premium.

During nurse evaluations and voice-of-the-customer studies, the MedPro cartridge-based system was heavily preferred by public health nurses where transport of temperature-sensitive drugs and vaccines in a mobile format is common. Having drugs supplied in a drug cube can reduce the footprint by 58% and allow transport of fewer cold-chain materials for the same dosage benefits.

PLATFORM SOLUTION INCLUDES IV DELIVERY

Originally designed for needlestick protection, the MedPro system also has applications for intravenous (IV) line access and drug administration. MedPro has designed the IV shuttle, an innovative IV delivery device that maintains a standard drug cartridge as the primary container. This device has movable core technology, giving pharmaceutical companies the option of staging the cartridge and device together until time of use.

"AT A TIME WHEN PHARMACEUTICAL COMPANIES ARE EVALUATING HIGHER PRICED COPOLYMERS TO SOLVE THE LUER COMPATIBILITY ISSUE, THE MEDPRO SYSTEM OFFERS A SOLUTION THAT IS COST EFFECTIVE AND AS STABLE AS A PRIMARY CONTAINER"

When asked about current solutions on the market and types of drug containers, 88% of the 500 pharmacists that were asked at last December's 46th American Society of Health System Pharmacists (ASHP) Midyear Clinical Meeting (New Orleans, LA, US), preferred for more drugs to be made available in a prefilled cartridge format.

It's not surprising that more than two billion prefilled cartridges are used per year, a number that will continue to grow.

In focus groups, nurses strongly preferred the IV Shuttle device (see Figure 3) and its cartridge over current methods, based on the ease of use, the plastic Luer tip, and the tactile feedback that the product gives. By using the drug cartridge, MedPro is able to offer pharmaceutical companies a packaging solution that has a plastic Luer tip, is compatible with all needle-free valves, and avoids the problems commonly associated with glass Luer prefilled syringes. It allows pharmaceutical companies to continue using their material of choice for the primary container. At a time when pharmaceutical companies are evaluating higher priced copolymers to solve the luer compatibility issue, the MedPro system offers a solution that is cost effective and as stable as a primary container.

Figure 3: MedPro IV Shuttle Delivery System.

PHARMACEUTICAL RISK AND COST ADVANTAGE

Just as patients and users are integral to the product development process, pharmaceutical

"WE FOCUS ON AUTOMATIC, IN-USE DEPLOYMENT OF PASSIVE SAFETY"

Figure 4: MedPro Cartridge in a Ready-to-Fill Nested Tub Format.

companies play a key role in product packaging and differentiation of the drug based on the delivery device associated with it.

MedPro has developed unique and cost-effective solutions for pharma companies, taking into consideration key factors in its decision making process:

- Primary container change risks
- Filling methods and infrastructure currently available
- Drug contact material considerations – by using a cartridge, the primary container does not provide risks associated with other staked-needle solutions such as tungsten and adhesive contact
- Economic value – how a packaging change can help grow or protect market share of a drug and the associated costs with that change, from validation, fill-finish operations, and capital investment

CARTRIDGE FILLING

Designed from a standard drug cartridge, MedPro technology works with commonly used cartridges available today. For pharmaceutical companies filling cartridges for auto-injectors, or niche applications, the MedPro technology allows them to increase their product offering by using current infrastructure and filling equipment. This cartridge gives the highest level of needlestick protection and cost-effective IV delivery as well.

READY-TO-FILL NESTED TUB

With the growth of prefilled syringes in Europe and more recently in the US, the capacity for prefilled syringe filling worldwide has increased at a greater rate than demand. There are many instances of excess capacity.

Addressing the needs of certain pharmaceutical customers, MedPro has designed the first ready-to-fill cartridge in a standard tub/nest format (Figure 4). The design can be filled on normal prefilled syringe lines. Unlike other products on the market that require significant capital investment after the aseptic filling operation, MedPro's ready-to-fill cartridge requires a simple machine for cap placement over the glass flange, low capital and short development time.

Figure 5: MedPro Cartridge Filled on a Conventional PFS Line (top), and Filled on a Conventional Cartridge Filling Line (bottom).

MATERIAL CONSIDERATIONS

Understanding the need for flexibility in material selection for pharmaceutical companies, MedPro has developed strong partnerships within the supply chain and can offer a range of material offerings for both the cartridge and ready-to-fill products (Figure 5).

THE MOST PRACTICAL SOLUTIONS

Prefilled can continue to be an elegant solution for pharmaceutical companies' drug delivery problems while addressing the threat of accidental needlesticks. Through strong customer input, inverting the typical prefilled syringe and plunger rod format, and finding additional ways to make our solutions work better, we've found again that the most practical solution does not always require new parts, just a new way of putting them together.

REFERENCES:

1. *Greystone Associates. Prefilled Syringes. 2009.*
2. *Pugliese G, Gosnell C, Bartley J, Robinson S. "Injection practices among clinicians in US healthcare settings." Am J Infect Control, 2010, 38(10), pp 789-798.*
3. *CDC, 2004; Panlilio A, et al. "Estimate of the annual number of percutaneous injuries among hospital-based healthcare workers in the United States, 1997-1998." Infect Control Hosp Epidemiol, 2004, 25(7), pp 556-562.*
4. *Stringer B, Haines T. "Ongoing use of conventional devices and safety device activation rates in hospitals in Ontario, Canada" J Occupational Environmental Hygiene, 2011, 8(3), pp 154-160.*

BioPharma Solutions

"Best Contract Manufacturing Organization"
BioPharma Solutions Wins Best CMO
at Vaccine Industry Excellence Awards
For Second Consecutive Year (2010-2011)

The Promise of Science Realized

Experience Makes the Difference

With 80 years of parenteral expertise, we can help to navigate the pathway of success for your molecule. We offer a broad spectrum of parenteral resources from formulation and development to sterile manufacturing solutions for traditional and complex molecules. BioPharma Solutions provides our clients with confidence of delivery, service, and integrity—we know the work we do is ultimately **vital to the patients you serve.**

For more information, visit
baxterbiopharmasolutions.com
or email us at
biopharmasolutions@baxter.com

Baxter

GERRESHEIMER

TRENDS IN PHARMACEUTICAL PRIMARY PACKAGING FOR INJECTABLES – SOLUTIONS FOR NEW CHALLENGES

Here, Claudia Petersen, Director of Business Development at Gerresheimer Bünde, provides an excellent insight into some of the most significant regulatory, technological, clinical and market trends affecting the parenteral drug delivery industry.

With a share of approximately 27%, injectables were the number two in the US$860 billion (£559 billion) global pharmaceuticals market in 2010, preceded only by oral medication. Double-digit growth rates, mainly triggered by biotech-derived products, and the rise of injectable generics, show that the importance of this segment is still on the rise. Besides prefillable glass syringes vials are still the most common primary packaging containers for modern injectables. However end user requirements and even marketing related reasons have led to a growing market for innovative devices such as safety syringes, pen systems and needle-free or intradermal injectors.

"IN 1997, THE EUROPEAN PHARMACOPOEIA INCLUDED 19 PAGES ON PRIMARY PACKAGING MATERIALS"

Various glass container systems are traditionally used for the storage of parenterals. All of them are standardised to facilitate processing on automated filling lines. The most common, a selection of which are pictured in Figure 1, include:

- Ampoule DIN EN ISO 9187-1
- Vial DIN EN ISO 8362-1
- Dental Cartridge DIN ISO 11040-1
- Insulin Cartridge DIN ISO 13926-1
- Prefillable Syringe DIN ISO 11040-4

With the exception of ampoules, all glass containers have pharmaceutical rubber closures. The so-called container closure systems (c/c system) are designed to protect the drug product from quality-diminishing environmental influences such as light, moisture and microbial contamination. However, the c/c system is not just a container. Over the product shelf life it also has to ensure that functionality and drug delivery accuracy always comply with the specifications.

Available container c/c systems and devices include vials, reconstitution kits, disposable or prefillable syringes, ampoules, auto-injectors and pen systems. Several factors have to be considered when choosing the right c/c system, such as drug product formulation properties, dosage, type of application and end-user friendliness. Examples of drug product formulation-related factors observed especially with prefillable syringes are high metal ion sensitivity and viscosity. A high sensitivity to metal ions may necessitate the use of new alternative primary packaging materials. In the case of high-viscosity syringe systems, features such as needle diameter have to be considered.

Furthermore, the dosage regime can influence device decisions, driven by the type of application, frequency and volume and fixed or variable dose. In connection with end-user friendliness, factors such as the place of application (clinic, home or emergency setting), the length of therapy, the target patient group and the dexterity of the operator have to be considered. It may be necessary to develop different packaging solutions for one product to satisfy different patient group needs.

Claudia Petersen
Director Business Development
T: +49 5223 164 242
E: c.petersen@gerresheimer.com

Arno Fries
Director Product Management Tubular Glass
T: +49 5223 164-401
E: a.fries@gerresheimer.com

Bernd Zeiss
Manager Technical Pre-Sales Support
T: +49 5223 164-309
E: b.zeiss@gerresheimer.com

Gerresheimer Bünde GmbH
Erich-Martens-Strasse 26-32
32257 Bünde
Germany

www.gerresheimer.com

Figure 1: A selection of the Most Common Glass Containers for Parenterals.

So, the offering from the parenteral primary packaging industry is diverse and complex, requiring manufacturers to consider a variety of factors. Not only this, but it is also an industry which has changed significantly in recent years, and will continue to do so. We have identified four of the key trends affecting companies involved in the development and manufacture of primary packaging for parenteral products. They are outlined here.

TREND 1 – OUTSOURCING OF CLOSURE PRODUCTION STEPS

A dominant trend in primary packaging is the evolution from simple bulk packaging materials towards ready-to-sterilise (RTS) or even ready-to-use (RTU) primary packaging containers. Process steps in the pharmaceutical production process such as washing, siliconisation and even the sterilisation of container system components are outsourced to suppliers which have to ensure that these processes are qualified and validated in accordance with current global regulatory requirements.

Even when pharmaceutical manufacturers opt for ready-to-sterilise products, they have a significantly lower investment in machinery and qualification/validation. The requirement of washing and siliconising equipment is eliminated and products are supplied with a certified endotoxin, bioburden and particle load. When rubber components and prefillable syringe systems are outsourced, this also includes the necessary siliconisation process.

Ready-to-use (RTU) quality is the next logical step. Pharmaceutical manufacturers outsourcing RTU components can thereby also eliminate the need to invest in sterilisation and the regular revalidation of this process. The sterility and shelf life of the products are certified by the primary packaging supplier.

While prefillable syringe systems are always EtO-sterilised, plunger stoppers undergo mainly gamma irradiation. A validated gamma sterilisation process has to provide a minimum sterility assurance level (SAL) of 10^{-6}. Dose mapping and setting have to conform to ISO 111337-2. In general, a package transport simulation and integrity validation should be performed on the sterilised goods and an expiration date has to be stated (Figure 2).

Ready-to-fill syringe systems have already been available for many years. In recent years pharmaceutical rubber suppliers have recognised this trend and now offer a broad range of ready-to-use (either gamma or steam-sterilised) rubber components. Glass suppliers have now begun working on RTU glass vials. It remains to be seen whether a packaging standard such as the tub packaging for prefillable syringe systems will be established for vials.

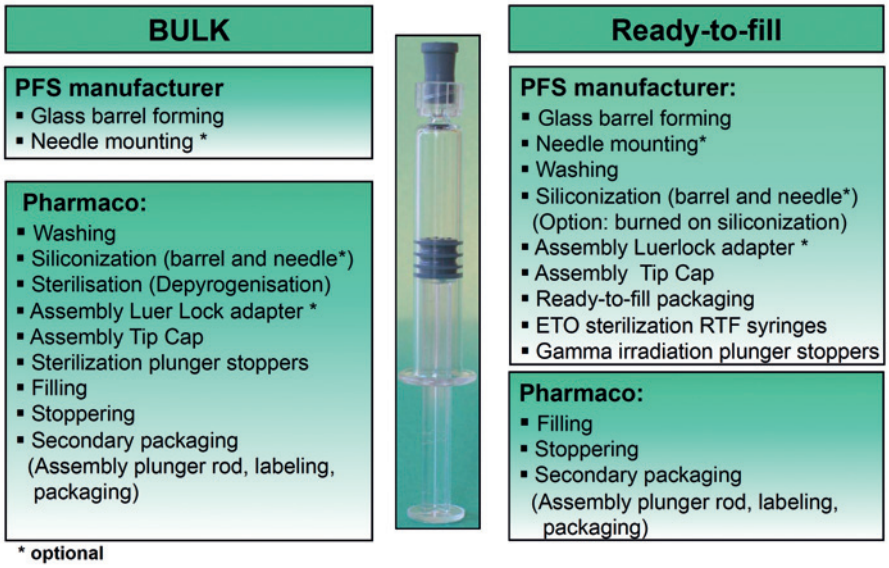


Figure 2: Comparison of Bulk *versus* Ready-to-Fill Prefillable Syringes.

TREND 2 – INCREASINGLY STRINGENT QUALITY REQUIREMENTS

Regulatory authorities all over the world are paying greater attention to the use of appropriate primary packaging materials with the consequence that standards have become very comprehensive and detailed. In 1997, the European Pharmacopoeia included 19 pages on primary packaging materials. Fifteen years later the number of pages had nearly tripled to 53. Within the same time frame, regulatory authorities around the globe issued new guidelines dedicated to primary packaging materials such as the Container Closure Guideline published by the US FDA in 1999 and the EMA Guideline on Plastic Immediate Packaging Materials dated 2005.[1,2] Another example is the DIN ISO standard 15378: "*Primary packaging materials for medicinal products – Particular requirements for the application of ISO 9001:2000, with reference to Good Manufacturing Practice (GMP)*", dated 2006.

The primary packaging industry has coped with these increasingly tough regulatory requirements by enlarging quality departments, installing dedicated regulatory affairs officers and intensifying technical support. ISO 15378-compliant production is standard practice nowadays in the European and US primary packaging industry.

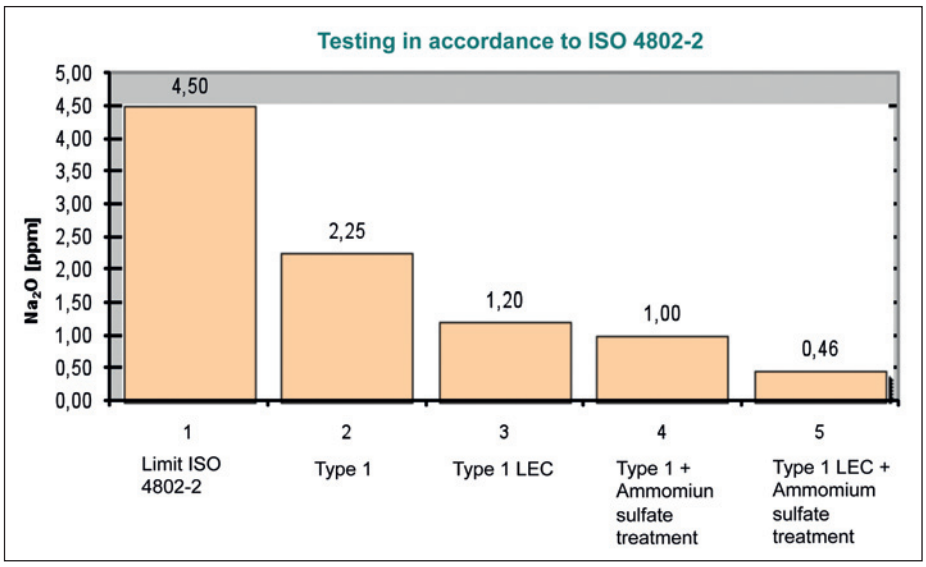


Figure 3: Influence of Ammonium Sulphate Treatment & Low Extension Glass on pH Shift.

Quality requirements for glass containers, which are likely to be tightened further, include specifications regarding the particle load, lower rates of cracks or cosmetic defects and smaller dimensional tolerances. Prefillable syringes are associated with specific requirements such as low hold-up volumes and reduced tungsten or siliconisation levels.

The tungsten oxide contamination resulting from the forming process of the bore inside the syringe cone can, for example, be avoided using pins made from other metals in the forming process. No official tungsten limit exists as yet. An upper limit of 500 ppb is under discussion. Superior quality requirements on the cosmetic and dimensional side can be met by improved manufacturing processes, the introduction of comprehensive process control with camera systems and packaging inside clean rooms. Automated visual inspections to check for dimensional and cosmetic defects allow constant sorting performance with high reliability and output.

Inevitable negative side effects are the cost of the equipment and a proper sorting process qualification to avoid an excessive scrap rate due to false rejects. Rubber component suppliers have developed similar visual inspection procedures.

TREND 3 – GROWING SYSTEM COMPLEXITY

Relentless progress in medical technology, the cost pressure of increasingly expensive healthcare systems and the necessity to operate profitability in a globalised economy all contribute to the complexity of decisions in the primary packaging market. Medical factors which must be taken into consideration include demands for simpler and safer administration and increased dosage accuracy.

Economic factors include the total cost of a system and the retail price of drugs. It is also necessary to consider that developed nations face an aging population which will double the percentage of people aged 60 and over by 2050.

Other factors are demands for optimised production processes or enhanced product value, specific regulatory frameworks or a company's IP position.

There are currently four major factors which are controversial in some respects in the drug delivery device market:

- More standardised, simpler and more robust packaging solutions to address the increasing cost pressure.
- Modern drug delivery systems as a means of differentiation from competitors.
- Modern drug delivery systems as a reflection of modern lifestyle.
- New regulatory and legislative requirements such as dose counting for metered dry-powder inhalers and needlestick legislation for injectables to be considered during device development.

In this complex situation, the requirements of the drug product, syringe/container and device are all interlinked which necessitates the close collaboration of all project participants. Pharmaceutical and primary packaging/drug delivery device manufacturers should share their expertise to specify system requirements and achieve a common understanding.

TREND 4 – NEW MATERIALS

There are a number of reasons why packaging and device suppliers should develop enhanced primary packaging solutions or even use new materials.

New, complex devices may require primary packaging which cannot be made from glass due to the limitations of its technical and material properties. As mentioned previously, modern biopharmaceuticals which are mostly based on large proteins are more likely to interact with traditional c/c system components. Also, biopharmaceuticals are often quite expensive so low overfills and excellent container drainability are essential.

Primary packaging manufacturers are responding to these challenges with new or modified materials. For example, elastomeric components such as plunger or injection stoppers can be coated with fluoropolymers. The FluroTec® closures manufactured by West are partially covered, whilst Daetwyler's Omniflex closures have a completely coated surface. Acting as a barrier, the coating improves compatibility with drugs and minimises extractables / leachables. This eliminates or drastically reduces the need for additional siliconisation of plunger stoppers for lubrication purposes while maintaining the functionality of the syringe system.

In cases where the technical limitations of glass prevent its use, modern plastics such as cyclic olefins can be a solution. They offer far greater design flexibility, facilitate tighter dimensional tolerances and are more break resistant than glass.

Surface treatments such as ammonium sulfate treatment can be applied to glass containers to minimise sodium ion leaching and a subsequent pH shift. The use of low alkali borosilicate glass, called low extension glass (LEC), has the same effect (Figure 3).

Another approach is based on thin-film technology. Pure silica (SiO2) coatings are applied to the inner surfaces of glass containers. The silica layer acts as a diffusion barrier, preventing interaction of the glass matrix with the drug without impairing compatibility with standard filling lines and sterilising procedures.

In the past, the high cost and complexity of meeting regulatory requirements discouraged manufacturers from considering materials other than the well-established combination of borosilicate glass and pharmaceutical elastomers. That has now changed and, as new types of drugs with unique properties are entering the market, innovative materials are being scrutinised more closely.

The polymers of choice are cyclic olefin polymers/copolymers (COP/COC) which have some properties comparable with those of glass. Both materials are transparent, durable and solvent-resistant. Cyclic olefins also have some properties which are superior to glass such as higher break resistance, broader pH-range toler-

Our comprehensive offering: RTF® syringe systems

- High-quality ready-to-fill syringes
- Innovative accessories
- Proprietary baked-on siliconization

www.gerresheimer.com

GERRESHEIMER

ance and no leakage of metal ions. One particularly important feature relating to the storage of biotechnological drugs is the excellent drainability of cyclic olefin containers which limits the need for excess overfill.

However, cyclic olefins also have some downsides. Compared with glass they are more susceptible to scratching, which requires a special handling on filling lines. Another parameter to consider during primary packaging material selection is the gas and water vapor permeability of cyclic olefins. Compared with other plastics, they have much lower permeation values. Glass, though, is gas impermeable.

Prefillable plastic syringes such as ClearJect™ from Taisei Kako Co Ltd (Osaka, Japan) are manufactured in "lights out" factories. In other words, the entire production process, providing highest injection molding accuracy, is fully automated and takes place inside clean rooms. Camera inspection systems are used for 100% quality control of dimensions, cosmetic defects and other product parameters such as the siliconisation. These syringe systems are gamma-sterilised. They offer the advantage over glass prefillable syringe systems that the tip cap and plunger stopper are made of the same modern latex-free, chlorobutyl-based pharmaceutical elastomer.

OUTLOOK

Present trends indicate that the future of pharmaceutical primary packaging will be characterised by continuous change. Although traditional disposable syringes with vials or ampoules will remain in use, the trend in biopharmaceuticals towards prefillable syringes, auto-injectors and pen systems as well as customised delivery systems will continue. Primary packaging containers will be made from either glass or plastic. Alternative coatings to standard siliconisation are being developed and will gain in importance.

For the primary packaging industry, this means an expanding market for more convenient and easier-to-use injectable products. This trend is closely related to rising demand for complex services that cover more stages in the supply chain. Primary packaging suppliers will assume an increasing number of production steps relating to closure preparation for the fill and finish process. As a result, they will evolve from component providers to system suppliers and product development project partners.

REFERENCES:

1. *Guideline on Plastic Immediate Packaging Materials, May 2005, CPMP/QWP/4359/03, EMEA/CVMP/205/04.*
2. *Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics, May 1999, US FDA.*

ABOUT GERRESHEIMER

Gerresheimer is an internationally leading manufacturer of high-quality specialty products made of glass and plastic for the global pharma and healthcare industry. Its comprehensive portfolio of products extends from pharmaceutical vials to complex drug delivery systems such as syringe systems, insulin pens and inhalers for safe medication dosage and application. Together with its partners, it develops solutions which set standards and have role model status in their respective market sectors.

The Group realises revenues of around €1 billion and has 10,000 employees at 45 locations in Europe, North and South America and Asia. It uses first-rate technologies, convincing innovations and targeted investments to systematically consolidate a strong market position.

DUOJECT MEDICAL SYSTEMS

VACCJECT: LOOKING TO THE FUTURE OF READY-TO-USE INJECTIONS

The need for effective needlestick protection is well established. With the passing into law of the US Needlestick Safety and Prevention Act in November 2000, the recent EU Sharps Directive, coupled with the emergence of many products pre-fitted with safety devices, the need is clear. In this article, Simon Williams, Business Development, DuoJect Medical Systems, asks whether as an industry we are approaching this challenge in the most efficient and effective manner.

In early 2009, convinced of the growing need for effective needlestick protection devices Duoject Medical Products examined the current device development trends and set out to try to develop a better solution. In particular we wanted to answer the question, does the inclusion of a needlestick prevention device have to increase the cost of a delivered dose of vaccine or parenteral drug?

The prefilled syringe has long been accepted as the preferred container for supplying and delivering a ready to use injection. However, syringes are relatively expensive and adding a safety system has considerable technical challenges and doesn't always result in an elegant solution. We did not want to develop a new primary container with all the regulatory hurdles and difficulties that would entail, so we restricted ourselves to well established proven packing systems. The obvious choice to us was the cartridge. It is being used in huge volumes throughout the industry, production capacities are freely available, high-speed filling and handling equipment is highly developed, and it's a reliable, effective, low-cost drug container.

"WE SAW CLEAR ADVANTAGES IN SEPARATING THE DRUG CONTAINER (THE CARTRIDGE) FROM THE DELIVERY DEVICE"

With the primary container selected, we set about developing a device that would safely deliver the drug to the patient. From the outset

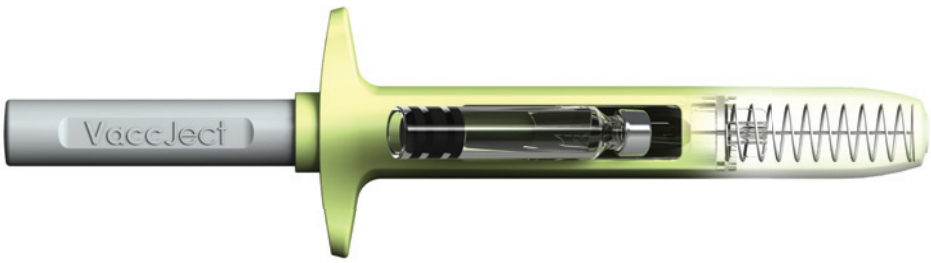


Figure 1: As the cartridge is inserted into the VaccJect device, the enclosed double-ended needle penetrates the cartridge septum, opening the fluid path for drug delivery.

Mr Simon Williams
Business Development
T: +1 450 534 3666
F: +1 450 534 3700
E: swilliams@duoject.com

Duoject Medical Systems Inc
50 Chemin De Gaspé, Complex B-5
Bromont (Quebec)
Canada
J2L 2N8

www.duoject.com

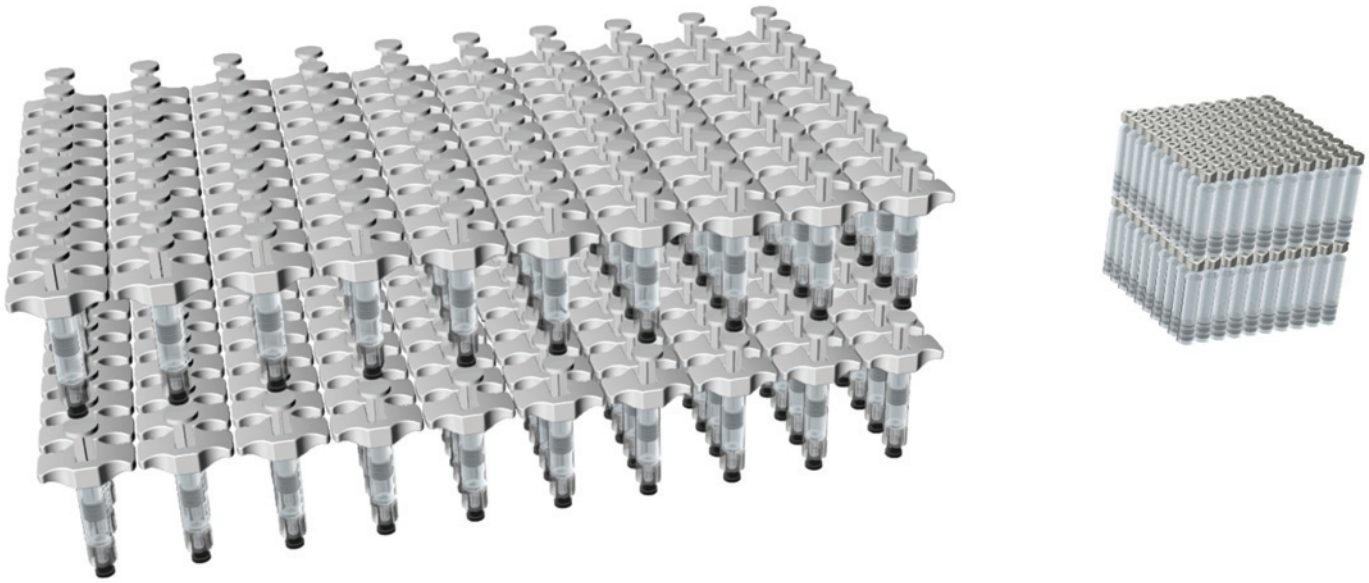


Figure 2: The cartridge (right) takes up approximately 10% of the storage volume of a typical 1 mL syringe (left).

we wanted to ensure that the needle was never seen: not before, during, or after injection. The device had to be low cost, passively activated and permanently disabled as soon as the injection was complete.

Our inspiration for the activation mechanism was the simple click-top ball-point pen but the resulting device – VaccJect – is innovative and has allowed us to obtain, broadly encompassing worldwide patent protection in this already crowded IP space.

HOW IS VACCJECT USED?

The end user (healthcare professional or home-medicating patient) takes the drug cartridge and inserts it into the open window on the VaccJect device (see Figure 1). As the cartridge is inserted, the enclosed double-ended needle penetrates the cartridge septum, opening the fluid path for drug delivery.

The VaccJect is then held directly to the skin and the plunger rod is pushed down to a stop. This first press inserts the needle into the patient to a preset depth. By coming to a hard stop, the needle can be inserted rapidly to minimise pain, without any risk of the needle penetrating too far. The finger or thumb pressure is then gently eased and the device clicks: it is now ready to deliver the drug. The delivery speed of the injection is controlled manually by the end user and feels just like any standard syringe. When the plunger rod has been completely depressed and the dose fully delivered, the needle automatically retracts as the plunger rod is released, at a rate controlled by the end-user. At this point, a reassuring light click is felt, giving the user feedback that the needle has fully retracted inside the device and that the device has locked and been permanently disabled.

WHY IS THE DRUG CONTAINER SEPARATE FROM THE VACCJECT DEVICE?

As the development progressed, we saw clear advantages in separating the drug container (the cartridge) from the delivery device.

Keeping the two parts separate until the point of use greatly simplifies the production process at the drug filling facility, eliminating all secondary packaging and letting the facility focus on the critical task of compounding and filling the drug cartridge. Keeping the drug cartridge separate also offers significant benefits where drugs must be kept at reduced temperatures. The cartridge takes up approximately 10% of the volume of a typical 1 mL syringe, thus providing substantial savings in the cold chain storage and distribution systems (Figure 2).

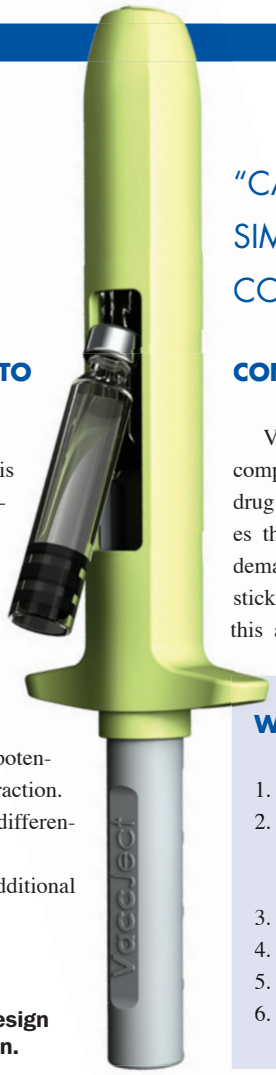
Acording to the 2011 *BioPharma Cold Chain Source Book* (Pharmaceutical Commerce), the pharmaceutical industry is expected to spend $4.6 billion (£3.0 billion) on cold chain transport and storage in 2012. Just a 1% reduction would equate to a $46 million saving to the industry.

Clinic and hospital healthcare workers also told us that refrigerated storage space is at a premium and when questioned in a study, they saw a significant benefit in being able to store the drug cartridge separately, especially as cartridge insertion into the device is so simple, "like putting a battery in a remote control", as one experienced nurse reported.

USER EVALUATION TRIALS

During user evaluation trials, some key points became clear:

1. Seasoned healthcare professionals found VaccJect very easy to use and expressed no reservations about switching to the device. They particularly loved that the needle was never exposed, neither before nor after the injection.
2. Both healthcare professionals and home patients found that inserting the cartridge was easy, and actually preferred this to a pre-inserted cartridge as it gave them the benefit of space saving in cold storage.
3. Paediatric professionals particularly liked that the device does not look like a syringe and that the needle is always covered. They felt that their patients would be more at ease receiving their injections from VaccJect rather than from a standard syringe.



"CARTRIDGE INSERTION INTO THE DEVICE IS SO SIMPLE, 'LIKE PUTTING A BATTERY IN A REMOTE CONTROL', AS ONE EXPERIENCED NURSE REPORTED"

WHAT ARE THE BENEFITS TO PHARMA COMPANIES?

1. As no secondary packaging is required, in-house manufacturing complexity and labour is reduced.
2. With the drug cartridge taking up only 10% of the space of a prefilled syringe, substantial cold chain shipping and storage savings will be realised.
3. Dry-needle system eliminates potential drug needle / adhesive interaction.
4. Unique design ensures product differentiation (Figure 3).
5. Needlestick protection at no additional cost.

Figure 3: Vaccect's unique design ensures product differentiation.

CONCLUSION

VaccJect is a unique solution to the complex challenges of a ready-to-use drug delivery container, that addresses the growing market and legislative demand for integrated passive needlestick protection. We are confident that this approach will generate significant savings and simplify some of the manufacturing complexities and challenges which now confront the pharmaceutical industry.

To appreciate the true simplicity of VaccJect you need to experience the device first hand, so call us, or visit us at Stand 468, at Pharmapack 2012 in Paris, and let us share with you why VaccJect is the future of ready-to-use injections.

WHY IS A CARTRIDGE BETTER?

1. No tungsten or needle adhesive to contaminate your drug.
2. Baked silicone to eliminate sub-visible particles (available at minimal cost by simply adding silicone oil to final wash station, prior to depyrogenation)
3. Well established standard drug container, easing FDA acceptance.
4. Exceptional glass surface, very resistant to risk of delamination.
5. All standard rubber formulations available, including coated plungers.
6. Proven high-speed filling equipment readily available.

VaccJect

The prefilled syringe alternative with free needlestick protection

Insert Inject Protected

DUOJECT MEDICAL SYSTEMS

www.duoject.com

COMPANY PROFILE – NOVOZYMES BIOPHARMA

Novozymes Biopharma develops and manufactures high quality, animal-free, and regulatory-compliant recombinant ingredients and technologies to provide pharmaceutical and medical device manufacturers with the knowledge-based solutions needed to address their challenges and develop innovative, safer and more consistent products.

With over 25 years' experience in the pharmaceutical industry, Novozymes is the world leader in the supply of recombinant products and technologies for biomedical applications. Currently, 14% of Novozymes' total revenue is spent on research and development with more than 6,000 granted and pending patent applications, demonstrating a commitment to scientific innovation.

Novozymes' large-scale manufacturing facilities worldwide are run to cGMP/Q7 quality standards ensuring customers receive product quality and consistency, as well as the security of long-term supply. The company's customer-integrated approach combines Novozymes' scientific know-how with the specific needs of customers to deliver improved products and performance.

NOVOZYMES' RECOMBINANT ALBUMINS

Novozymes offers a range of recombinant albumins (rAlbumins) developed to provide customers with a safe and consistent regulatory-compliant product. The company's rAlbumins are manufactured to large-scale using a proprietary *Saccharomyces* yeast strain to cGMP/Q7 quality standards, free of animal- or human-derived products and supported by a strongly documented safety package and drug master file.

DRUG DELIVERY

Facilitating drug delivery with the use of recombinant albumin and albumin fusion

Whether it is to improve the half-life of the active molecule or to enhance the stability and solubility of therapeutics, Novozymes can help drug manufacturers with a solution suited to the desired application.

NOVOZYMES' rALBUMINS IN FORMULATION

As the purest and most homogenous rAlbumins available, Novozymes' Albucult® and Recombumin® (see Figure 1) are ideal for stabilising drugs in a range of formulation conditions, for example pH and temperature, and can help:

- Achieve liquid formulations in protein therapeutics
- Limit product loss due to non-specific adsorption
- Prevent functional or structural changes caused by oxidation
- Reduce aggregation and sub-visible particle formulation to minimise immunogenicity concerns

ALBUCULT® – RECOMBINANT ALBUMIN HUMAN USP-NF*

Suited to drug, vaccine, and device manufacturing

Expressed in a proprietary *Saccharomyces cerevisiae* expression technology and manufactured in a large-scale, cGMP compliant facility, Albucult is designed with stringent quality requirements in mind. Albucult has been developed and supplied as an ingredient for the manufacture of pharmaceutical drugs, medical devices and advanced cell therapy products. Albucult has been approved for use in the manufacture of several medical devices. It delivers quality and unprecedented performance benefits to customers' applications.

Figure 1: Novozymes' Albucult® and Recombumin® are ideal for stabilising drugs in a range of formulation conditions.

Figure 2: Novozymes has dedicated a significant proportion of its recent R&D activity to developing solutions that will ultimately improve treatment regimes for patients.

RECOMBUMIN® – RECOMBINANT ALBUMIN HUMAN USP-NF*

Ideal for drug delivery and formulation

Also expressed in *Saccharomyces cerevisiae*, Recombumin was the world's first commercially available, GMP-manufactured, animal-free rAlbumin developed specifically as a drug and vaccine manufacturing ingredient. Recombumin has been fully approved for use in the manufacture of human therapeutics. The product's batch-to-batch consistency and regulatory compliance reduces processing and testing times to drive product efficiency.

NOVOZYMES' rALBUMINS FOR HALF-LIFE EXTENSION

Novozymes range of half-life extension technologies based on recombinant albumin products, combine the therapeutic effect of a peptide or protein with the naturally extended plasma half-life of human albumin.

ALBUFUSE® - ALBUMIN FUSION TECHNOLOGY

Building on proprietary expertise within cloning and expression, Albufuse® technology has been developed to enable the genetic fusion of a customer's target protein to albumin at the molecular level. The resultant moiety is secreted as a contiguous peptide linked via a peptide bond and enables the user to enhance the pharmacokinetics of their target protein with retained efficacy.

ALBUFUSE® FLEX AND RECOMBUMIN® FLEX– TAILORED TO DELIVER

An extension of Novozymes existing scientific know-how of albumin fusions, the new platform exploits the natural interaction between albumin and the neonatal Fc receptor (FcRn). Albumin is the most abundant protein in blood where it has a pivotal role as a transporter of fatty acids and drugs. It also has a naturally long serum half-life, protected from degradation by pH-dependent recycling mediated by it's interaction with FcRn.

Figure 3: Novozymes' Hyasis® offers safety, consistency and performance, all in one raw material.

Specific albumin variants have been designed with altered binding affinities for the receptor, making it possible to modulate the serum half-life of the albumin molecule. By coupling a drug to these variants, through genetic fusion (Albufuse® Flex) or chemical conjugation (Recombumin® Flex), the technology confers the extended or reduced circulatory half-life onto the drug molecule.

This technology will enable drug developers to design new efficacious products, or life-cycle manage existing drugs, with longer serum half-life, reduced toxicity and improved pharmacokinetic profiles (see Figure 2).

NOVOZYMES' HYALURONIC ACID – HYASIS®

Bacillus-derived hyaluronic acid (HA) is used in the manufacture of medical devices and pharmaceutical products offering safety, consistency and performance all in one raw material (Figure 3).

Due to its intrinsic biocompatibility, biodegradability and diverse biological functions, HA is widely used in medical device and pharmaceutical applications, for example eye drops, viscoelastic devices, and topical formulations. HA adds new and improved attributes to existing products, whilst also offering numerous opportunities when developing new ones.

HA is an attractive carrier for drug delivery applications, because it can interact with drugs in many different ways to enhance their stability and aqueous solubility. For intravenous drug delivery, HA can, for example, promote tumor targeting, reverse drug resistance, and increase the sensitivity of tumor cells to chemotherapeutics. In dermal applications, HA exerts anti-inflammatory properties and enhances permeability of a topical drug, among many other benefits.

EXPERIENCED REGULATORY SUPPORT FOR RECOMBINANT PRODUCTS

Novozymes offers up-to-date and efficient regulatory support services to fast track customers' regulatory filings through:

- Experienced dealings with regulatory agencies; e.g. FDA, EMEA, TGA, Health Canada
- Support of Novozymes' animal-free recombinant products and technologies
- Preparation and maintenance of regulatory support dossiers; e.g. drug master files, clinical trial applications, product dossiers
- Application of QbD principles to remove animal-derived materials from manufacturing processes

QUALITY ASSURANCE AND CONSISTENCY

Novozymes' quality assured, consistent products and technologies are designed with an understanding of the regulatory landscape. Dedicated product support and expertise delivers a rapid response to regulatory queries facilitating the regulatory process of customers' products and technologies.

Novozymes Biopharma US Inc
One Broadway, 14th Floor
Cambridge, MA 02142
United States

T: +1 617 401 2500 (US sales office)
T: +45 4446 2896 (EU sales office)
E: biopharma@novozymes.com

www.biopharma.novozymes.com

The producers of Pharmapack Europe present...

Pharmapack NORTH AMERICA

Drug Delivery and Packaging Technology Conference and Exhibition

20687_E_PhP12

May 22–23, 2012

Pennsylvania Convention Center
Philadelphia, PA

- North America's leading educational and networking forum for leaders in pharmaceutical and biopharma packaging
- Two days of cutting-edge technical sessions focused on the key challenges, trends, and innovations in drug delivery systems and packaging technology
- Speaker faculty including packaging professionals from big pharma and world-class case studies from today's leading innovators
- Top manufacturers and suppliers of innovative packaging and advanced drug delivery device technologies
- Additional solutions at the co-located EastPack, ICSE (International Contract Services Expo), and Medical Design & Manufacturing (MD&M) East shows

For details about attending or exhibiting, visit: PharmapackNA.com

Produced and Managed by: UBM Canon

Event Partners: Pharmapack Europe; Pharmaceutical & Medical Packaging News

Media Partner: Packaging Digest

Co-located with: EastPack; Medical Design & Manufacturing M&M East; iCSE International Contract Services Expo

NOVOZYMES **STABILITY** BIOPHARMA

IS OUR MIDDLE NAME

Stabilizing your drug formulation is simpler with rAlbumin

Our high quality animal-free recombinant albumins (rAlbumin) have been developed and optimized for your drug delivery and formulation needs. Manufactured to cGMP quality standards in large-scale facilities, Novozymes Biopharma's rAlbumins are USP-NF* compliant and are supported by a strongly documented safety package and drug master file.

Ideal for stabilizing drug formulations, they can help you to:

- Achieve liquid formulations of protein therapeutics
- Limit protein loss due to non-specific adsorption
- Prevent functional or structural changes caused by oxidation
- Reduce aggregation/sub-visible particle formation and therefore potential immunogenicity concerns

Find out more about stabilizing your drug formulation with rAlbumins, and the additional benefits that these products offer you, by visiting our website or emailing **biopharma@novozymes.com**

*Meets National Formulary (NF) standards as published by United States Pharmacopeia (USP)

www.stabilizeyourformulation.com

MAKING PRODUCTS BETTER TOGETHER

novozymes®
Rethink Tomorrow

HIGHLY FLEXIBLE AUTOMATION SOLUTIONS FOR ASSEMBLING & TESTING MEDICAL DEVICES

team technik
PRODUCTION TECHNOLOGY

Diabetics are able to inject themselves with their daily dose of insulin quickly and safely, thanks to their insulin pens. Similarly, asthmatics have fast access to their medication through inhaler systems. Medical products such as pens and inhalers make it possible for chronically sick people to live largely unrestricted lives. Because they are so easy to use they have long been in great demand and are produced in high volumes. And the trend is growing. The requirement for increasingly flexible solutions to automate the manufacture of medical products from assembly to the complete packaged unit, including functional testing, is therefore also increasing. teamtechnik Group is one of the leading suppliers developing and implementing turn-key production systems for medical devices.

Based in Freiberg, Germany (Figure 1), teamtechnik has been making intelligent and reliable automation solutions for the automotive and solar technology and for medical and pharmaceutical industries for over 35 years. With their focus on assembly and testing, the systems are distinguished by their consistently modular and standardised process-oriented structure.

teamtechnik is considered an international leader in highly flexible automation technology. With a total of 700 employees throughout the world, the company achieves sales of over €130 million (£114 million). The teamtechnik Group has production sites in Germany, Poland, China and the US.

teamtechnik Group
Planckstraße 40
71691 Freiberg
Germany

T: +49 (0) 7141 7003 0
F: +49 (0) 7141 7003 70
E: info@teamtechnik.com

www.teamtechnik.com

Figure 1: teamtechnik's Facility in Freiberg, Germany

teamtechnik develops innovative process-optimised production solutions for medical technology that meet customers' requirements right up to serial production. The systems are designed with a modular approach, a highly-flexible concept which allows the manufacturers of medical devices to adapt their production quickly and economically to changes in the market.

In the new TEAMED system, its latest system platform, the company has brought to market a highly flexible and upgradeable linear system for assembly and testing, realising almost 80% of all customer solutions in the medical technology sector. Sophisticated process technology and 100% end-of-line testing can be integrated in the platform specifically for the assembly of medical devices and pharmaceutical products.

TEAMED (shown in Figure 2) allows production compliant with global guidelines and monitoring systems such as GAMP 5, FDA

Figure 2: A TEAMED Production Line

and CE and meets class 6 clean-room specifications. The special feature is that TEAMED also incorporates processes from clinical Phase I and II prototype production directly in serial production, thus verifying critical processes in advance of the original configuration later on and providing the person responsible with reassurance for future serial production from the start. TEAMED-based systems can be adjusted to accommodate increasing unit numbers quickly and with little extra effort.

AN EXAMPLE: A SYSTEM TO ASSEMBLE AND TEST THE FUNCTION OF A HORMONE PEN

The assembly of a hormone pen with integrated 100% functional testing illustrates the possibilities offered by systems based on TEAMED. One of the delicate processes in the manufacture of this component involves using a laser to mark the gradations on the dose barrel. In this case, this process is carried out away from the main production line in a standalone TEAMED satellite. The gradations are drawn onto the delicate surface of the dose barrel and checked in-line, improving the quality of the product and also making it more flexible. As the blanks are fed in bulk, an expensive tray solution is not required.

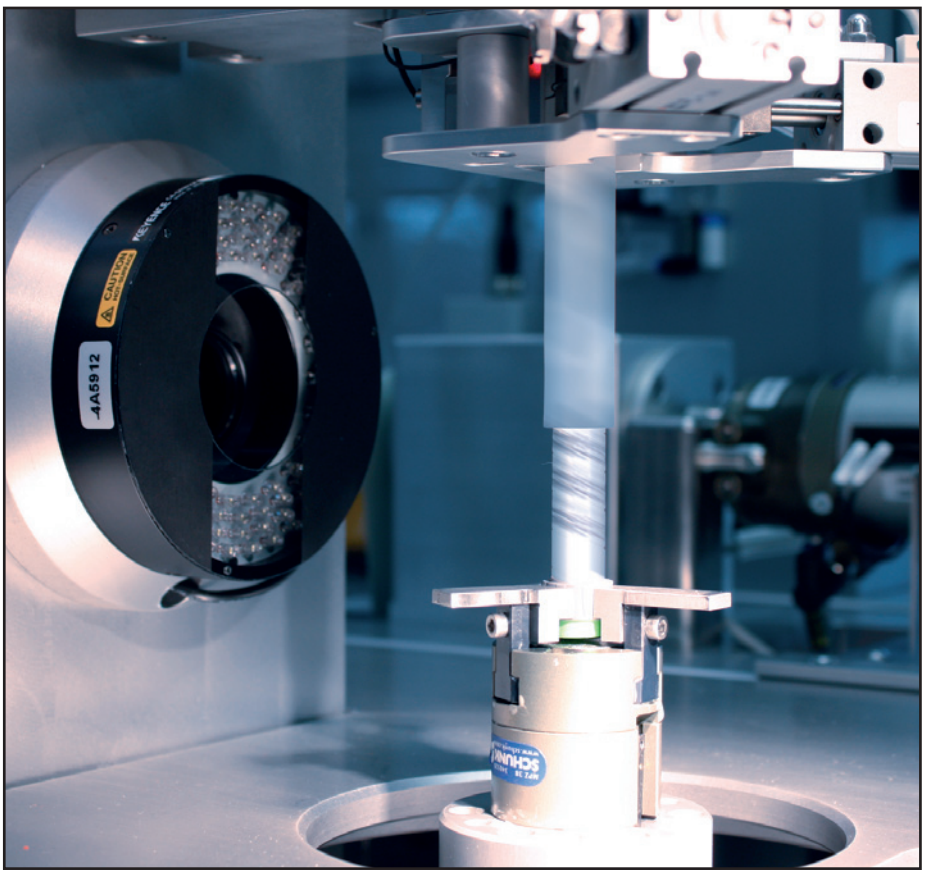


Figure 3: Integrated Pen Testing Application

Once the pens have been fully assembled, TEAMED checks that they are functioning perfectly. In the integrated test application (Figure 3), the pen mechanics are pulled up and pressed down again. The torque applied when drawing up can be determined to an accuracy of 0.001 Nm and the ejection force to 0.01 N. Marked and placed in a tray, the pens leave the production line.

Pharmapack EUROPE

15–16 FEBRUARY 2012, PARIS

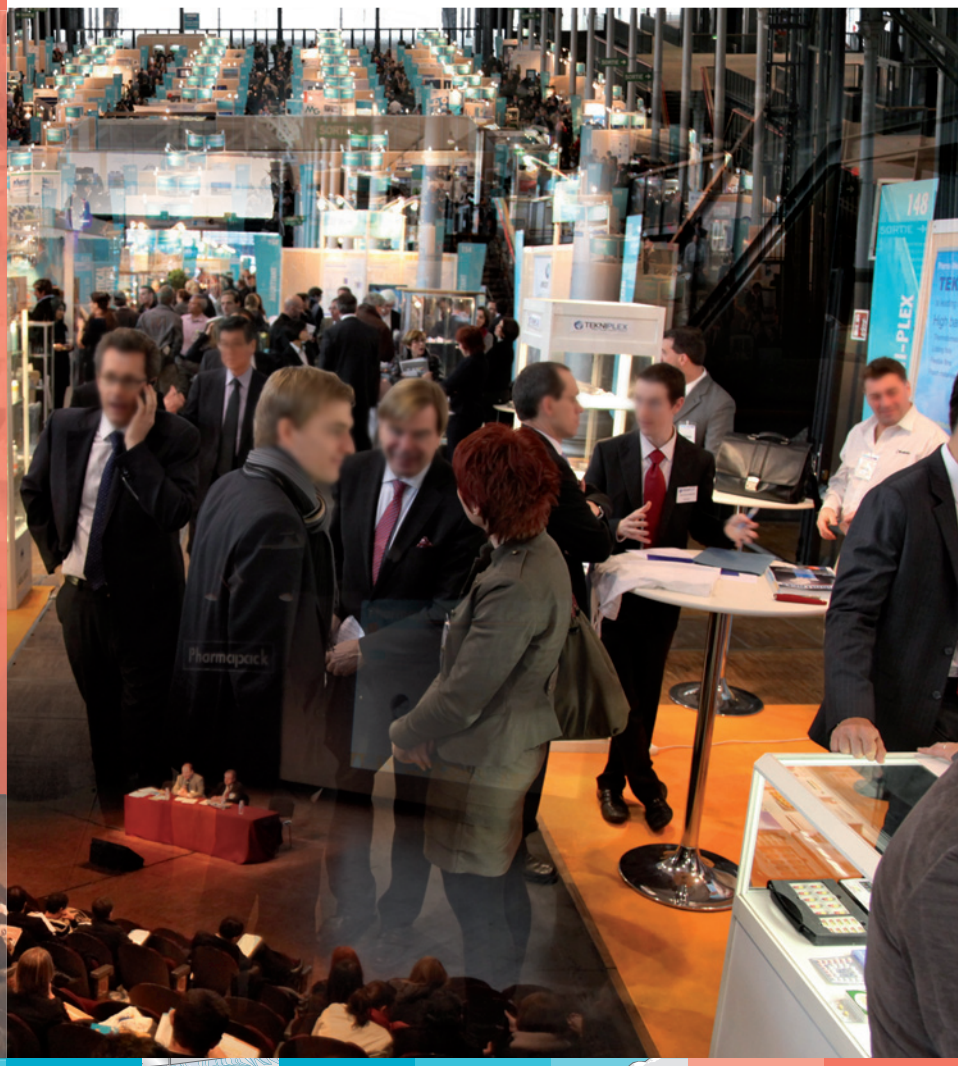
DRUG DELIVERY AND **PACKAGING TECHNOLOGY CONFERENCE** AND **EXHIBITION**

- Annual event in Europe for over 2,800 key decision-makers from the pharmaceutical industry looking for packaging and delivery technologies for their drugs
- Exhibition brings together more than 250 international leading manufacturers and suppliers of packaging and advanced drug delivery technologies
- Two days of cutting-edge technology lectures focusing on the latest international market trends and packaging developments

Pharmapack AWARDS 2012

- Please visit our website to find out how to participate

www.pharmapack.fr



NEW!

TERTIARY PACKAGING & COLD CHAIN

TECHNICAL SYMPOSIUM

Bringing innovative tertiary packaging solutions to secure sensitive or thermosensible drugs transport

In partnership with: KNAUF INDUSTRIES Healthcare

UBM Canon

For more information and to register, please visit www.pharmapack.fr

21167_FR_PHP12

RUNS 24/7

PRODUCTION SYSTEMS FOR DRUG DELIVERY DEVICES.

TEAMED

- Flexible and expandable platform
- For assembly and test systems
- Excellence and reliability

Get inspired for the future.
www.teamtechnik.com

team technik
PRODUCTION TECHNOLOGY

BD

Helping all people
live healthy lives

COMMERCIALISING DRUG DELIVERY INNOVATION

The intradermal route has a number of attributes that make it attractive for drug delivery. However, traditional methods for administering an intradermal injection have proven problematic. In this article, Patrick Jeukenne, Associate Director, Strategic Alliances and Global Commercial Development, BD Medical - Pharmaceutical Systems, describes the factors that prompted BD to develop a prefilled microneedle delivery system for intradermal injection, with a particular focus on the collaboration with Sanofi Pasteur which resulted in the successful launch of an influenza vaccine in the BD microneedle device.

OVERVIEW

As a result of public health concerns and fears of pandemic influenza, the flu vaccine market has experienced annual growth of more than 65% between 2008 and 2010. The seasonal influenza vaccine market is expected to exceed US$4 billion (£2.6 billion) by 2015.

Assuring protection from this infectious disease requires not only health system advances, but also new vaccines and appropriate delivery devices to enhance access, uptake, coverage and protection while meeting public health goals.

One new device from BD integrates dose-sparing design and microneedle technology that has the potential to offer positive impact to clinicians, patients and public health. This article describes the development of BD Soluvia™ Microinjection System, a novel microneedle delivery system, and the successful collaboration between Sanofi Pasteur and BD to bring this innovative delivery system to market.

"THIS PREFILLABLE SYRINGE INTEGRATES BD MICRONEEDLE TECHNOLOGY AND PRIMARY PACKAGING, WHICH ARE SPECIFICALLY DESIGNED TO PROVIDE RELIABLE DELIVERY OF DRUGS AND VACCINES INTO THE INTRADERMAL LAYER OF THE SKIN."

THE INTRADERMAL ROUTE – A NEW APPROACH

The dermal layer (dermis) is one of the three primary layers of the skin and is found just below the epidermis (the outermost layer of the skin). The dermis, typically 2-3mm thick, contains a dense network of blood capillaries, which allow for quick drug uptake into the bloodstream and enhanced bioavailability relative to intramuscular and subcutaneous routes.

Furthermore, the lymph flow within the dermis provides open access to the lymphatic system through draining lymph nodes bypassing the metabolic first pass effect of the liver. These attributes may allow for improved speed of drug uptake and pharmacological effect for many drugs, including those used to treat pain, shock, cancer and metabolic conditions, such as diabetes.

Patrick Jeukenne
Associate Director, Strategic Alliances and Global Commercial Development
T: +1 201 847 4017
F: +1 201 847 4847
E: patrick_jeukenne@bd.com

BD Medical - Pharmaceutical Systems
1 Becton Drive
Franklin Lakes
NJ, 07417
United States

www.bd.com/pharmaceuticals

The dermal layer also contains a populated contingent of immunocompetent cells characterised by a powerful capability to induce immune response. This unique characteristic of dermal tissue is a key element for improving immune response after vaccine delivery.

Today, the most common method of intradermal vaccine delivery is the Mantoux technique. This technique uses a 26 gauge or 27 gauge needle inserted into the skin at an angle, with the bevel point upwards. Such techniques have not been widely adopted due to the difficulty associated with intradermal injections using conventional needles and syringes.

BD began the development of microneedles in the late 1990s in order to facilitate intradermal drug delivery and has a long history developing devices specifically for intradermal injection.[1] The result of this work is BD Soluvia™ (see Figure 1).

This prefillable syringe integrates BD microneedle technology and primary packaging, which are specifically designed to provide reliable delivery of drugs and vaccines into the intradermal layer of the skin. BD's proprietary technology assures reliable delivery directly to the dermal layer of the skin regardless of age, gender, ethnicity and body-mass index, as demonstrated in clinical trials.[2]

As compared with the current intradermal injection technique, BD Soluvia™ allows for a clinician to use an injection technique that is perpendicular to the skin, which helps simplify and improve the success of intradermal injections.

BD has published numerous scientific studies and articles on the administration of various drugs using microneedle technology. Examples of drugs delivered in this way include insulin, vaccines, large-molecule biologics and drugs requiring rapid onset of action, such as lidocaine. But, the critical milestone of microneedle prefill technology – and in many ways its scientific and medical validation – was the market launch of the influenza virus vaccine using this innovative intradermal delivery.

"THE CRITICAL MILESTONE OF MICRONEEDLE PREFILL TECHNOLOGY – AND IN MANY WAYS ITS SCIENTIFIC AND MEDICAL VALIDATION – WAS THE MARKET LAUNCH OF THE INFLUENZA VIRUS VACCINE USING THIS INNOVATIVE INTRADERMAL DELIVERY."

Integration of the device with the influenza vaccine involved years of product and scientific development. Much of the success can be attributed in part to organisational commitment by the two companies involved. A seamless collaboration was developed and followed by Sanofi Pasteur and BD, a vaccine company and a device company, respectively.

Figure 1: The BD Soluvia™ Microinjection System, a Novel Microneedle Delivery System.

FORGING A COLLABORATION

Identifying the appropriate partner for bringing innovative products to market is necessary for ensuring successful product development. BD and Sanofi Pasteur embarked on a multi-year collaboration to develop and launch Sanofi Pasteur's flu vaccine, Intanza®, in BD Soluvia™.

The disciplined collaboration between Sanofi Pasteur and BD was a critical factor in the success of this project. The collaboration was headed by a core team formed between both organisations. The team met regularly and defined the work of numerous sub-teams that included functional and subject matter experts from both companies, such as immunology, regulatory and clinical.

BD and Sanofi Pasteur are members of the Association of Strategic Alliance Professionals. In one of their key publications, the association listed the important factors for successful alliances.

- Shared Success: both parties understand why they want to succeed and what the other party will gain. Understanding the other party's motivations has helped us through the development.
- Common vision, philosophy, and understanding but also communication supported by cultural similarities.
- Both partners must develop internal "champions" who are more than project managers. They need to be absolutely committed to the project's success and transmit that commitment to all team members. Close collaboration and communication between champions instills trust between the partners, which is truly tested in hard times.
- Facing "failure factors" constructively. By failure factor we mean market conditions, a shifting economic environment, contract discussions, and the arrival of newcomers to the alliance teams, or even new management.
- Regular benchmarking is a key success factor, both for the achievements themselves and the processes leading to them.

OPERATIONAL, CLINICAL AND REGULATORY INTEGRATION

Industrialisation of such a novel device as Soluvia™ required critical product development advances and the associated investment and resource commitments. For example, delivering a vaccine dose repeatedly at a 90-degree angle required numerous changes and modifications to the tip contour/geometry, and a higher level of needle placement precision.

This was necessary to ensure a precise, reliable and consistent administration into the intradermal route and to do so without leakage.

The small dose volume now being used for vaccination – 0.1 ml versus the standard 0.5 ml used in intramuscular injection – required novel syringe-filling and pumping technologies specifically designed for low volumes and high accuracy. Furthermore, all of these changes and modifications needed to be industrialised in a high speed fashion to meet the high volume “campaign” nature of bringing an influenza vaccine to the market.

Sanofi Pasteur performed extensive clinical studies on its flu vaccine. In parallel, BD independently performed numerous clinical studies, including two pivotal trials for market introduction of the product.

“DELIVERING A VACCINE DOSE REPEATEDLY AT A 90-DEGREE ANGLE REQUIRED NUMEROUS CHANGES AND MODIFICATIONS TO THE TIP CONTOUR/GEOMETRY, AND A HIGHER LEVEL OF NEEDLE PLACEMENT PRECISION.”

The first study, on skin thickness, provided the scientific validity to the idea that intradermal injection at 1.5 mm depth could be effective. BD carried out measurements in four different anatomical locations (waist, thigh, deltoid, and suprascapular) to ensure that injection would deliver vaccine into the dermal layer regardless of the subject’s sex, age, ethnicity or body mass index.

The second study compared the clinical performance of BD Soluvia™ with the age-old Mantoux technique and assessed ease of use in the hands of naïve or untrained practitioners. Confirmation that BD Soluvia™ intradermal micro-injection was safe, reliable, easy to perform, and superior to the Mantoux method set the stage for broader clinical application of intradermal vaccine delivery.

The most significant regulatory challenge was the introduction of a new route of administration for an existing product. Both parties worked closely to overcome these challenges successfully.

CONCLUSION

Bringing innovative products to market to enhance health outcomes is a priority for our industry today. To optimise success, it is important to identify the right technologies, drug products and appropriate partner with a common vision and goals.

REFERENCES:

1. *http://www.me.berkeley.edu/~liepmann/assets/Stoeber.HiltonHead.2002.pdf.*
2. *Laurent A, et al. “Echographic measurement of skin thickness in adults by high frequency ultrasound to assess the appropriate microneedle length for intradermal delivery of vaccines,” Vaccine 2007, Vol 25, pp 6423-6430.*
3. *Laurent, P, et al. “Evaluation of the clinical performance of a new intradermal vaccine, administration technique and associated delivery system,” Vaccine, 2007, Vol 25, pp 8833–8884.*

BD Medical—Pharmaceutical Systems

Help your product reach its full potential

The world is moving to prefills and, to stay competitive, you need to move with it.

Only BD offers the range and depth of expertise and customizable packaging solutions to guide your drug from early phase development through product launch.

BD's approach can also give you an edge. Our knowledge of drug development trends and our progressive initiatives for advancing drug delivery means that you'll have a strategic advantage—both today and tomorrow.

Contact a BD expert today.

Call 800-225-3310 or e-mail BDPS_marketing@bd.com.

BD

Helping all people live healthy lives

BD Medical
Pharmaceutical Systems
1 Becton Drive
Franklin Lakes, NJ 07417
www.bd.com/pharmaceuticals

The Parenteral Drug Association presents...

2012 PDA Europe
Parenteral Packaging

The main Topics of the Conference:

- Container Materials: Glass and/or Polymer
- New Types of Containers and Application Systems
- Container Integrity: Testing for Development and Online in Manufacturing
- Final Container Testing
- Case Studies: From Components, Processes and Product Qualities Training Courses on "Container Closure Development" and "Selection and Utilization of Glass Containers in Pharmaceutical Packaging"

13-15 March 2012

Berlin Marriott Hotel
Berlin | Germany

CONFERENCE 13-14 March | **EXHIBITION** 13-14 March | **TRAINING COURSES** 14-15 March

https://europe.pda.org/ParPack2012

REDUCING QUALITY RISKS TO DRUG PRODUCTS AND MEETING NEEDS OF PATIENTS WITH ENHANCED COMPONENTS FOR PREFILLED SYRINGE SYSTEMS

In this article, Tibor Hlobik, Associate Director, Marketing for PFS Technologies, West Pharmaceutical Services, explores how the use of the right delivery system can be a means of mitigating the risk of parenteral product manufacturing delays and product recalls.

The quality dynamic is a critical element to the successful marketing and commercialisation of drug products. Relevant factors are associated with development time, drug product approvals, manufacturing efficiencies and patient loyalty. Strategies employed in early phases of drug development, which consider delivery devices such as prefilled syringes and their components, can mitigate risk to quality and position the product to meet needs throughout the drug product lifecycle.

The return on investment is realised once a drug product is commercialised and has gained patient and caregiver loyalty. Ease of use, therapeutic benefit and confidence in the drug product help to build patient loyalty. A patient or caregiver will recognise the availability of needed medicines, accurate dosing, administration options, and increased safety and efficacy. The drug product manufacturer faces multiple challenges to meet these needs and can benefit from early investment in the right drug delivery system.

Numerous drug product shortages due to recalls and manufacturing delays have included small molecules, therapeutic proteins and monoclonal antibodies. Sterile injectables account for the majority of shortages and have been related to product quality and significant cGMP issues – particulates, contamination, impurities and capacity, for example,[1] which can jeopardise brand loyalty and market share.

Not fully understanding risks associated with manufacturing sterile drug products can potentially lead to delays. Delivery systems play a major role in manufacturing drug products, and appropriately selected components can mitigate risks to quality.

ADDED VALUE OF DRUG DELIVERY WITH PREFILLABLE SYRINGE SYSTEMS

Prefillable syringe systems have advantages for use in the vaccine and biopharmaceutical industry. Market trends are towarda home use and patient-administered delivery for drugs used to treat chronic conditions, such as multiple sclerosis and rheumatoid arthritis.

Prefillable syringe systems offer convenient fixed dosing and are adaptable to automatic injection devices that may enhance drug product delivery. The use of high-quality components in prefilled syringe systems will facilitate efficient manufacturing processes and support a reliable supply of drug products. The components and materials of construction for prefillable syringe systems can impact the drug product quality, and there are multiple options and combinations of components to be assessed for the intended use.

Development studies indicate suitability of component materials with preparation and sterilisation techniques, and compatibility with manufacture and fill/finish equipment. The combined quality attributes and performance characteristics of the plunger, barrel, needle shields or tip caps are necessary for effective administration of medicines to the patient.

Mr Tibor Hlobik
Associate Director, Marketing for PFS Technologies
T: +1 610 594 3126
E: Tibor.Hlobik@westpharma.com

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

www.westpharma.com

COMPONENT ATTRIBUTES

Plungers for prefilled syringe systems are typically made from butyl rubber and can be coated with a fluoropolymer film that can increase lubricity and serve as a barrier between the drug and the elastomer, reducing the potential for extractactables inherent in all materials.

Chemicals migrating from the elastomers into the drug product are known as leachables, but the reverse process of the drug product adsorbing or absorbing onto the plunger can also occur. Other concerns related to chemical migration include interaction products and degradation products, both of which have the potential to cause safety concerns for a patient.

To answer demands for improved manufacturing processes, the pharmaceutical industry has moved toward ready-to-use (RU) plungers for prefillable syringe systems. These components are washed and sterilised prior to delivery to the drug manufacturer with specifications for particulate and endotoxin, thereby reducing the risk of introducing microbiological contamination to the drug product during final packaging.

The risk of product rejects can be mitigated through the use of RU components, which are processed in sterile conditions. Methods for sterilisation of plungers should be assessed to understand potential impact on chemical and physical characteristics of the components. Studies have shown that an increase in extractable breakdown products has been observed under high levels of gamma radiation when compared to autoclave steam sterilisation.[2]

Component defects can occur throughout the manufacturing process. Defects can be recognised and eliminated through use of an automated vision inspection system based on customised libraries and verified to ensure product is acceptable prior to shipping. An example of this is West's technically advanced Envision™ vision verification system, which leads to increased efficiency in the drug fill/finish operation.

Glass prefillable syringe barrels sealed by Tyvek® medical packaging in a nested tub, with an elastomer needle shield or tip cap, are also offered in a ready-to-use format and sterilised with Ethylene Oxide (EtO). Needle shields and tip caps are most commonly manufactured with isoprene rubber (suitable for EtO penetration), and the selected elastomer formulation must be free from natural rubber and latex to eliminate patient risk for latex protein-related allergies. Innovative and clean elastomer formulations with a low extractable profile and manufactured with 100% synthetic isoprene are recommended for NDAs to ensure high quality for the patient.

Figure 1: When used in conjunction with an auto-injector such as West's ConfiDose auto-injector system, molded plastic syringes like the Daikyo Crystal Zenith 1 mL insert needle syringe can reduce variability through consistent and tight dimensional tolerances.

MATERIALS TO ENHANCE SYSTEM PERFORMANCE

Glass prefilled syringe barrels still dominate the market despite several limitations, including quality and performance issues that may directly affect patients and caregivers. Switching from a glass to a cyclic olefin polymer molded prefillable syringe can reduce variability and breakage issues associated with glass, as well as reduce the need for silicone oil, another potential source of drug product contamination.

With the development of novel materials, including cyclic olefin polymers such as the Daikyo Crystal Zenith® polymer, manufacturers can now select a high-quality, transparent, break-resistant material that is more inert than glass, is scratch resistant and can reduce potential for particulate contamination from the syringe barrel.

These components also can be stored and shipped at low temperature, which is a common requirement of many biologics. With a prefilled syringe system using a Daikyo Crystal Zenith syringe barrel and plunger coated with a fluoropolymer film such as FLUROTEC® barrier film, superior and consistent break-loose and extrusion forces can be achieved without the use of silicone oil as a lubricant. The film is molded to the surface of the plunger and provides a barrier against constituents from the elastomer leaching into the drug product. Another benefit of a silicone-oil-free system is the reduced risk of silicone-induced protein aggregation.

In addition, since a Daikyo Crystal Zenith barrel is manufactured using injection molding technology, the dimensional tolerances are very tight, which helps to assure consistent functionality (for example, break-loose and extrusion) and minimise the risk of incompatibility with secondary devices such as auto-injectors.

Cyclic olefin syringe systems, which have been used in the market for many years in Japan, Europe and the US, continue to gain strong acceptance from pharmaceutical and biotech drug makers. Daikyo Crystal Zenith cyclic olefin polymer syringes offer a clear advantage over traditional glass syringes through:

- **Durability:** Daikyo Crystal Zenith polymer offers high break-resistance and consistent break-loose and glide force, as well as excellent low-temperature characteristics.
- **Low Risk of Reactivity:** The Daikyo Crystal Zenith polymer is silicone-free and offers low exposure to extractables and leachables as well as low particulate levels, minimum levels of adsorption and absorption, and improved drainability
- **Visibility:** Daikyo Crystal Zenith polymer has high transparency.

OVERCOMING VARIABILITY IN GLASS SYRINGES

As the industry trends toward the use of prefillable syringe systems, which are often used in devices or delivery systems to aid with the increased need for injection in the home setting, Daikyo Crystal Zenith polymer is an ideal solution. Because of flexibility in molding, this polymer can be used in a variety of drug delivery systems including auto-injectors and custom cartridges.

When comparing glass with plastic syringe barrels, the limitations are easy to distinguish. Glass is a formed product. To create the component, the glass is heated and mandrels are used to form the overall syringe length, nose

or tip, and flange. These actions create dimensional variability.

When the syringe is used manually, such variability is overcome by the human user, but with delivery devices such as auto-injectors, the device itself must overcome the variability. Since the device cannot judge the pressure required to do so, failures – including incomplete injections or incorrect needle depth upon injection – may occur. In contrast, a plastic component is molded. This process creates dimensional tolerances that are very consistent and much tighter than in a glass product.

For example, the West ConfiDose® disposable auto-injector system (Figure 1) has been designed to overcome much of the inherent variability with a variety of glass syringes, including dimensional variability and variable lubrication. Novel design of the force mechanisms and location on the front-end of the syringe allow higher forces to be used, enabling consistent delivery of drugs, even those with higher viscosities, a consistency that is common for biopharmaceutical drugs.

IMPACT OF SILICONE OIL ON DELIVERY

Silicone oil is currently used on the inside of glass barrels to provide lubricity. During the manufacturing process, the silicone may be applied unevenly, particularly toward the bottom of the syringe, which is less accessible to the siliconisation process. Over time, the silicone may become uneven. Such issues can create higher break-loose-force or glide-force variability, particularly at the end stroke of the piston, resulting in an incomplete injection in a delivery device such as an auto-injector.

In extreme cases, the syringe may "stall" before the end of the stroke, and the full drug dose may not be delivered to the patient. Such patient reports or findings may prompt drug product recalls.

BIOLOGIC DRUGS AND OVERFILL

Because biologics are often expensive, manufacturers are seeking new ways to minimise waste. Prefillable syringes, with their premeasured doses, have the advantage of reducing dosing errors and potentially saving manufacturers money. Unlike single- or multi-dose vials that may be overfilled by as much as 20% to ensure adequate withdrawal, a prefillable syringe can virtually eliminate the need for excess overfill, thus conserving expensive drug product. This is important where manufacturing and product costs are high, bulk manufacturing capacity is limited, or where a critical vaccine is needed for patient care.

Additionally, there is some degree of variability when removing drug product from a vial with a conventional disposable needle and syringe. With a prefillable syringe system, the very nature of its design removes the withdrawal step and delivers drug product directly to the patient, which results in a more accurate dose of the drug with less exposure to needles.

MITIGATING RISK FOR PROTEIN AGGREGATION

Many biotech drugs are highly sensitive to both silicone and tungsten. As mentioned previously, silicone is used to add lubricity to the syringe barrel in glass syringes. Tungsten

Figure 2: With the development of novel materials, including cyclic olefin polymers such as Daikyo Crystal Zenith® polymer, manufacturers can now offer high-quality, transparent, break-resistant material that is more inert than glass.

originates from the tungsten pin used in the glass barrel forming process. Should tungsten contaminate a protein product, aggregation can occur, resulting in rejected product. Also, glues and adhesives are used to hold the needle in place once it has been staked into the syringe. These potential sources of leachables and particulates can contribute to the rejection of contaminated drug product. The use of Daikyo Crystal Zenith syringe barrels can minimise exposure to potential leachables, protecting the drug product and enabling a reliable drug product supply.

In a true benefit over the glass prefilled syringes, a Daikyo Crystal Zenith barrel can be molded around a needle, eliminating the need for tungsten pins, glues and adhesives. This in turn minimises the exposure to leachables and offers manufacturers an option to provide additional protection for the drug product.

CONCLUSION

The prefillable global syringe market is expanding rapidly, and drug manufacturers are facing increasing pressures as new generations of biopharmaceutical drugs enter the market. Cyclic olefin products such as the Daikyo Crystal Zenith polymer offer an attractive alternative to glass which, while being the industry standard for many years, has limitations in precision of dose delivery and poses contamination and other risks for biopharmaceuticals.

Cyclic olefin prefillable syringe solutions minimise drug product waste that can occur due to excessive vial overfills or loss due to breakage, and provide for silicone-free systems that reduce the risk of protein aggregation. Together with fluoropolymer film-coated plungers in a ready-to-use (sterile) format, cyclic olefin prefillable components present benefits that are gaining attention from manufacturers who seek new answers to efficiency, drug delivery and administration challenges.

Characteristics for successful drug marketing include a wide range of attributes with the patient in mind, such as ease of administration, protection of the drug product, safety of components, and manufacturing with appropriate measures of quality and control.

Drug shortages are among the issues highlighted through the US FDA's transparency initiative to communicate among the FDA, drug manufacturers, health professionals and the public, in helping to reduce the impact such shortages have on public health.[3] Choosing delivery systems that will mitigate risks to drug product quality will enable needed medicines to be delivered to patients, thus reinforcing a reputation for providing safe and effective drug products.

REFERENCES:

1. *http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM273360.pdf*
2. *Goodfield C, Polini E, Miller A & Curry W, "An Evaluation Of The Impact Of Sterilisation Processes On Elastomeric Container Closure Components Used To Store And Administer Parenteral Drug Products" West Pharmaceutical Services, 2011.*
3. *http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm*

West
Delivering Innovative Solutions

West PFS Solutions.
True to Our Core.™

So you can rest easy.

Visit us at Pharmapack Paris,
February 15-16, 2012
Booth #560

West's Prefillable Syringe System Technology

You need prefillable syringe systems and components designed to compete in a rapidly evolving industry.

You need the management, expertise and support of a manufacturer capable of creating solutions that will mitigate risk and differentiate your product in a crowded market.

You need West.

Pharmaceutical and biopharmaceutical customers trust West to provide answers to their prefillable syringe challenges. West's expertise allows you to bring products to the market safely, reliably and with the integrity you've come to expect from West. Our global technical expertise and services provide prefillable solutions that are true to our core goal of reducing regulatory risk while ensuring high quality and patient safety.

Contact West today.
North America +1 800-345-9800
Europe +49 2403 7960
Asia Pacific +65 6860 5879
www.westpharma.com
www.WestPFSsolutions.com

Get the free mobile app at:
http://gettag.mobi

#6709

COMPANY PROFILE – TERUMO

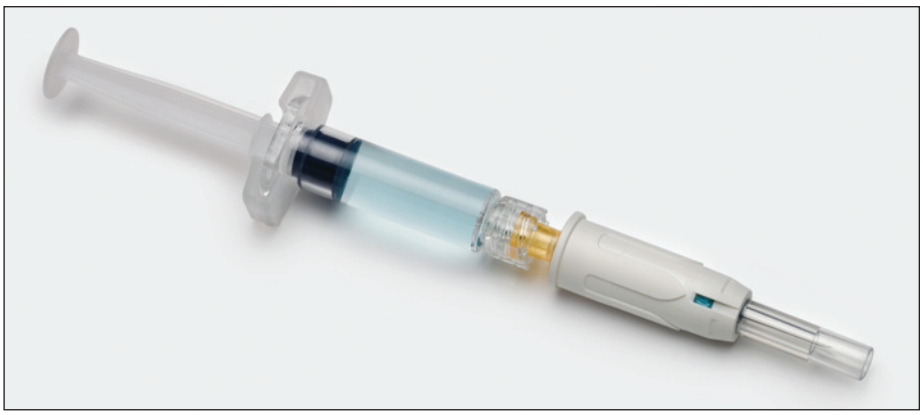
TERUMO®

In August 2011, Forbes Magazine ranked Terumo Corporation 14th of the top 100 global companies on its "World's Most Innovative Companies" list. According to Forbes, the rankings were based on findings from an eight-year study led by a team of independent industry researchers who assessed each company's "innovation premium," a measure of investor expectation for future innovation such as new product development, services and market development.

Terumo is a globally operating medical technology company of Japanese origin. Since its founding in Tokyo in 1921, Terumo Corporation has based its business activities on a corporate philosophy of "Contributing to Society through Healthcare". The company pursues global business development designed to improve the quality of healthcare for people all around the world.

Over the past 90 years Terumo has continuously broadened its business scope by promoting the increased use of disposable products which has led to safer medical treatment by developing medical systems and equipment to comprehensively support advanced medical treatment.

Our advantage is combining product development capabilities for medical devices with pharmaceuticals, medical supplies and systems. Hence, we can continue to develop products that meet new market needs.



K-Pack Surshield™ is an innovative hypodermic needle with an integrated passive sharps protection feature for use with (pre)-filled syringes.

With decades of expertise and core competences in parenteral drug delivery and injection technology, Terumo strives continuously to research and develop advanced, innovative devices (see examples as illustrated). This is underpinned by our relentless pursuit of biocompatibility and elemental technologies centred on materials technology driven by each product's distinct characteristics and technological aptitude in production capabilities.

Dedicated to the pharmaceutical and biotechnology industry, Terumo Global Pharmaceutical Solutions (GPS) offers unique solutions in medical technology. In addition to our valued products, our specialised team also provides customised and dedicated solutions designed to meet the specific needs of the pharmaceutical industry.

Global Pharmaceutical Solutions
Terumo Europe N.V.
Interleuvenlaan 40, 3001 Leuven
Belgium

T: +32 16 38 15 00
F: +32 16 38 16 04
E: gps.info@terumo-europe.com

www.terumo-europe.com/pharmaceutical

www.terumo.com

With over 12 years' experience in manufacturing plastic prefilled syringes, TERUMO introduces PLAJEX™ ready-to-fill plastic prefilled syringe systems.

K-Pack® II hypodermic needle is individually packed and geometry allows for automated handling manipulations during packaging.

Email: gps.info@terumo-europe.com – Phone: +32 16 38 15 00 – www.terumo-europe.com/pharmaceutical/

Next generation of sharps protection technology

- *Truly passive system*
- *Sharps never exposed*
- *Easy to use*
- *Compact, individually packed*
- *Suited for automated manipulations*
- *Terumo's high quality needle*

GPS17GB-0811FKII1(12.11)E

Pharmapack Paris
15 – 16 February 2012
Booth N° 454

K-Pack Surshield™

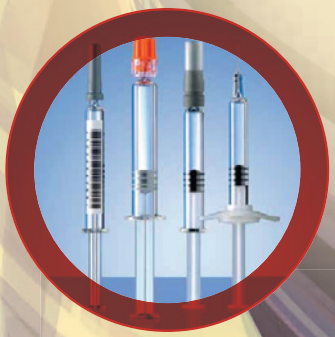
Hypodermic needle with integrated passive sharps protection

TERUMO®

PDA
Parenteral Drug Association

Save The Date and Join PDA for

The Universe of Pre-filled Syringes and Injection Devices



October 15-17, 2012

Red Rock Resort | Las Vegas, Nevada

www.pda.org/prefilled2012

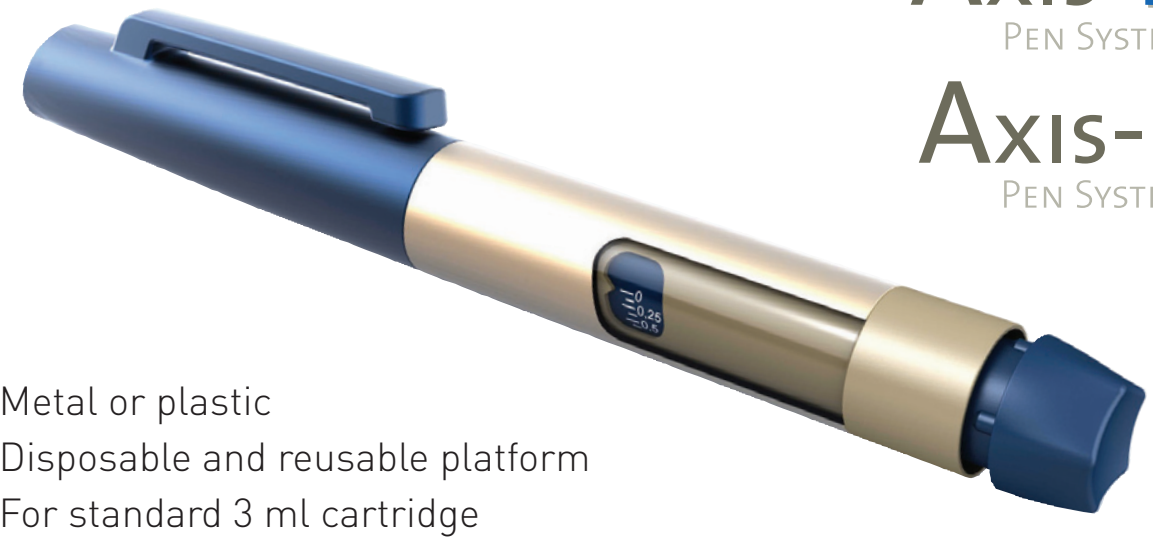
HASELMEIER

We Deliver Solutions

Introducing the new Axis Pen System

Axis-D
Pen System

Axis-R
Pen System



- Metal or plastic
- Disposable and reusable platform
- For standard 3 ml cartridge
- Dose increments customizable to your needs
- Distinctive dose indication
- Easy to use with no or minimal priming

7.13.1.1-01

**FOR MORE INFORMATION,
PLEASE CONTACT US OR VISIT US AT
WWW.HASELMEIER.COM**

Haselmeier USA 517 Benfield Road, Suite 301 - Severna Park, MD 21146 - USA
Contact: Robert J. Kilgore - r.kilgore@haselmeier.com - T +1 (410) 647-7300

Haselmeier GmbH Dufourstr. 32 - 8008 Zürich - Switzerland
Contact: Volker Wirth - v.wirth@haselmeier.com - T +41 (0)44 250 52 41

Nuova Ompi
glass division

RECOMMENDATIONS ON DELAMINATION RISK MITIGATION & PREDICTION FOR TYPE I PHARMACEUTICAL CONTAINERS MADE OF TUBING GLASS

Here, Boris Schmid, Corporate QA Director, and Daniele Zuccato, R&D Project Manager, both of Stevanato Group, describe studies conducted to investigate delamination of Type I glass containers, and outline the company's resulting recommendations for mitigating and predicting the risk of delamination.

The delamination of glass when it is exposed to certain environments, is a very well-known phenomenon. For instance, the occurrence of flakes in soda-lime glass bottles intended to get into contact with food and beverages is documented since the early 1940s. In that case, storage of the empty bottles under uncontrolled conditions of humidity and temperature were found to be a key factor.[1,2]

The most recent cases of product recall due to the presence of particles in the filling liquid,[3] have involved Type I glass containers carrying formulations of active pharmaceutical components with known ability to corrode glass and to dissolve the silica matrix. As this action is strongly affected by time and temperature, flaking may become visible only after a long incubation during storage and requires systematic monitoring to be detected at an early stage.

Reducing the risk of delamination is therefore a serious problem as one has to consider and keep under control all the production stages, including the optimisation of the conversion process, the choice of the most appropriate glass type as a function of the chemistry between glass and the parenteral solution, the filling operations and the shelf life conditions of the product. Therefore the industry is challenged together with the pharmaceutical companies to investigate in order to limit the risk for the patients. (Author's note: it is also true that not all particles observed in vials were identified as a result of glass delamination.)

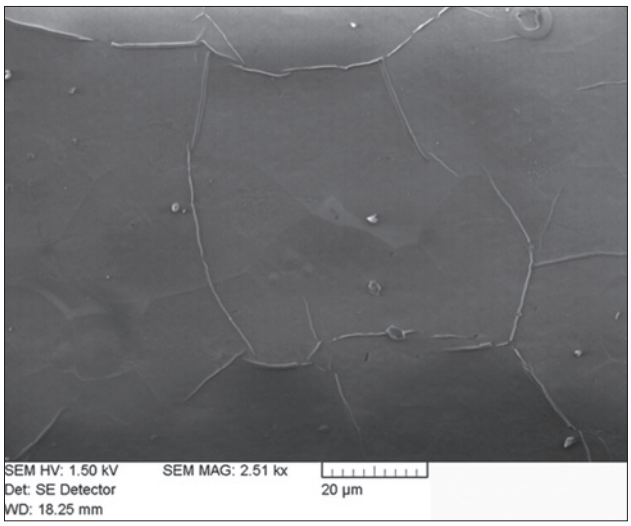


Figure 1: SEM Image Showing Evidence of Flakes Detachment on Glass Surface after Accelerated Ageing Test Using 0.9% KCl as Extraction Solution.

Many open questions require a precise answer. For example: How can we predict delamination? Are European Pharmacopoeia (EP) titration values a reli-

Boris Schmid
Corporate QA Director
Stevanato Group
T: +39 049 9318111
F: +39 0499366151
E: boris.schmid@stevanatogroup.com

Daniele Zuccato
R&D Department
Nuova Ompi, Stevanato Group
T: +39 049 9318111
F: +39 0499366151
E: daniele.zuccato @stevanatogroup.com

Nuova Ompi, Stevanato Group
Via Molinella, 17
35017 Piombino Dese (PD)
Italy

www.stevanatogroup.com

able indicator of delamination resistance? Which glass types are more suitable for which preparations? What can we do along the supply chain in order to mitigate delamination risk?

To answer these questions and to understand in detail the delamination phenomenon, one year ago Stevanato Group started a study of a stepwise approach in collaboration with external institutional laboratories. The aim of the study was to highlight the influence of key parameters like the tubing glass raw material, conversion process and filling conditions.

As a first step, we investigated the raw material in order to reduce risk for delamination. The interaction between several glass types in contact with different extractants, including slightly alkaline preparations, was studied. Investigations were carried out to establish whether there was a correlation between EP titration values and evidence of delamination, as surface alkalinity of the finished products, based on ISO or EP testing for instance, is often used to characterise the influence by the conversion process.

Several Types of borosilicate tubing glass, both sulfur treated and untreated, were tested in contact with different extraction media for repeated autoclave cycles of 1h at 121°C. The propensity for delamination was observed by measuring the SiO_2 concentration in the extraction solutions using Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES). The altered surface was evaluated by a colorimetric method and SEM micrographs, while the presence of particles was monitored by optically assisted visual inspection.

Based on these studies, including an extensive design of experiments, we published [4] some recommendations to mitigate the risk for glass delamination focusing on raw materials and sulfur treatment in combination with buffer solutions (see Box 1: "Recommendations on Delamination Risk Mitigation").

We also highlighted that evaluating EP values without considering the influence of the nature and the treatments of the glass as raw material, may be misleading. It is well known in fact, that low expansion borosilicate glass (expansion 33) or sulfur treatments will lead to a lower surface alkalinity [5,6] but low ISO and EP values are not always a guarantee against the risk of delamination, for instance when the filling liquid is an alkaline solution [7] and/or a corrosive organic acid like citric acid.[8]

As a second step, we wanted to develop a test protocol which could be useful for delamination prediction. The protocol was tested on empty containers directly after conversion as well as on filled containers after a prolonged storage time. The results were compared with data from similar tests made on delaminated filled containers.

Figure 2: Result of Colouring Agent Test Showing Strong Colouration of Altered Glass Surface After Accelerated Ageing Test Using 0.9% KCl as Extraction Solution.

The conclusions developed by this study [13] are useful to provide both to pharmaceutical manufacturers and glass converters with information needed to help prevent glass delamination and give some indication about the delamination resistance of glass containers. The colorimetric test is a powerful method which can be used immediately after production in order to put in evidence a properly controlled thermal process or an early alteration of the inner glass surface. In combination with further accelerated ageing test, Stevanato Group has an effective tool to control the delamination characteristic of the empty container before filling (see Box 2 on page 42: "Recommendations on Delamination Prediction").

As a third step, we applied the abovementioned protocol to containers obtained in the Stevanato Group conversion lines after a careful controlled modification of the conversion parameters. It is well known that forming the container with a tightly controlled process has an overall positive impact on the delamination characteristic as it creates less thermal stress that could lead to the formation of enriched silica layers.

The flame settings on finish and bottom forming, machine speed and annealing conditions were identified as the most critical parameters. For each of these parameters, we purposely created a stressing environment for

BOX 1: RECOMMENDATIONS ON DELAMINATION RISK MITIGATION NOTE 2

Delamination prevention requires a proper selection of the glass tubing raw material combined with a thermally controlled converting process.[Note 1] Exhaustive information about the intended use of the container is essential. With these conditions in mind, the following recommendations can be given: [Note 2]

For low pH formulated drugs (pH <7.0), aqueous neutral solutions

Any kind of Type I glass container can be used. We would recommend that the glass containers shall meet Pharmacopoeia specifications before any specified sulphur treatment is applied. Furthermore the sulphur treatment, if required by the client, should be designed so as to guarantee that the modified surface layer is reduced to the minimum necessary thickness.

For high pH formulated drugs (pH >8.0)

In-house testing of high silica borosilicate (expansion 33) and sulphur treated vials in contact with alkaline extraction solutions, showed a steep increase of undissolved silica particles.[9] We recommend the use of untreated normal borosilicate glass [Note 1] (expansion 51) and possibly reduction of the exposure time.

For drug buffered with silica complexing agents (e.g. organic acids like citrate, tartrate, glutarate, EDTA etc)[8,10]

As these acids are known to behave as strongly alkaline solutions, we recommend to use untreated normal borosilicate glass [Note 1] (expansion 51) and to possibly reduce the exposure time. Heat treatments and final sterilisation are additional risk factors.

For drug buffers with a high ionic strength (high NaCl or KCl content) [11,12]

We recommend the use of untreated normal borosilicate glass [Note 1] (expansion 51). The use of sulphur treated vials is to be restricted to preparations with pH around 7 or lower.

BOX 2: RECOMMENDATIONS ON DELAMINATION PREDICTION NOTE 2

Stevanato Group recommends using following tests in order to analyse and predict delamination resistance for empty and previously filled containers: Note 2

EP titration values can be used as indicators of the chemical durability of the glass against neutral aqueous solutions only. When containers are in contact with alkaline solutions and similarly aggressive media, the glass performance is better represented by the **concentration of the extracted silica**.

Coloring agent test and SEM are useful tools for obtaining information on the inner surface characteristics and morphology of the vials. This analysis could be performed both on the as received vials, and on the vials after accelerated ageing treatment (see Figures 1 and 2 on previous pages).

Measurement of an increase in silica concentrations indicates glass corrosion and an increasing risk for further delamination. An exception is sulphur treated glass, where delamination can occur even at low SiO_2 concentration.

Extractions with 0.9% KCl solution can be used as an accelerated test to highlight the propensity of a glass to delaminate. (Note that this can never be taken as a guarantee that the glass shall not delaminate when it is exposed to the pharmaceutical drug, whose extraction ability requires to be studied case by case.)

the glass surface during conversion process. The inner surface of the containers produced was analysed immediately after production with the combined test protocol consisting of colorimetric test, SiO_2 concentration in the extraction solution, and SEM method.

The result confirmed the significant influence of the critical process parameters mentioned on the delamination characteristics of the inner glass surface. Therefore it is important using appropriate burner- and forming technology and to keep machine speed, flame positions and energy constant during forming, and to control the annealing conditions.

Stevanato Group has a long tradition and large experience in producing glass on vertical indexed machines, of our proprietary design and production, using the appropriate technology. As a consequence, the containers have potentially a lower risk for future delamination.

Ageing tests under real conditions, involving both glass converter and pharmaceutical manufacturer, should be conducted in order to proof the delamination resistance of the containers where required.

NOTES:

1. *Glass containers from a controlled thermal forming process, such as the Ompi process.*
2. *As the recommendations are based on a specific testing design by Stevanato Group in collaboration with an external laboratory, they are not covering all possible parameters and shelf life conditions which can be met by any filled product. Therefore it is necessary to evaluate and to approve each application based on real ageing and stability tests established by the customer.*

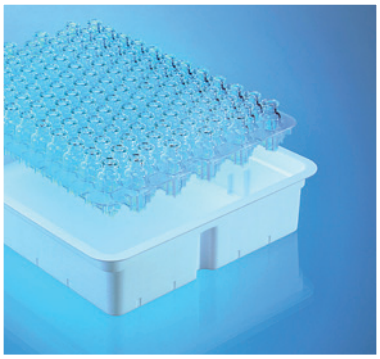
REFERENCES:

1. *Bacon F & Burch O, "Effect of time and temperature on accelerated chemical durability tests made on commercial glass bottles." J of Am Ceramic Soc, 1940, 23(1), pp 1-9.*
2. *Guadagnino E, Geotti-Bianchini F, Workshop, "Alteration of glass containers during storage." Stazione Sperimentale del Vetro, Murano-Venezia, Italy, June 11, 2004.*
3. *"Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs." US FDA Advisory, March 25, 2011.*
4. *Schmid B & Guadagnino E, "Glass Delamination: Facts – Prevention – Recommendations." Stevanato Group Market Update, Newsletter, Italy 2011.*
5. *Geotti-Bianchini F, Guadagnino E, Verità M, Pantano C, Paulson T, Hamilton J, "Surface reactions of Type II sulfur treated glass containers during autoclave testing in water." Proc XVIII International Congress on Glass (ICG XVIII), San Francisco, CA, US, July 5-10, 1998, pp6.*
6. *Harris N, "Effects de traitment de desalcalinisation on la reactivitè hydrolytique d'un verre sodo-calcique." Riv. SSV, No 5, 1984, pp 91-97.*
7. *Clark D, Pantano C & Hench L, "Corrosion of Glass." Books for Industry, New York, 1979. Bacon F & Raggon F, "Promotion of attack on glass and silica by citrate and other anions in neutral solutions." J Am Ceram Soc, 1959, 92(4), pp 199-205.*
8. *Borchert S et al, "Accelerated extractable studies of borosilicate glass containers." J Parenteral Sci Tech, 1989, 43(2), pp 67-79.*
9. *Paul A, "Influence of complexing agents and nature of buffer solutions on the chemical durability of glass." Part I, Glass Technol, 1978, 19, pp 162-165.*
10. *Scholze H, "Bedeutung ausgelaugten Schicht fuer die chemische Bestaendigkeit: Untersuchung an einer Kalk-Natronglass." Glastech Ber, 1985, 58(5), pp 116-124.*
11. *Biavati A, "Correlation between hydrolytic ion release and pH changes in Type II glass containers." Pharm Ind 1997, 59(2), pp 175-178.*
12. *Guadagnino E, Zuccato D, "Delamination propensity of pharmaceutical glass containers by accelerated testing with different extraction media." PDA Letter, July/August 2011.*

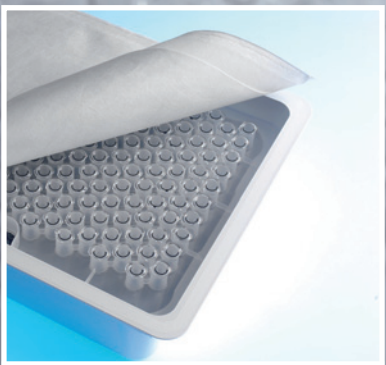
EZ-fill™
Ready to fill
The EZ Way

www.ez-fill.com

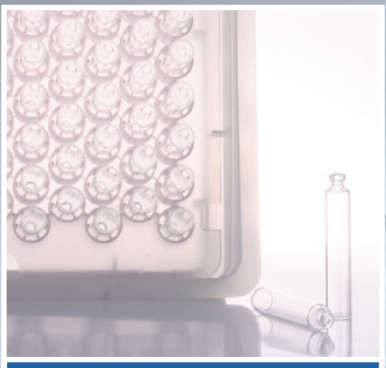
EZ-fill syringes, vials and cartridges is the scalable cGMP industrial solution which combines expert glass production and container processing in flexible "ready to be filled" packaging.



EZ-fill vials



EZ-fill syringes



EZ-fill cartridges

Nuova Ompi
glass division
Stevanato Group

www.stevanatogroup.com
nuovaompi@stevanatogroup.com

YDS YpsoMate®

Go for simplicity.

The 2-step autoinjector

- Push-on-skin release for most simple and ergonomic handling
- Clear confirmation “clicks” and large viewing window for optimal patient confidence and control
- Slim, short and pleasing design provides distinct differentiation for your drug

Visit us at Pharmapack in Paris, booth 253

For more information visit **www.ypsomed.com/yds**

More confidence. More success. With Ypsomed Delivery Systems.

YPSOMED SELFCARE SOLUTIONS