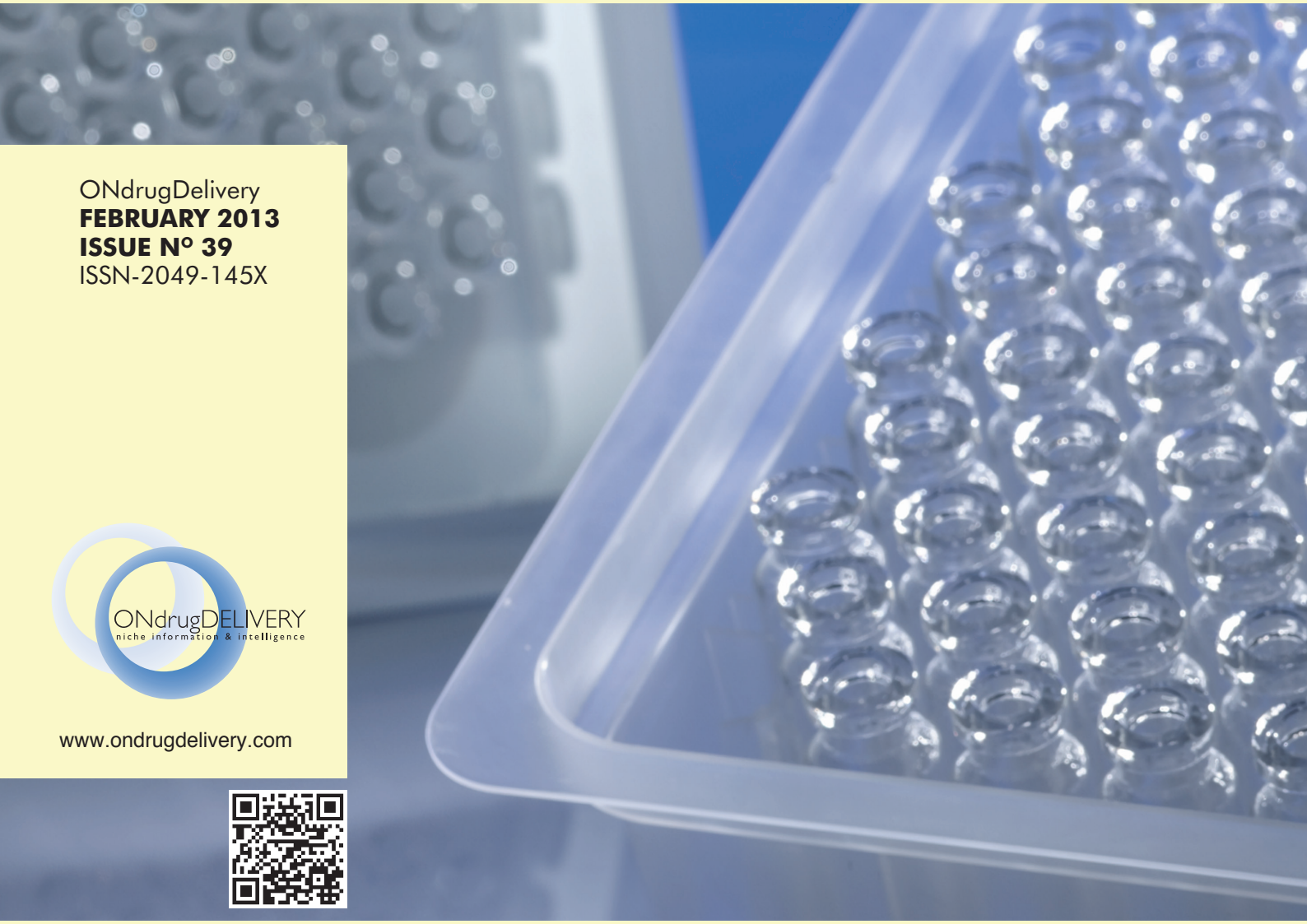
PREFILLED SYRINGES:

IN THE OPERATING ROOM & THE HOME, FROM EMERGENCY MEDICATIONS TO LONG-TERM BIOTHERAPEUTICS



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"Prefilled Syringes: In the Operating Room & the Home, from Emergency Medications to Long-Term Biotherapeutics"

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.

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Mar	Transdermal Delivery, Microneedles & Needle-Free Injection
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Formulations Focus
Jun	Injectable Drug Delivery: Devices Focus
Jul	Oral Drug Delivery
Sep	CROs & CMOs Offering Drug Delivery Solutions
Oct:	Prefilled Syringes
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Front cover image "Ompi EZ-fill™ vials - available and validated, from clinical trials to large scale" (see this issue, page 19). Image provided by Nuova Ompi. Reproduced with kind permission.

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US FDA ISSUES FINAL RULE FOR COMBINATION PRODUCT QUALITY SYSTEMS

On January 22, 2013, the US FDA published the long-anticipated Final Rule: "*Current Good Manufacturing Practice Requirements for Combination Products*", with the purpose of clarifying regulatory requirements for quality systems used to design, develop and manufacture combination products and to help ensure consistent and appropriate application and enforcement of these requirements. In this article, Michael Gross, PhD, RAC, Principal Consultant, Chimera Consulting North America, focuses on how the Final Rule effects the development and manufacture of drug delivery systems, such as prefilled syringes and auto-injectors.

The US FDA Final Rule: "*Current Good Manufacturing Practice Requirements for Combination Products*", codified as 21CFR4,[1] is largely unchanged from its initial publication as a Proposed Rule on September 23, 2009.[2] It applies to marketed combination products and many products in development.

Manufacturers of combination products have 180 days to comply with the Final Rule.

"THE FINAL RULE DOES NOT CREATE NEW REQUIREMENTS, NOR DOES IT MODIFY EXISTING PREDICATE RULE REQUIREMENTS; RATHER IT CLARIFIES HOW TO APPLY THESE REQUIREMENTS TO COMBINATION PRODUCTS"

FDA intends to apply a risk-based approach to combination product facility inspections and has stated that it will offer manufacturers a reasonable opportunity to correct quality system deficiencies before taking compliance or enforcement actions.

THE FINAL RULE

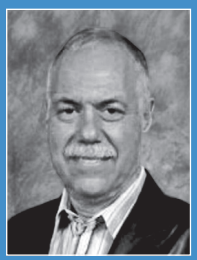
The Final Rule states that Current Good Manufacturing Practice regulations for drugs and biological products (21CFR210 and 211) apply to combination products that include a drug or biologic constituent part. Current Good Manufacturing Practice regulations for medical devices or the Quality System Regulation (QSR, 21CFR820) apply to combination products that include a device constituent part. Additional regulatory requirements and standards apply if certain biological products described in

21CFR 600-680 are incorporated as a constituent part into a combination product. And, Current Good Tissue Practice requirements, including donor eligibility requirements, for human and cellular and tissue-based products (HCT/Ps) described in 21CFR1271 apply to combination products that incorporate an HCT/P.

With respect to manufacturing components, device manufacturing components are not subject to Final Rule but drug manufacturing components are. Prefilled drug delivery systems, including prefilled syringes, are combination products subject to the Final Rule.

Compliance with combination product quality system regulations must be achieved by utilising a quality system that is demonstrated to comply with Predicate Rules (for example, drug-cGMP and device-QSR regulations) applicable to each constituent part of a combination product. Two options exist for demonstrating compliance with applicable regulatory requirements: demonstration of compliance with the specifics of all quality system regulations applicable to each constituent part or, under certain conditions, demonstrating compliance with the specifics of either the drug-cGMP or device-QSR regulations, rather than both. Under the later circumstance, to demonstrate full compliance with both regulations, a manufacturer that chooses to base its quality system on a cGMP-platform is required, as applicable, additionally to demonstrate compliance with specified provisions of the QSR, thus creating a streamlined (i.e. hybrid) quality system. These specified provisions are:

- Management Responsibility (21CFR820.20)
- Design controls (21CFR820.30)
- Purchasing controls (21CFR820.50)
- Corrective and preventive action (21CFR820.100)
- Installation (21CFR820.170)
- Servicing (21CFR820.200)



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Additionally, for combination products that incorporate certain types of biological products, compliance with the requirements of 21CFR 600-680 must also be demonstrated. For a combination product that incorporates human cells or tissues (i.e. HCT/Ps) compliance with the requirements of 21CFR1271 must be demonstrated.

When two or more types of constituent parts to be included in a single-entity or co-packaged combination product are held at the same facility, or when the manufacture of a combination product proceeds at the same facility while utilising these constituent parts, compliance with all applicable quality system regulations must be demonstrated.

DISCUSSION

The Final Rule does not create new requirements, nor does it modify existing Predicate Rule requirements; rather it clarifies how to apply these requirements to combination products. Entities that engage in only certain regulated manufacturing operations are subject only to those portions of Predicate Rules that apply to those operations.

The Final Rule preamble states that certain container closure systems which also serve as drug delivery devices (such as a prefilled syringes, for example) may be considered as drug manufacturing components. Yet they are still in fact constituent parts of combination products and are thus subject to the Final Rule. Therefore, if a facility is manufacturing a finished prefilled syringe from drug and device components, the facility must comply with both QSR and cGMP regulations.

The preamble also addresses "convenience kits", which are combination products that only include two or more types of medical products which are legally and independently marketed and subsequently co-packaged for independent marketing with the same labelling as that used for independent marketing. Generally no additional cGMP requirements apply to these kits, except for those requirements applicable to the assembly, packaging, labelling, sterilisation, or further processing of the kit itself.

However, if any of the products included in a kit are repackaged, relabelled or otherwise modified for the purpose of their inclusion in the kit, the kit is no longer considered to be a convenience kit. Under these circumstances all of the quality system requirements which are applicable under the Final Rule apply.

The preamble discusses how combination product manufacturers are required to demonstrate compliance with the Predicate Rules as they apply to a particular combination product. Demonstrating compliance includes establishing and maintaining written procedures and records that document and verify the utilisation of applicable quality system requirements described in the respective Predicate Rules.

Under cGMP Requirements for Combination Products, each of the constituent parts of a combination product when manufactured and marketed separately, are subject only to the individually applicable predicate quality system regulations pertaining to that type of constituent part. The constituent parts of a single-entity and co-packaged combination product retain their drug, biologic or medical device regulatory status before and after they are combined. Thus, facility where a single type of constituent part is manufactured must demonstrate compliance with the quality system requirements applicable to that type of constituent part. Quality system requirements that apply to the individual constituent parts of a combination product continue to apply even after they are combined to form of a single-entity or co-packaged combination product.

The Design Controls requirements of the QSR apply when a device constituent part is incorporated into a combination product. The QSR requires device manufacturers to establish and maintain Design Controls procedures that ensure that design requirements are appropriately established and that intended use and user needs are considered and satisfied. In utilising Design Controls, manufacturers may rely on existing information for the constituent parts. Should a combination product developer wish to use an existing or off-the-shelf product as a constituent part of a combination product, the utilisation of Design Controls must ensure that the existing product meets appropriate and prospectively established design requirements which assure that the combination product will be safe and effective.

This may result in modification of the existing product for use as part of the combination product. Modification of such a device must occur under Design Controls.

Within the meaning of the Final Rule, a device constituent part of a combination product is a finished device and a drug constituent part of a combination product is a drug product. Specification developers

"MANUFACTURERS OF DEVICE COMPONENTS, SUCH AS SYRINGE PLUNGERS, STOPPERS OR BARRELS, ARE NOT CONSIDERED TO BE DEVICE MANUFACTURERS UNDER THE QSR AND ARE THEREFORE NOT SUBJECT TO THE FINAL RULE"

and contract manufacturers are considered to be manufacturers subject to the Final Rule if they manufacture combination products or combination product constituent parts. However, manufacturers of device components, such as syringe plungers, stoppers or barrels, are not considered to be device manufacturers under the QSR and are therefore not subject to the Final Rule, even if that component will be incorporated into a combination product or constituent part of a combination product at another facility.

The Final Rule does not change any quality system requirements described in Predicate Rules for constituent parts (i.e. drug, biologic, device) described in master files (DMFs or MAFs for example). If the manufacture of an article described in a master file is subject to cGMP or QSR requirements, these requirements must still be met under the Final Rule. If the manufacture of such an article is exempt from certain Predicate Rule requirements, it may still be subject to other Predicate Rule Requirements (e.g. QSR Purchasing Controls in the case of device constituent parts).

CONCLUSION

Manufacturers of combination products and combination product constituent parts have six months from the date of publication of the Final Rule to implement changes to their quality systems, at all affected manufacturing facilities, to demonstrate full compliance with the requirements of the Final Rule. Prudent manufacturers will assess the impact of the Final Rule on their manufacturing and quality operations and those of their suppliers and contractors. Risk-based gap assessments should be applied which should include review of purchasing agreements, SOPs and conducting audits. Additional SOPs and training programmes may be needed, and implementing this will take time and planning.

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ABOUT THE AUTHOR

Michael Gross, PhD, RAC, is the Principal Consultant for Chimera Consulting North America, which specialises in quality, regulatory and technical consulting for drugs, biologics, medical devices and, in particular, combination products. Over his 30 year career, Michael has worked for the US FDA as a chemistry reviewer and inspector, and in senior regulatory affairs, quality assurance and compliance roles for drug, biological product and medical device manufacturers. He can be reached at michaelgross.chimera@gmail.com.

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TECHNOLOGICAL BREAKTHROUGH: AGUETTANT SUCCEEDS AGAIN

In this impassioned article, Danielle Labreche, Director, Business Development & Innovation, Laboratoire Aguettant, describes the current situation regarding the presentation and administration of emergency drugs in the critical care setting, and makes the case that this market must be provided with a prefilled syringe alternative.

Prefilled syringes is a fast growing market and the pharmaceutical industry is rapidly expanding the use of PFS applications in the hospital and in the homecare setting, especially for newly released drugs and therapeutic areas such as infectiology (vaccines) and oncology. A 2010 visiongain study predicted a growth from two billion prefilled syringes sold in 2009, to 6.83 billion in 2025.[1]

With all that has been written and said about prefilled syringes over the last decade, new solutions brought by leading world-class component providers and contract manufacturers for the pharmaceutical industry, is there still anything truly important remaining to be said?

I would argue that yes, there definitely is! Specifically: large-scale industrially manufactured and quality controlled drugs presented in prefilled syringes are still almost non-existent in the critical care emergency therapeutic arsenal where, not surprisingly, they are mostly expected for patient safety.

We are talking about well-known drugs, commercialised for decades around the globe and sold in glass ampoules or vials in million of units monthly to hospital at a value perhaps reaching €1 per dose. Drugs used day in, day out, to a point that they become commonplace, and despite all the best efforts and awareness of medical staff, are not handled according to the hazardous underlying risk to the patient.

"LARGE-SCALE INDUSTRIALLY MANUFACTURED AND QUALITY CONTROLLED DRUGS PRESENTED IN PREFILLED SYRINGES ARE STILL ALMOST NON-EXISTENT IN THE CRITICAL CARE EMERGENCY THERAPEUTIC ARSENAL WHERE, NOT SURPRISINGLY, THEY ARE MOSTLY EXPECTED FOR PATIENT SAFETY"

These are drugs that can save your life, or may kill you. They are still prepared, diluted and dosed in syringes by thousands of critical care nurses around the world, every day to treat patients – some of them, in case of need only – during planned/routine and emergency anaesthesia and surgery.

These are drugs such as, to name but two, atropine and ephedrine.

But, as the title of a 1999 US Institute of Medicine report states: "To Err is Human".[2]

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F: +33 4 78 61 09 35

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Figure 1: A Selection of Sterile Polypropylene Needle-free AGUETTANT Prefilled Syringes.

Here are some key figures:

6 500 000
Number of operations each year in France.[3]

8 000 000
Annual number of anaesthesia procedures in France.[4]

180 000
Estimated number of avoidable medical errors with severe adverse effects* during hospitalisation in France per year.[5] (* *Prolonged hospitalisation, disability, death.*)

48 000 AND US$8.1 BILLION
Number of deaths each year attributable to nosocomial infection in the US, and the additional costs related to prolonged hospitalisation due to nosocomial infections in the United States in 2006.[6]

71.5%
Of accidents reported in the hospital environment in France are needle stick injuries which induces for the medical staff a risk of exposure to blood.[7]

5 000 000
The number of atropine glass ampoules sold in France every year, which are manually prepared in syringes in hospitals with risk of glass cuts for the medical staff.[8]

70%
Of atropine syringes prepared by the hospital staff for use in case of emergency situation and ultimately wasted due to lack of necessity for the patient during the operating procedure and lack of proof of product stability and sterility for a later usage (unpublished market survey data from Laboratoire AGUETTANT, France, 2010).

In light of these numbers, it is not surprising that the European Board of Anaesthesiology (EBA) recommends: "Prefilled syringes should be used wherever possible".[9]

Laboratoire AGUETTANT has taken up the challenge to develop and make available to hospitals what is now and should be in evidence: a STERILE POLYPROPYLENE NEEDLE-FREE PREFILLED SYRINGES (Figure 1) for the operating room and emergency room (OR/ER) with emergency drugs.

Laboratoire AGUETTANT succeeded in regulatory approval with up to 36 month proven stability (with no special temperature conditions) of two drugs, ephedrine and atropine, in ready-to-use sterile polypropylene prefilled syringes for in-patient use. The commercial launches are progressing rapidly in Europe (France, the UK, Belgium and, via commercial partnerships, in Sweden, Finland, Denmark and Norway), with launch in Canada expected shortly. An AGUETTANT syringe in a blister pack is shown in Figure 2.

Having successfully completed pilot research on injectable WFI (water for Injection), a NaCl 0.9% drug application, and with two other resuscitation drugs in the completion phase of development, the goal of Laboratoire AGUETTANT is dramatically to increase security and improve ergonomics in the critical care arena worldwide.

AGUETTANT's aims are to:
- Contribute to Medical Errors eradication
- Eliminate the nosocomial infection risks
- Prevent the risk of exposure to blood and accident for the medical staff
- Reduce drugs and supplies waste and provide to the medical staff more valuable time; to attend to their patients' needs while spending less time in drug preparation
- Secure and simplify drug reconstitution for the hospital and homecare market.

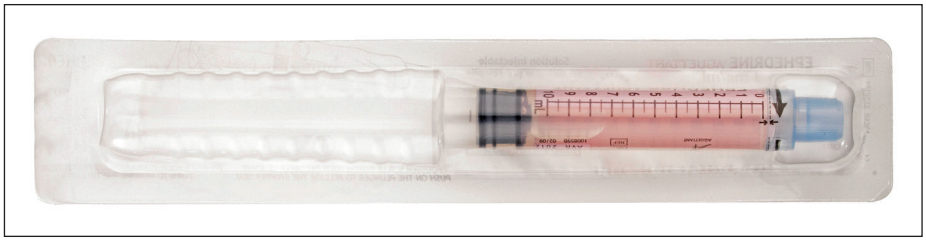

Figure 2: An AGUETTANT Prefilled Syringe Packaged in a Blister Pack.

AGUETTANT's ready to use prefilled syringe quality design includes:

- Needle-Free system with a Luer Lock connection (ISO 594-2 compliant)
- Tamper evidence and guarantee against leakage
- Outer Sterility of the PFS in its sturdy blister pack (Terminal steam sterilisation)
- Clear identification of the drug with compliance to ISO Colour coded label (NF ISO 26825)
- Double sided graduation for improved ergonomics.

The main benefits linked with polypropylene are that it is lightweight and ergonomic; robust against shock and cracks; and is an affordable material, widely known by and familiar to medical staff.

AGUETTANT's Sterile Polypropylene Prefilled Syringes are covered by two international patents (sterility of rubber stopper and opening system).[10]

AGUETTANT's sterile polypropylene prefilled syringe is part of the AGUETTANT System® portfolio, which includes also the unique MULTI DOSE, MUTI USAGE after first use, disposable Self Injector Pen for subcutaneous application.

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10. *WO 2007/028876 & WO 2007/083034.*

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Ready to use
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Tamper evident
- Patented opening system with pre-perforated label

Needle free
- Secure connection with its universal Luer Lock

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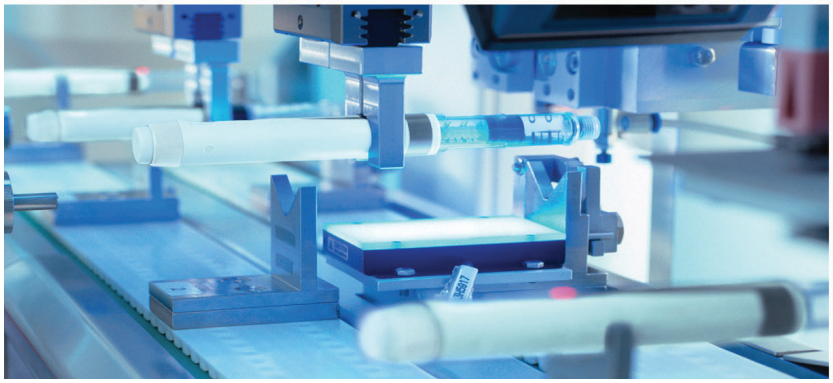
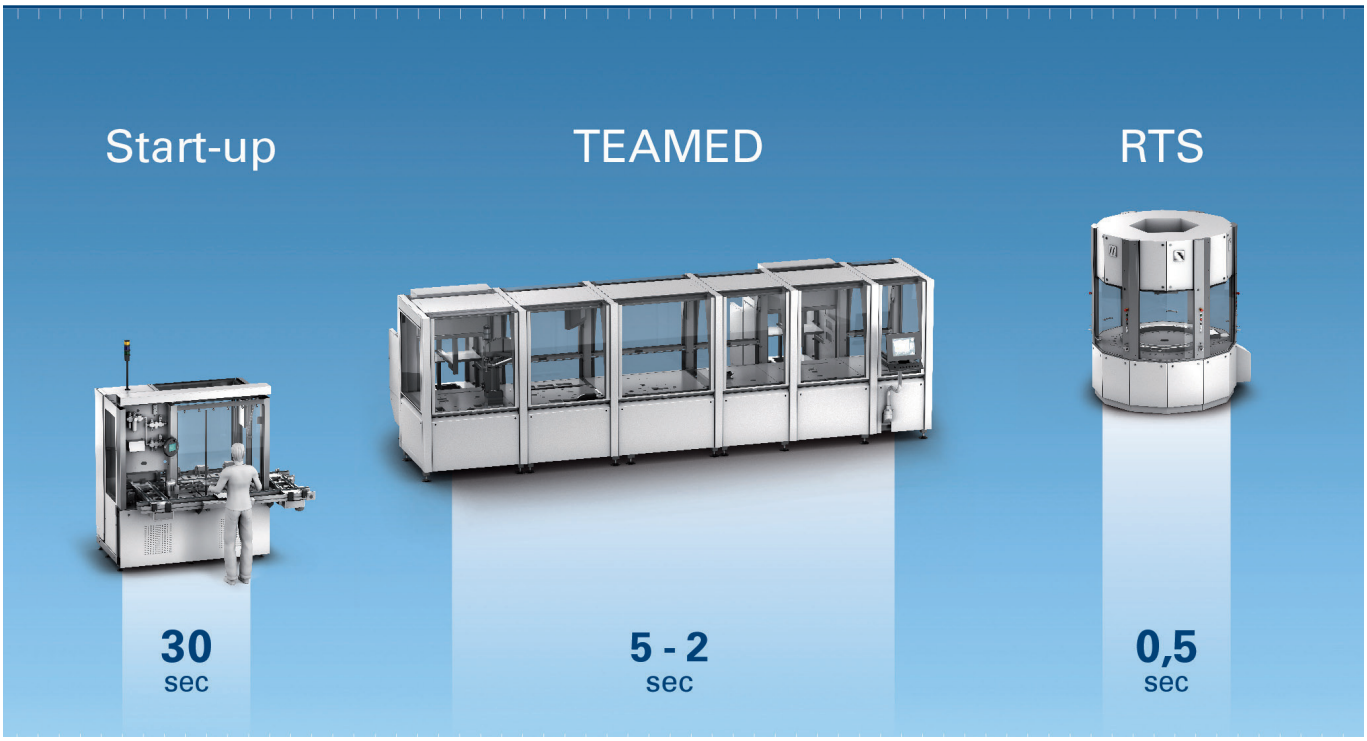


Proven Production Systems

Based in Freiberg/Germany, teamtechnik has been making intelligent and reliable automation solutions for medical and pharmaceutical industries and for the automotive and solar technology for over 35 years. teamtechnik is considered an international leader in highly flexible automation technology. With a total of 750 employees throughout the world, the company achieves sales of over €145 million. The teamtechnik Group has production sites in Germany, Poland, China and the USA.

Innovative Process Technology

teamtechnik develops innovative process-optimized 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.



From Start-up to High-Speed

For cost effective production from Start-Up to High-Speed production the company has brought to market three different platforms: START-UP, the platform for prototype production to verify processes early in their final execution and for clinical trial production; TEAMED, a highly flexible and upgradeable platform for assembly and testing; and RTS, the high-speed platform for economical mass production.

Quick Ramp-up and high Reliability

These platforms are realizing almost 80% of all customer solutions in the medical technology sector. Superior process technology, SPC test systems and 100% end-of-line testing can be integrated specifically for the production of medical devices and pharmaceutical products. The teamtechnik production systems allow production compliant with global guidelines and monitoring systems such as GAMP5, FDA and CE and meet class 6 clean room specifications.

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PRODUCTION TECHNOLOGY

DESIGN OF A SAFETY DEVICE TO MEET THE NEEDS OF BIOLOGICS

In this article, Sarah Baer, Marketing Product Manager, Safety Syringes, Inc (now part of BD Medical – Pharmaceutical Systems), describes how a clinically proven safety device has been adapted to meet increasingly complex biotechnology drug requirements including self-injection and viscosity.

Historically, safety devices have been primarily added to prefilled syringes to meet anti-needlestick legislation around the globe. Today, we see a growing number of biotechnology drugs in pharmaceutical company pipelines that require devices to meet self-injecting patient needs. For example, patients with chronic diseases often suffer from impaired dexterity, making it difficult to perform an injection. And, many biologics have more complex properties which make them harder to inject subcutaneously. Therefore, the design of an injection device to support biotechnology drugs must be able to address these requirements.

THE STATE OF NEEDLESTICK SAFETY

The exposure of healthcare practitioners to blood-borne pathogens as a result of injuries caused by needlesticks is of significant public health concern. The US Centers for Disease Control and Prevention (CDC) has estimated the number of sharps injuries in healthcare to be at 385,000 each year,[1] with about half of those injuries, or approximately 1,000 injuries per day, occurring in U.S. hospitals.[2]

Given the high incidence of needlestick injuries, we have seen an increase in legislation on a global scale. In 2000, the US enacted the Needlestick Safety and Prevention Act,[3] in 2008 the Province of Ontario passed 474/07.[4] Brazil passed rule Norma Regulamentadora NR32 in 2005 and Portaria MTE N° 939 in Nov 2008 with a deadline to implement in Oct 2010.[5] Germany implemented TRBA250 in 2007 and the EU passed a mandate 2010/32/EU which requires all EU member countries to address the danger of accidental sharps injuries (including needlesticks) by enforcing this legislation by May 13, 2013.[6] In Europe, local legislation is already in the process of being amended to meet these requirements. For example, in Germany, the website for the German Ministry of Labor and Social Affairs provides a link to new draft legislation to be implemented to address the EU Directive's mandate to minimise injury risk from sharps. It is anticipated that this increasing legislation will impact the presentation of injectables, especially those in prefilled syringes.

Although this legislation has not specifically targeted the pharmaceutical manufacturer, many pharmaceutical companies are using this as an opportunity for brand differentiation as they are seeing value in offering safer injection presentations for end-users.

REQUIREMENT – PASSIVE ACTIVATION

Several studies have confirmed that the safety aspect of an injection device is highly valued with nurses and self-injecting patients and preferred over a bare prefilled syringe.[7] However, it is very important that the correct device is selected. A passive safety technology has been shown to be the most effective as demonstrated by the 2010 Tosini study, conducted by Groupe d'Etude sur le Risque d'Exposition des Soignants (GERES), which confirmed that

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Figure 1: The clinically proven UltraSafe® Passive Needle Guard.

passive, fully automatic safety devices offer significantly better protection against accidental needlestick injuries.[8] The UltraSafe Passive® Needle Guard (shown in Figure 1) uses an innovative passive safety technology. The superiority of the passive safety technology arises because most needlestick injuries happen in the few moments after needle withdrawal.[9] Because of this, it is critical that the needle is shielded right after the injection without the user having to actively or manually initiate the safety mechanism. Any extra steps required by the user may result in no activation of the safety mechanism resulting in an unshielded and potentially infectious needle until disposal.

SUPPORTING BIOLOGICS

The growth in the biologics segment, estimated at US$176.4 billion in sales for 2012,[10] is driving the need for novel delivery systems. The majority of the over 550 biologics in development are monoclonal antibody (MAb) therapies targeting chronic and auto-immune diseases such as rheumatoid arthritis (RA), psoriasis or multiple sclerosis (MS).[11] These biologics are typically administered by a subcutaneous injection by the patient or caregiver at home rather than at a clinic or doctors office. This provides convenience for the patient while also reducing healthcare costs.

Many self-injecting patients suffering from chronic diseases may also suffer from reduced dexterity, making self-administration especially difficult. Self-injecting patients are trained when they receive treatment for the first time. However, intuitiveness and ease-of-use are essential factors in overall injection device design. To address this, many devices are provided in a variety of designs and different activation mechanisms to suit patient requirements.

In addition, biotech drugs, specifically MAbs, can be quite viscous, which then make them even more difficult to inject. This is especially true for patients who suffer from debilitating disease such as RA.

Furthermore, biologics often are administered in varying doses and volumes, requiring that the injection device design be able to support a range of fill volumes.

FACTORS INFLUENCING SELF-INJECTING DEVICES

Currently, there are several device options available for biotech drugs, yet there is not one solution that meets all patient requirements. Size, shape, sound, drug dispensing speed and injection angle are just some of the factors that need to be considered when designing a device for self-injecting patients.

INTRODUCING ULTRASAFE PLUS

Safety Syringes, Inc (SSI), now part of BD Pharmaceutical Systems, has developed a novel injection device, UltraSafe PLUS™*. It is based on the clinically proven UltraSafe Passive® Needle Guard platform. The UltraSafe Passive® Needle Guard, designed primarily for use in a clinical setting, has been marketed for over [12] years and successfully commercialised with more than 30 different drugs.

The design of the UltraSafe PLUS™ Passive Needle Guard (see Figures 2 and 3) is specifically to support biotechnology drugs and provide improved handling. Specific features are described below:

- Extended built-in finger flanges and ergonomic plunger head provide a better feel for the self-injecting patient.
- Robust plunger rod (Figure 4) supports injection of viscous drugs.
- Larger drug inspection window improves drug visibility.

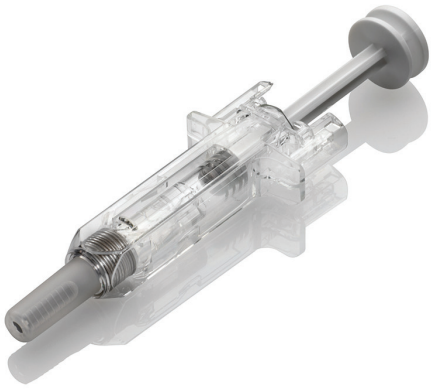

Figure 2: The UltraSafe PLUS™ is specifically designed to support self-injecting patients.

Figure 3: The UltraSafe PLUS™ provides intuitive one-handed passive activation.

Figure 4: The UltraSafe PLUS™ ergonomically designed plunger rod.

HUMAN FACTORS AND DESIGN

The overall design of the UltraSafe PLUS™ was validated by performing handling studies with both nurses and self-injecting patients. In June 2012, SSI conducted a large Human Factors user study of PLUS which involved 500 injections by self-injecting patients and nurses. Patients in this study suffered from RA, MS, cancer, Crohn's disease and asthma. These diseases can have very different effects on dexterity so it was important to validate the PLUS design with a broad range of patients.

Results from the Human Factor user study confirmed that PLUS was intuitive and easy to use with a 100% activation success rate for all 500 injections.[12] In addition, the added design features such as the wider finger flanges and ergonomic plunger rod were positively received by all users for providing additional injection support.

The results of the Human Factors user study not only validated the added design features but also the ability of PLUS to provide additional support in injecting drugs of higher viscosity. All users preferred to inject viscous solutions using PLUS than with a standard prefilled syringe.[13]

SUPPORTING MANUFACTURING CAPABILITIES

After the design of the UltraSafe PLUS™ was confirmed, SSI consulted with leading automation machine builders to ensure assembly of the UltraSafe PLUS™ was compatible with minimal modifications to existing or planned secondary packaging lines for the UltraSafe Passive® device. PLUS has been designed to fit ISO standard 1.0 mL long prefilled glass syringes.

SUMMARY

The market for biotechnology drugs is ever growing and there is a need for pharmaceutical companies to offer injection devices that support both the complex properties of the biologic as well as the needs of the end-user who will be performing the injection. Patients, especially those with limited dexterity, have very specific needs and requirements for the injection device. Providing a prefilled syringe with a safety device specifically designed for patients with reduced dexterity and for drugs with high viscosity ensures that both requirements are being met.

"ALTHOUGH THIS LEGISLATION HAS NOT SPECIFICALLY TARGETED THE PHARMACEUTICAL MANUFACTURER, MANY PHARMACEUTICAL COMPANIES ARE USING THIS AS AN OPPORTUNITY FOR BRAND DIFFERENTIATION AS THEY ARE SEEING VALUE IN OFFERING SAFER INJECTION PRESENTATIONS FOR END-USERS"

ABOUT SAFETY SYRINGES, INC

Safety Syringes, Inc (SSI) produces high-quality, clinically proven safety devices to help reduce the incidence of needlestick injury. On December 24, 2012, BD completed the acquisition of SSI and both companies look forward to continuing to bring innovative safety technologies to the market. Our experienced teams are committed to providing comprehensive support from product conception through to launch. We ensure rapid and efficient integration of our products to give unmatched time-to-market capability.

* Pending Regulatory Clearance

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ONdrugDELIVERY
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ONdrugDelivery 2013 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
March 2013	Transdermal Delivery, Microneedles & Needle-Free Injection	February 4th
April 2013	Pulmonary & Nasal Drug Delivery	March 4th
May 2013	Injectable Drug Delivery 2013: Formulations Focus	April 2nd
June 2013	Injectable Drug Delivery 2013: Devices Focus	May 6th
July 2013	Oral Drug Delivery	June 3rd
September 2013	CROs & CMOs Offering Drug Delivery Solutions	August 5th
October 2013	Prefilled Syringes	September 2nd
November 2013	Pulmonary & Nasal Drug Delivery (OINDP)	October 7th
December 2013	Delivering Biotherapeutics	November 4th

NEOPAC
THE TUBE

NEOPAC FLEXIMED® PARENTERAL TUBES: EASIER HANDLING

Parenteral packaging alternatives offering market differentiation by providing end-user benefits represent a mostly unmet need. With Fleximed®, Neopac offers a full range of innovative parenteral tubes which require fewer steps for giving an injection compared with conventional glass vials and ampoules.

The new Fleximed® tubes are available with two different specially engineered high-tech laminates that satisfy the strict requirements of the pharmaceutical industry providing high barrier properties, high transparency, excellent container closure integrity and a very low and well characterised extractable profile. The tubes are thus suitable for a broad range of small-molecule drugs all the way to complex protein molecules. Their silicone oil and tungsten-free materials offer key benefits compared to glass.

With Fleximed® Vial, the tube can be directly connected to a syringe for immediate and seamless delivery of medication, so there is no need to change needles thus saving valuable time with every single injection and reducing the risk for handling errors.

Fleximed® Luerlock, fitted with a male Luer Lock, eliminates the need for syringes to release medication from the vial. Instead, by removing the seal, medical staff can quickly pour the medicinal product directly from the medical tube into the catheter or IV bag.

Neopac also created Fleximed® Easymix (shown in Figure 1) a tube with two or more chambers to mix different components (dry/liquid or liquid/liquid). In doing so, Neopac addressed its customers' needs for reliable and easy mixing of two or more components immediately before application.

Fleximed® tubes are produced in Switzerland under fully qualified clean-room conditions (Figure 2).

ABOUT HOFFMANN NEOPAC AG:

Neopac is a subsidiary of the Hoffmann Neopac Group domiciled in Thun, Switzerland.

Figure 1: Selection of Neopac Fleximed® parenteral tubes, including Fleximed® Easymix tubes.

Based in Oberdiessbach, Switzerland, Neopac is a leading tube manufacturer for the pharmaceutical and related industries.

The properties of Neopac tubes always provide a strong barrier against light, moisture, oxygen, and organic and chemical substances, resistance to corrosion and high aesthetics due to all-around printing. Each new tube line stands in a fully qualified clean room where the whole environment is monitored for particles and microbes to certify the cleanliness of the tubes.

Hoffmann Neopac also owns the Hoffmann company in Thun/Switzerland and the Tu-Plast company in Debrecen, Hungary. Hoffmann in Thun produces pocket packs and tins out of metal and metal with plastic dispensers for the confectionery, tobacco, cosmetics and food industries, Tu-Plast in Debrecen produces plastic tubes.

Hoffmann Neopac employs over 600 people. Roughly 85% of production is exported, in particular to European customers but also the USA, Japan and China. In the US and South Korea the company works with partners holding Hoffmann Neopac production licences.

Figure 2: Fleximed® tubes are produced in Switzerland under fully qualified clean-room conditions.

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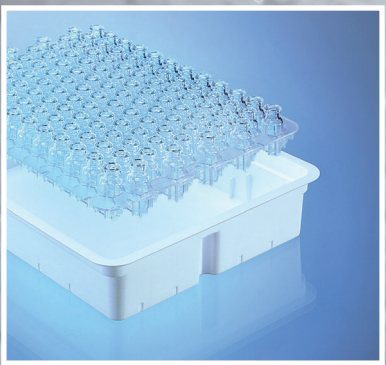
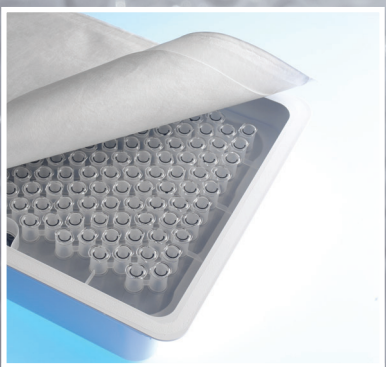
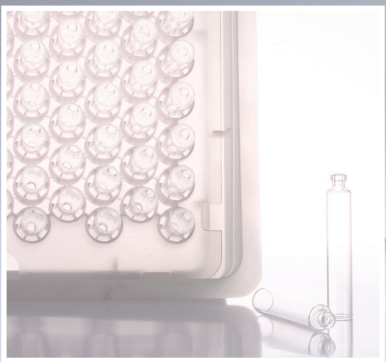


EZ-fill vials



EZ-fill syringes



EZ-fill cartridges

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DUOJECT MEDICAL SYSTEMS

DUOJECT INTRODUCES PENPREP EVO

Here, Simon Williams, Business Development, Duoject Medical Systems, provides a short introduction to the company's new simplified Penprep device, which reconstitutes lyophilized drug with a diluent stored in a cartridge and ensures that the volume of diluent transferred into the drug vial is exactly the same volume of reconstituted drug transferred back into the cartridge, minimising hold-up and air transfer to the cartridge.

Approximately five years ago, Duoject identified the need for a device that would simply and effectively reconstitute a lyophilized drug vial with a diluent stored in a 3ml cartridge. The device would allow the diluent to be transferred into the drug vial and the resulting add-mixture would then be transferred back into the 3ml cartridge for subsequent injection. The cartridge would be easily removed and then placed into any of the available multi-dose pen injectors, such as those frequently used in the insulin market, for multi-dose drug delivery.

"THE BREAKTHROUGH CAME WHEN WE IDENTIFIED THAT USING A VACUUM TO PULL THE CARTRIDGE PISTON TO TRANSFER THE ADD-MIXTURE BACK INTO THE CARTRIDGE WOULD SIGNIFICANTLY SIMPLIFY THE DEVICE'S TRANSFER PROCESS AND ALSO ENABLE THE DEVICE TO SELF-ADJUST"

Our initial prototype was well received by the market, so we were confident that we had identified a product for which there was clear demand. Over the next few years, we engaged in a number of user studies with interested pharmaceutical companies and were pleased by the wide variety of different therapeutic classes of drugs that, once reconstituted, could be delivered in multiple doses over a period of one week to a month or more. As these studies progressed, we discovered that there were a significant number of challenges to bring such a product to the market. Therefore, despite ours and our partners' best efforts, and despite continued development of the device, we were unsuccessful in getting the product launched on the market.

Jump forwards to last year when we decided to take up the challenge of revisiting this device, once again benefiting from the support of an enthusiastic pharmaceutical partner in search of a reconstitution solution for multi-dose drug delivery. We went back to the drawing board, radically simplifying the design and, as a result, were able to produce an effective device that overcame all of the challenges that we had uncovered in our previous years of development. The breakthrough came when we identified that using a vacuum to pull the cartridge piston to transfer the add-mixture back into the cartridge would significantly simplify the device's transfer process and also enable the device to self-adjust to automatically accommodate a wide range of diluent fill volumes.

This new concept, Penprep EVO (shown in Figure 1) essentially ensures that the volume of diluent transferred into the drug vial is exactly the same volume of reconstituted drug transferred back into the cartridge, thus minimising hold-up and air transfer to cartridge. This new design was our simplest to date and, as the user studies show, is by far the

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Figure 1: The new PenPrep EVO device, which can be easily configured using either a 13mm or a 20mm version of the EZ-Link vial adaptor.

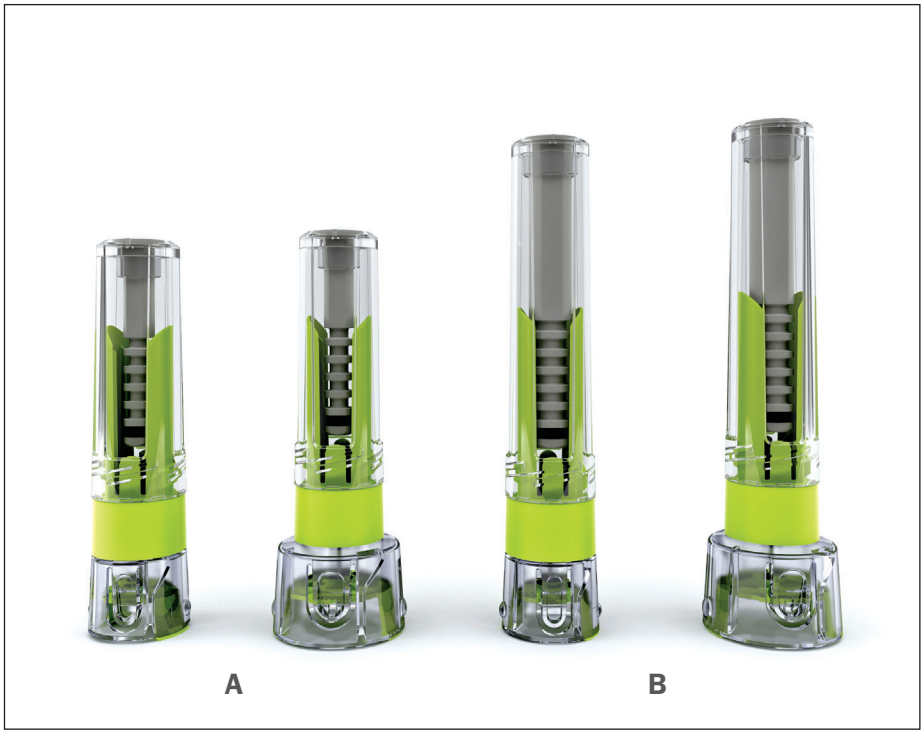


Figure 2: The PenPrep EVO "mini" (A) allows any 13mm or 20mm lyophilized vial to be reconstituted with a diluent supplied in a 1ml cartridge. (Standard 3ml version of the device shown on the right (B) for comparison.)

most effective. We felt that this version of the device had truly earned the name "EVO", as our device history file clearly shows the many evolutions the concept went through to result in the one we are proud to launch this year.

Over the last two years, Duoject has been following a strict philosophy of modular design. This is evident in the new PenPrep EVO and will continue to be seen in other exciting products we are working on for the future. The new PenPrep EVO device can be easily configured using either a 13mm or a 20mm version of the EZ-Link vial adaptor, which includes Duoject's proven and highly regarded needle-safety and auto-disable technology. This modular approach significantly reduces development time and risks. It opens up new possibilities for future devices and will substantially reduce inventory requirements as the products move into high-volume production. The modular approach brings further benefits to our pharmaceutical partners such as:

- reduced device costs
- streamlined product ecosystem and
- fast turnaround of customized solutions to fulfil their specific requirements.

Building on the modular approach, we have simultaneously developed a miniature version of the PenPrep EVO (Figure 2). This "mini" version will allow any 13mm or 20mm lyophilized vial to be reconstituted with a diluent supplied in a 1ml cartridge and then used in our VaccJect "safety syringe" device (Figure 3). This means that any drug or vaccine already on the market in a lyophilized or powder form can now be easily reconstituted to take advantage of the low-cost VaccJect safety delivery device, without modification to the primary drug container. This added capability will help to support the growing interest we are seeing for VaccJect in the market and provide more options to pharmaceutical companies seeking novel and versatile drug delivery solutions.

In addition, this is beneficial when considering that, as the administration of vaccines moves from established locations such as clinics and medical centres to new locations, such as the pharmacies now widely used to administer vaccines in the US, devices that enhance safety, simplify administration and drastically reduce the space needed for cold-chain storage, become increasingly important.

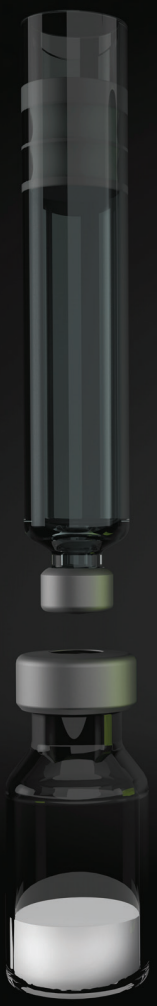
VaccJect's unique approach to the cold chain, coupled with the best-in-class integrated safety – a needle never seen before or after injection – and its patient- and administrator-friendliness, allows pharmaceutical companies to offer a solution to these new challenges and truly differentiate their product from the competition.

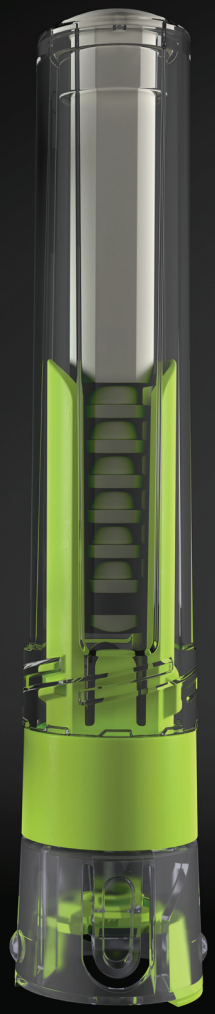
With clinical and US FDA-registered device production facilities and an FDA-approved facility qualified to manufacture sterile diluent filled cartridges, Duoject is ready to meet your every need. Make a bold improvement to patient compliance and truly differentiate your drug or vaccine from the crowd using Duoject's medical devices.

Figure 3: The VaccJect device.

PENPrep EVO The solution to cartridge-based reconstitution

Challenge





Solved

DUOJECT MEDICAL SYSTEMS

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YPSOMED
SELFCARE SOLUTIONS

SPEED UP TIME-TO-MARKET WITH CUSTOMISED PLATFORM PRODUCTS

Here, Ian Thompson, Vice-President, Business Development, Delivery Systems, Ypsomed, provides a useful and succinct run-down of the company's range of self-injection devices, and their various applications.

Innovative and patented technologies offer our customers user-friendly injection systems with which they stand out successfully in the market. All our products are characterised by reliable and well-thought-out technical concepts, which are optimised for the highly automated manufacture of large series. We are constantly expanding our platform portfolio to cover new therapy and patient needs, including disposable autoinjector platforms for the treatment of autoimmune diseases and other indications. One of our latest platform products is YpsoMate®, an easy, intuitive 2-step autoinjector.

YPSOMATE®: 2-STEP AUTOINJECTOR

The YpsoMate® autoinjector (Figure 1) is an automated disposable injection device for 1ml long prefilled glass or plastic syringes suitable for all patient groups. The device is triggered by push-on-skin activation which is convenient, ergonomic and preferred by patients. The injection is administered in two easy steps. First, the cap of the autoinjector is removed and then the injector is simply pressed against the skin, which will initiate the injection. The patient is always in our focus, and YpsoMate® includes the following user-friendly features:

- The needle is hidden at all times, before, during and after injection for increased comfort
- Audible confirmation "clicks" after needle insertion, end of injection, and activation of needle protection, increase patient confidence
- Mini-spikes on the front surface of the device gently stimulate the skin of the patient, masking needle insertion.

The YpsoMate 2-step autoinjector continues to impress in handling studies performed by big pharma and biotech companies. Encouraged by this success Ypsomed has launched YpsoMate Control - giving the patient full control over needle insertion and injection (see Figure 1). Inspired by the pen injector world YpsoMate Control allows the patient to control needle insertion by pushing against the skin and separately controlling the start of the injection with the push button.

The YpsoMate® does not only meet the needs of patients, it also fulfils all pharma industry requirements:

- Configuration capabilities for different fill volumes, syringe formats and viscosities allow the use of the platform for multiple projects
- Simple end-assembly process and technical support from Ypsomed assures low cost of goods
- Off the shelf product from experienced ODM manufacturer assures short timeline and low project risk.

An increasing number of highly potent drugs necessitate different injection volumes for various patient groups. Although the YpsoMate® is easily customisable to work with different fill volumes in the primary package, filling of a fixed dose and application using a variable single-dose injector can be advantageous. For such products Ypsomed offers VarioJect™.

VARIOJECT™: THE VARIABLE SINGLE DOSE INJECTOR

The VarioJect™ is a simple-to-use, variable-dose injector for prefilled syringes or cartridges. It guides the patient through priming followed by dialing the dose to then inject the set dose volume. After use the device is locked and no further dosing is possible.

Moreover, VarioJect™ is designed to be highly customizable. It works with 1ml pre-

Figure 1: The YpsoMate™ and Ypsomate™ Control autoinjectors.

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Figure 2: The VarioJect™ facilitating a 1ml pre-filled syringe.

Figure 3: The ServoPen®, YpsoPen® Twist and UnoPen™.

Figure 4: The LyoTwist™ in a configuration for automatic injection of a variable dose.

filled syringes (see Figure 2) as well as 1.5ml cartridges. For marketing and usability purposes the shape and colour may be varied to provide distinct differentiation.

The variable single-dose injector, VarioJect™, sets a new standard in the field of self-injection devices that is dominated by variable multi-dose pen systems. Ypsomed offers a variety of re-usable and disposable pen system platforms that meet all patients and pharma industry requirements.

SERVOPEN®, YPSOPEN® TWIST, UNOPEN™: A COMPLETE RANGE OF PEN INJECTORS

The ServoPen® is Ypsomed's most advanced automatic re-usable pen – it is an intuitive spring driven insulin pen providing an effortless, yet familiar, handling experience. Patients appreciate the comfort of drug delivery: the ServoPen® has the shortest available injection stroke distance on the market. During dosing, dose correction and delivery, the patient receives audible and tactile feedback. Pre-injection dose indication ensures correct dosing up to the last drop.

The re-usable YpsoPen® Twist is designed for simplicity and maximum value. It is equipped with a gearing optimised for maximum force reduction with minimum dose-knob extension for optimal user experience. For many customers who sell their product in cost-sensitive markets, the attractive pricing of the YpsoPen® Twist enables them to compete successfully.

Whereas the ServoPen® and the YpsoPen® Twist are both re-usable pen injectors, Ypsomed also offers an intuitive disposable pen solution, the UnoPen™ (all three devices are shown in Figure 3). The UnoPen™ is ideally leveraged for use with other injectable therapies such as human growth hormone (hGh), follicle stimulating hormone (FSH), parathyroid hormone (PTH) and glucagon-like peptide-1 (GLP-1).

The UnoPen™ product platform is easily customised according to a customer's individual primary packaging, drug and therapy needs.

For lyophilized drugs, Ypsomed has developed a new generation of dual-chamber monodose devices, LyoTwist™

LYOTWIST™: DUAL-CHAMBER SINGLE DOSE DEVICE

The LyoTwist™ monodose device family for dual chamber cartridges is based on Ypsomed's proven twisting method for reconstitution and priming. The devices provide excellent visualisation of the reconstitution, priming and injection steps. A complete range of device versions ensure that various drug, therapy and patient needs are met. Ypsomed offers different technical solutions covering manual and automatic injection, fixed and variable dose injectors. In Figure 4, for example, LyoTwist™ is configured for automatic injection of a variable dose. Needle safety is guaranteed when used in combination with Ypsomed's Clickfine® AutoProtect™ safety pen needle.

COMPANY OVERVIEW

Ypsomed is the largest independent developer and manufacturer of custom-made injection systems for self-administration, with pens ranging from simple disposable pens to those that are re-usable pens and include variable dosing and spring-assisted injection. The company also develops and manufactures autoinjectors for use with prefilled syringes as well as innovative injection devices for use with double-chamber cartridges. Unique click-on needles that function for our own and all other widely-available pens complete our product portfolio.

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

Ypsomed has well established partnerships of many years with numerous leading pharmaceutical and biotech manufacturers such as Sanofi-Aventis, Pfizer, Roche/Genentech, Merck-Serono and Lilly.

YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed Delivery Systems provides a complete range of technologies and services for reliable and user-friendly injection systems for self-medication. From technical development and design to manufacturing and packaging, Ypsomed makes a crucial contribution to the safety and market success of the products. Our modular and proven platform technologies guarantee that Ypsomed injection systems are rapidly available for clinical studies and market introduction.

Dividella

Pharma Packaging Technology

THE SIGNFICANCE OF PACKAGING FOR BIOTHERAPEUTIC PRODUCTS IN PREFILLED SYRINGES

This article from Christoph Hammer, Chief Technical Officer and Deputy CEO, Dividella, explores how innovative carton packaging solutions can enhance pharmaceutical product presentation whilst meeting the stringent requirements of product protection, particularly considering biotherapeutic products.

Today, more than 45% of new approvals are for drugs which contain biotechnological elements. This trend will continue to strengthen; in the next few years, a total of 200 new approvals are expected on the world market. Biotech products are becoming increasingly important because of their extraordinary pharmaceutical potential.

Since biological molecules are usually too unstable for formulation as solid pharmaceutical products (tablets or powders), more than 90% are presented as liquids in syringes, vials or ampoules. Since biotherapeutics are significantly more expensive than small-molecule pharmaceuticals, they must be packed as securely as possible. Moreover, they often have to be transported in a precisely defined temperature environment. Cold-chain logistics ensure the correct temperature is maintained throughout, from manufacture, through transport and storage, to administration.

Many pharmaceutical companies produce and market a wide range of products worldwide. Differing demand in the respective markets and product segments therefore requires a highly flexible packaging system which can handle a wide range of different items and, at the same time, provide optimal product protection. It is also essential to guarantee efficient, low-cost packaging of small, medium and large lot sizes. Other requirements of a modern packaging system include item and code checks (vision systems), printing and checking of variable data, the shortest possible machine set-up times, and compliance with cGMP standards.

THE REQUIREMENTS OF THE PACKAGE

All packages must safeguard the product throughout its route, from manufacture to final point of use. The package must also convey sufficient information to ensure that the product is used correctly. Each package provides the vital link between manufacturer and consumer; it is an essential component of the product itself.

The prefilled syringe is an example of a high-value product that must be safeguarded throughout a long shelf-life and yet be readily and accurately used whenever required. The proper selection of the package and the attention to its design will promote the benefits of the product in addition to fulfilling these fundamental functions. The syringe is not viable without its packaging.

The package must enable rapid access to each of the prefilled syringes it contains, and must remain intact until the last of the syringes has been removed, if that last syringe is to be safeguarded. The printing of the package will clearly present essential product information. Further features may confirm that the syringe is untouched until required for use.

A reclosable package can be retained for subsequent use without difficulty. If the package contains a course of treatment for a single patient, features to assist dosage compliance are appropriate. If the contents are to be used over an extended period, opening features that release only one syringe at a time can assist the user.

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With regard to the logistics of distribution, cost is affected by the volume of the package itself. Where the product must be held in a temperature-controlled environment, it is particularly important to adopt a package of minimum volume relative to its contents. Minimising package volume also benefits storage immediately prior to use; for example in a hospital pharmacy.

The immense cost pressure within the medical sector encourages the increasing trend towards self-medication. The branch of liquid pharmaceuticals is also drawn into this development with the use of prefilled syringes on the increase. They are not only easy and safe to handle by the patients themselves, but are also favoured by both doctors and hospitals. The potential dangers involved with breaking the ampoule are therefore avoided. Another important factor for this development is found in the low logistical costs which, thanks to optimal packaging solutions, are easily accomplished.

DIVIDELLA'S MODULAR FEEDING SYSTEMS

Requirements are changing rapidly, and often this brings along significant reorientations in the production process and requires high investment. Dividella provides modular and extendable packaging systems so its clients not stuck on one implementation; enabling a flexible and efficient production.

With this in mind, Dividella develops quality feeding equipment and specialised product-handling systems in the scope of packing a vast range of medicinal products and devices, parenterals or solid forms.

THE DIVIDELLA PACKAGING PROCESS MAKES IT ALL POSSIBLE

Implementing customer-orientated top-loading concepts for the pharmaceutical industry has been our specialty for many decades. The top priority is always to find the optimal cardboard-based packaging solutions. In a second stage, the appropriate machine is chosen, depending on production volume and batch sizes. The packaging systems are carefully designed down to the last detail and have proved themselves in practice every time.

The packaging process starts with the erection of the Toploading box. Dividella uses all three spatial dimensions by applying the rotor principle. This achieves an unrivalled performance ratio for the available production area. The active erection process ensures consistent high quality of the boxes.

Then the Toploading boxes are placed on a vacuum conveyor system and carried through the machine without any lateral guides. The boxes remain precisely in position and never have to be moved. Various other proprietary systems such as cameras, marking systems, labelling machines, etc. can be integrated into the machine without any problems. This is made possible by modular construction and a clear differentiation between the operator side and the 'automation side'.

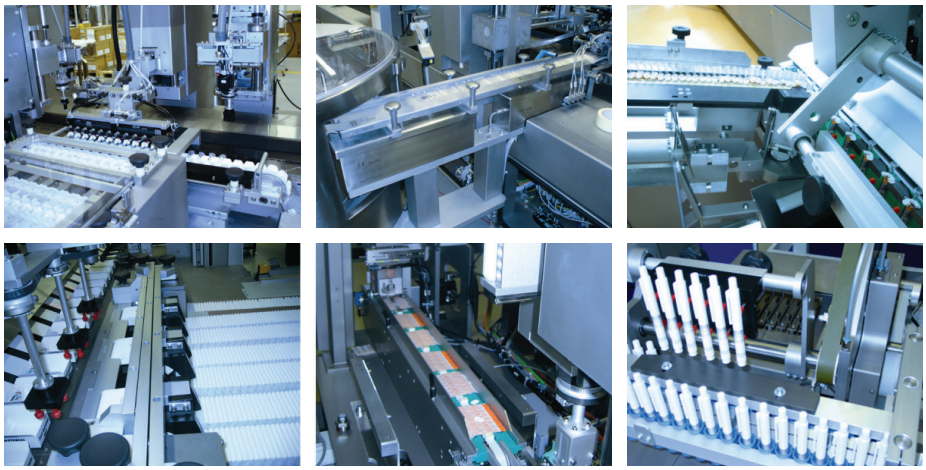


Figure 1: Customised feed systems for (clockwise from top left): syringes in trays; plungers; prefilled syringes with backstops; extra-large booklets; needles in soft blisters; and pens.

DIVIDELLA FEEDING TECHNOLOGY

One of the most difficult tasks involves a gentle, flexible feeding system for items such as syringes, vials, pens and softblisters. In this area Dividella is able to apply a very wide range of feeding technologies.

On the basis of Dividella's many years of experience in object handling, we have developed new modular feeding systems. This means that up to 500 objects per feeding unit per minute can be packaged; before they are inserted they can also be aligned, spread and individually checked.

Apart from the actual pharmaceutical products, placing inserts can present major challenges. The handling of inserts is a critical area, especially in the case of high-output machines such as the Dividella NeoTOP 804, which can produce up to 240 packs per minute. Dividella has developed a wide range of scalable feeding systems for this purpose. Consequently, very large, thick inserts can be fed in at full speed, using minimum labour.

In recent years, Dividella, on the basis of its particular expertise in this area, has already developed many different customised feed systems, linked to upstream machines – for example for pens, prefilled syringes, plungers, and soft blisters (see Figure 1).

Dividella feeding systems are also used successfully by their sister company MediSeal, which specialises in thermoformers. These synergies ensure that systems are used in many different situations, field-tested and further developed to guarantee maximum operational reliability.

Assembly of module and feeding systems at Dividella's site in Grabs, Switzerland, is shown in Figure 2.

Figure 2: Module and feeding systems assembly at Dividella's site in Grabs, Switzerland.

FOCUS ON PACKAGING COSTS: CARDBOARD VS PVC

Inevitably, over the last few years, sober economic considerations have put the spotlight on packaging costs. The pressure on costs is affecting the packaging industry in particular. Some companies only take the costs of packaging materials into account, whilst others have a more holistic approach, which also encompasses operating and investment costs, personnel, set-up times, the cost of format parts and material losses.

Dividella has been able to demonstrate cost benefits in terms of the packaging material alone. The NeoTOP solution wins out against PVC blisters and the additional horizontal folding box which is required. The key principle is that the more product in the folding box, the greater the cost saving.

One of the reasons for this is the low volume of the pack in comparison with PVC blisters. One study by a Swiss pharmaceutical company has shown that savings of up to 30% in volume are possible, if using the NeoTOP concept for disposable syringes. If this is applied to the annual production of just one product, it corresponds to considerable financial savings.

If the product has to then be refrigerated until it reaches the patient, a smaller pack is another major cost benefit. However, looking at packaging costs alone is short-sighted; the greater benefits lie with the machine, or rather the process side. These include:

- Only one installation instead of a thermoforming machine and a cartoning machine
- No thermoforming process
- Fewer personnel required
- Setup in 30 minutes
- Packaging of mono-material/independent of changes in oil prices
- Higher machine efficiency
- Flexibility in machine allocation
- Retrofitting/conversion of installations is very simple thanks to machinery's modular construction

ANTI-COUNTERFEITING & TAMPER-EVIDENT SEALS

The Swiss have been concerned with guaranteeing originality for many years. The problem is solved quite simply by applying a spot of hot-melt in the right place. If the box has been opened, this is immediately apparent to the user – and it involves virtually no extra machine costs and has no effect at all on performance.

PROTECTION FROM COUNTERFEITING AS LIFE INSURANCE

Biotechnology products in particular require a lot of effort to produce and are therefore expensive to manufacture. However, the risk of these products being counterfeited or manipulated is unfortunately omnipresent and has already become a major issue on some continents. If a counterfeit product is used for cancer therapy, or even for antibiotic therapy, the consequences for the patient could be fatal.

Concepts relating to guaranteeing originality and counterfeit protecting have been developed, which can also be implemented in the short term on existing packaging solutions. An invisible code for the pack, and product and information on usage, ensure the necessary security – and also permits effective track and trace.

ENERGY AND ENVIRONMENTAL FACTORS

Until very recently, it was seriously frowned upon to discuss the energy and environmental aspects of a packaging concept. The argument frequently given is that this topic has no resonance among the management… but personally, individuals clearly see the advantage.

Today, if a manager in the pharmaceutical industry were to try to sweep this topic under the carpet, it would certainly not be advisable, for the following reasons:

- Energy costs are rising – a difficult variable to predict
- Production costs (including packaging costs) are clearly a competitive advantage
- Customers decide whether packaging is environmentally friendly
- Costs of disposal are rising
- Major consumers such as hospitals will exert pressure

For example, Germany's Federal Office for the Environment has made figures available that clearly show that merely to manufacture one kilogram of PVC in granulate form generates the equivalent of 2.2kg of CO_2 and requires approximately 500 litres of water. Today these figures perhaps do not mean much to us, but in the medium term these values will become an instrument for industry regulation.

Managers in the pharmaceutical industry make a far-reaching strategic decision when they opt for mono-material solutions and give them preference over PVC and paperboard variants. However, this decision is likely to bring commercial advantages, both in the day-to-day packaging process and in terms of greater systems flexibility.

One point is absolutely clear – switching over existing products packaged in PVC without question involves considerable effort. But the market looks at things differently and asks: in the long term, can potential savings be sacrificed in terms of costs and flexibility?

CONCLUSION

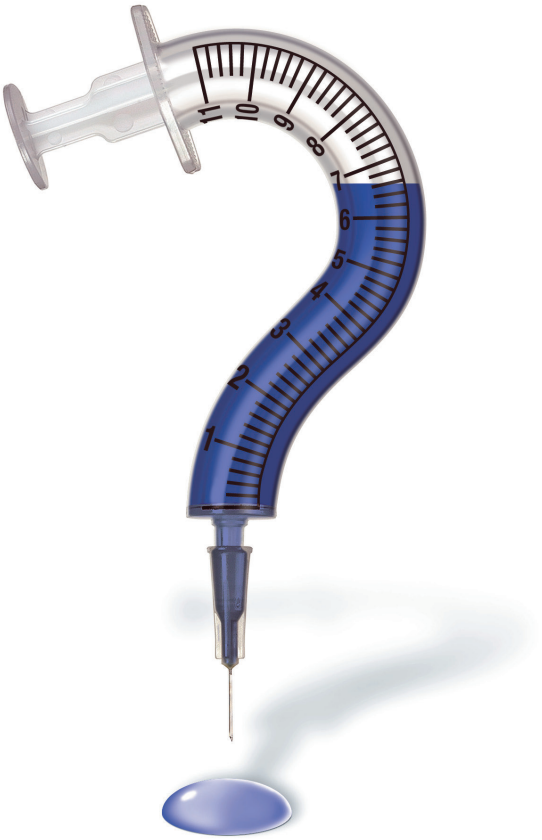
The packaging needs of the prefilled syringe are rigorous if it is to perform safely and effectively. The top-load carton more than meets these packaging needs, whilst enhancing the benefits of the prefilled syringe.

The distinguishing advantage is the low volume, the easy user handling, low production costs and the high flexibility of the packaging solution. Furthermore, the small volumes are reflected in the low transport costs within the cooling chain.

There are a number of additional advantages, such as opening the packaging from the top (top loading), meaning that the user has an immediate overview of the remaining product. The leaflet or information brochure can be extracted without any problem, and can be read and placed back. The packaging is suitable for printing additional information on the package interior and exterior, and needles or vials can also be integrated into the package without any problems. Opening protection is provided either by the opening mechanism itself or by means of additional relevant labels. These packaging systems also widen their remit through being not only suitable for syringes (with or without needle protection), but also for pens, injectors, inhalers and other similar products.

Dividella

Pharma Technology Solutions



Beyond Pharmaceuticals

Packaging without limits.

NeoTOP 804 TopLoading Cartoner

Every pack is a promise to the customer. Fortunately, Dividella's packaging machines mean that no other packaging solution is as modular and flexible. In addition to optimal product protection, compact dimensions and easy access, Dividella provides highly flexible system solutions with feeding systems for products of all shapes and sizes. That gives you the freedom to focus on your ideas without packaging restrictions. After all, that's the road to success!

Dividella, expect flexibility & swiss perfection.

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Every day, injectable drugs are administered to improve the lives of millions of patients around the world. And every day, West is working by your side to design and manufacture drug packaging and delivery systems that will bring our customers' drugs from concept to the patient more efficiently, reliably and safely. West understands our customers' challenges and helps with solutions every step of the way, with cutting-edge production technologies, an unmatched expertise in global regulatory compliance, and an ever-growing knowledge base of pharmaceutical drug product testing, development, packaging and delivery. Whether focused on one piece of the process or an end-to-end solution, West is by your side for a healthier world.

SOLUTIONS FOR PACKAGING, ADMINISTRATION & DELIVERY

West is a leader in developing and manufacturing packaging and delivery systems that enhance the administration of pharmaceuticals. The products we make and the services we provide help improve health care for people around the globe. West supports its customers from locations in North and South America, Europe, Asia and Australia.

A HISTORY OF INNOVATION AND EXPANSION

Since its founding by Herman O. West in Philadelphia in 1923, West has played a major role in advancing the progress of health care. In its early years, West provided components for packaging injectables. Our pioneering efforts enabled the widespread distribution of life-saving drugs such as penicillin and insulin. Today, West works with its health care partners to design and manufacture drug packaging and delivery systems that bring their drugs from concept to the patient more efficiently, reliably and safely.

PROVIDING SOLUTIONS FOR GLOBAL HEALTH CARE

West provides innovative solutions for injectable drug administration for pharmaceutical and biopharmaceutical companies around the world. Where appropriate, West facilities have earned ISO certifications and comply with applicable cGMP requirements. In addition, our facilities meet applicable standards for registration with the US FDA and DEA, if appropriate. Regulators are requiring drug companies to provide an increasing amount of data about the safety and effectiveness of their products. West Analytical Services, an FDA-registered laboratory, can help fulfill many of these needs by providing testing as part of the drug development process, specialising in packaging and delivery system support.

TOMORROW'S SOLUTIONS DELIVERED TODAY

Today's pharmaceutical and biotech discoveries lead to innovative new therapies that will become tomorrow's health care solutions. West is at the forefront of advancing those therapies with delivery systems that enhance the effectiveness of pharmaceuticals. West provides an array of innovative products, services and support – helping our customers deliver drugs that are pure and safe.

NovaPure® Components
Patient safety influenced the design process for NovaPure stoppers and syringe plungers from start to finish. West developed NovaPure components by incorporating Quality-by-Design principles to help ensure enhanced component reliability and an unrivaled level of quality.

Westar® Processing
Eliminates work-in-process and component preparation issues for ready-to-sterilise and ready-to-use components. The Westar process is a documented, validated process for preparing pharmaceutical components in accordance with international regulatory requirements.

West Spectra® Seals
Tamper-evident West Spectra seals help ensure patient safety and product security by incorporating multiple layers of protection to combat drug counterfeiting and help keep supply chains safe.

Injection System Platform Technologies
West's platform technologies provide solutions for self-injected drugs covering a range of dose volumes and drug viscosities. West's platform technologies include the ConfiDose® and SmartDose® injector technology platforms.

Needle Safety Systems
West's needle safety systems provide protection for health care workers and patients against accidental needlestick injuries. West provides both passive and active needle safety systems.

Daikyo Crystal Zenith® Ready-to-Use Solutions
The Crystal Zenith polymer is break-resistant and highly transparent. Available in a variety of vials, containers and syringes, a solution using Crystal Zenith polymer is the answer to drug product lifecycle management.

Administration Systems
West develops and manufactures safety and administration systems for the reconstitution, mixing, transfer and administration of injectable drugs. Mixing and transfer systems include MixJect®, Mix2Vial®, Vial2Bag® and vial adapters.

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HASELMEIER

Haselmeier is dedicated to meeting the self-injection needs of pharmaceutical manufacturers and patients.

In 1920, Wilhelm Haselmeier established a medical device company in Stuttgart, Germany. Since that time, Haselmeier has continued to develop and create injection devices designed for patient comfort and ease-of-use.

Today, Haselmeier is one of the leading designers and manufacturers of pen and auto-injector systems. Many of these systems feature Haselmeier's patented hidden needle system, which is designed to help patients overcome the fear of self-injection, provide a more comfortable injection and help increase compliance of the patient's medication.

PRODUCT DESIGN

Our capabilities include design and development from concept to finished device using Haselmeier's strong IP portfolio or tailoring of existing Haselmeier designs to meet customer and therapeutic needs.

All designs undergo comprehensive testing, in addition to risk management, risk analysis and FMEA design review. Three-dimensional CAD designs are utilised for creation of customer-specific concepts or customisation of existing designs.

MANUFACTURING AND QUALITY

As a specialist in the manufacture of complex system assembly, product integrity is assured by Haselmeier's manufacturing processes. All new device concepts are created with an "Integrated Design Approach" which focuses on both, the device and the efficiency of manufacture and assembly.

All manufacturing is within compliance with applied standards EN ISO 13485:2003 and Annex ll, Section 3 of the European Directive 93/42/EEC on medical devices. CE certification is certified by TÜV SÜD Product Service (Munich, Germany).

PLATFORM & PRODUCTS

Axis Pen System: variable-dose injection device

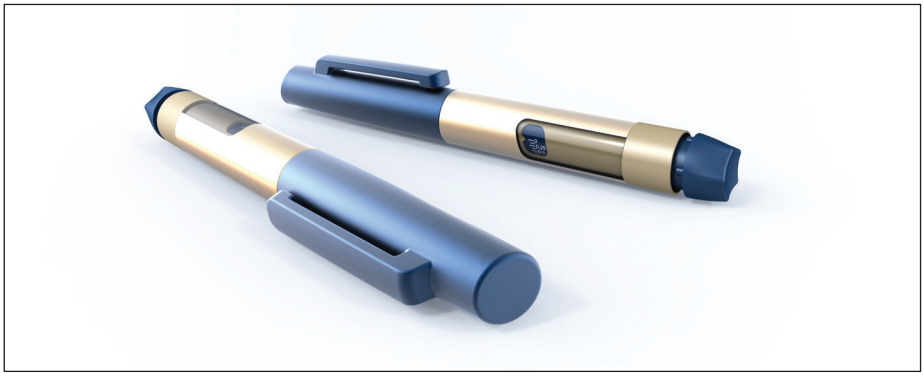

Figure 1: Axis Pen System – variable-dose injection device.

The Axis Pen System is a variable-dose injection device for manual injection. It is available in a disposable or re-usable presentation. The Axis-D and Axis-R Pen Systems (Figure 1) provide a new, unique technical function.

Figure 2: i-pen: re-usable – variable dose injection device.

Figure 3: i-pen²: re-usable – variable dose all-plastic injector device.

Technomics

THE NEW i-pen②

- All plastic reusable pen
- Dose increments from 0,01ml to 0,6ml
- Easy and safe dose correction
- Large and easy-to-read dose indicator
- Haselmeier quality at economic cost

HASELMEIER

Fore more information please contact us at
info@haselmeier.com or visit us on **www.haselmeier.com**

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The Axis pens feature:
- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale

i-pen: re-usable, variable dose injection device

The Haselmeier i-pen is a re-usable, variable-dose injection device for use with a standard 3 ml cartridge. The i-pen (see Figure 2) features an elegant non-medical design which is the result of extensive research and patient testing.

The i-pen is available as a standard Haselmeier design or can be customised to your specific requirements. It features:
- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body

i-pen²: re-usable, variable dose all-plastic injector device

The i-pen² (Figure 3) is a reusable, variable dose injection device for use with a standard 3ml cartridge. The i-pen² was specifically created to provide a high-quality pen at economic cost.

The i-pen² is available as a standard Haselmeier design or can be customised to your specific requirements. It features:
- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components

Softpen – reusable injection device

The Softpen (Figure 4) is a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution. The Softpen features:
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3 ml cartridge

Figure 4: Softpen – a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design.

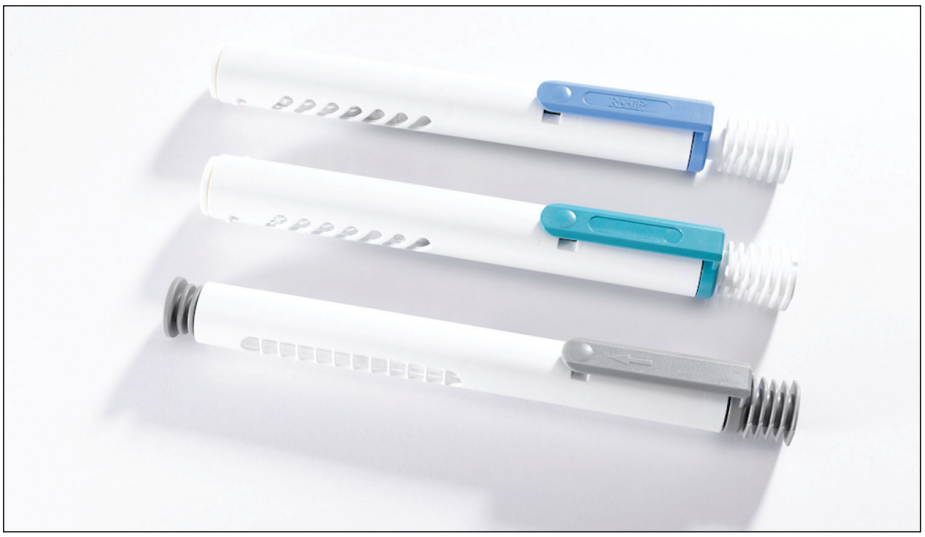

Figure 5: The disposable Penlet is a fully automatic, fixed-dose injection device designed for use with a standard 3 ml cartridge.

Penlet – disposable, fixed-dose injection device

The Haselmeier disposable Penlet is a fully automatic, fixed dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue which is followed by delivery of the solution. The Penlet features:
- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection

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