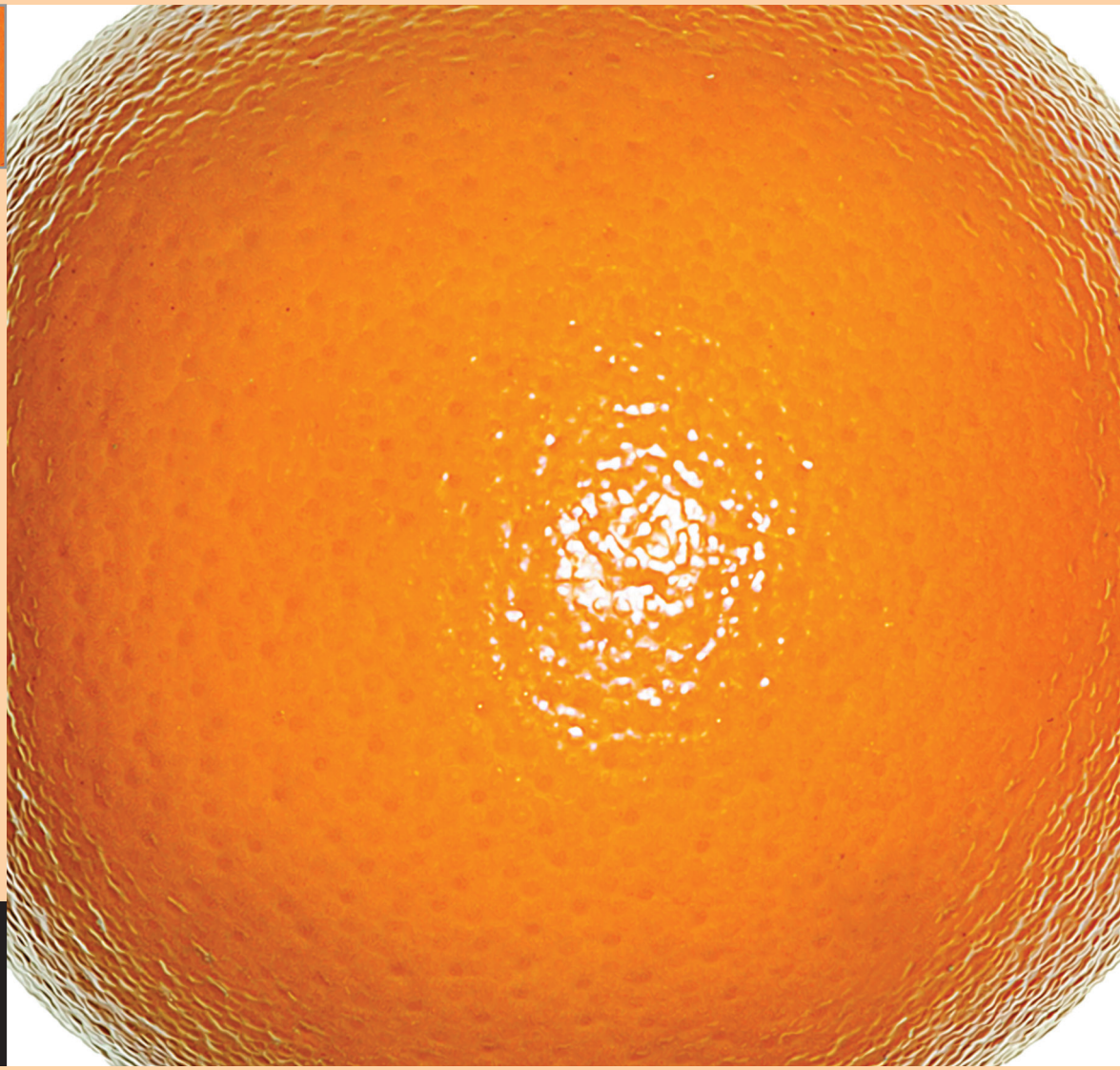
PREFILLED SYRINGES:

WITH THE PATIENT & SAFETY AT ITS CORE, THE MARKET RE-ALIGNS



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"Prefilled Syringes: With The Patient & Safety At Its Core, The Market Re-Aligns"

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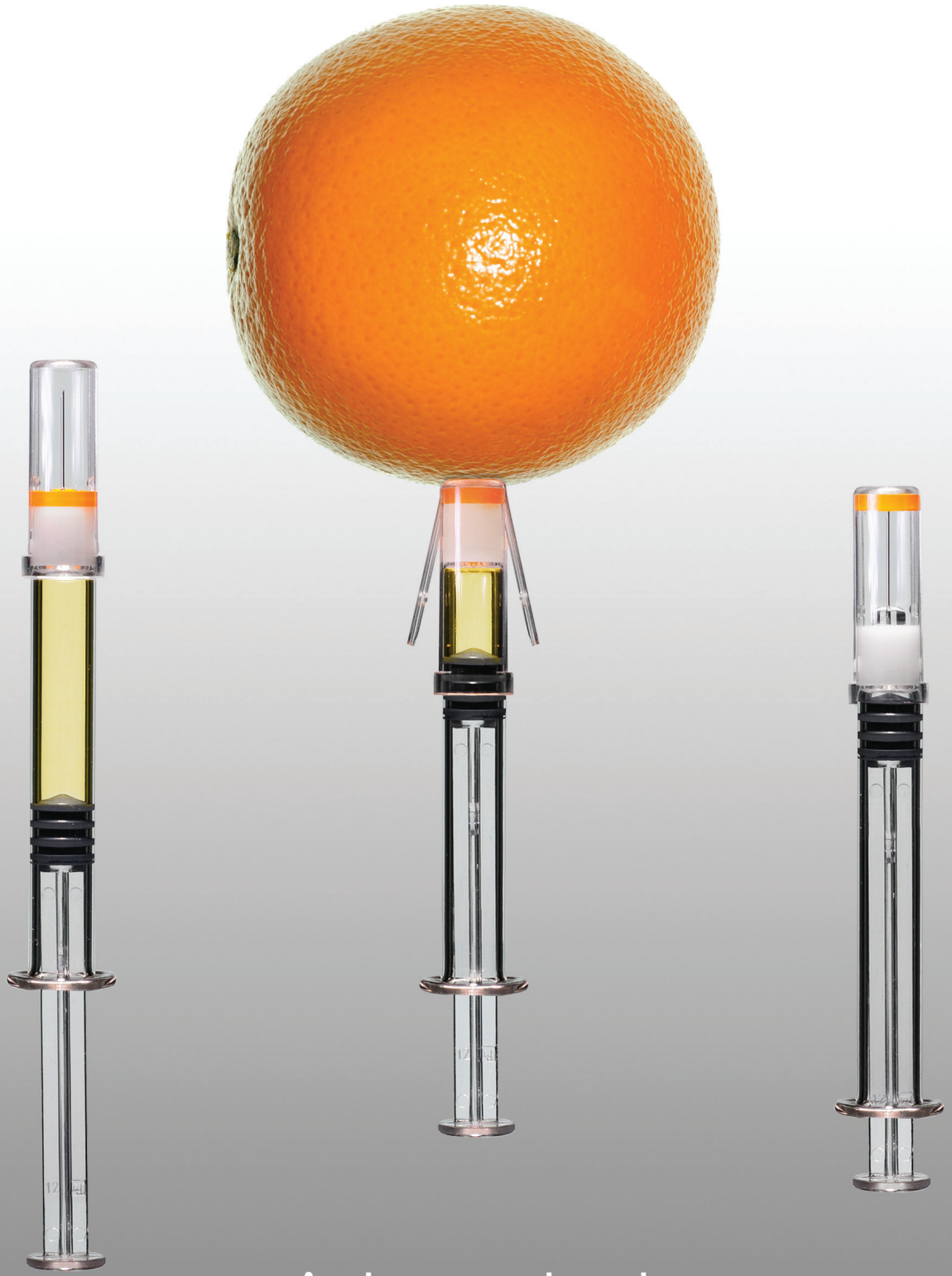

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SAFETY-ENGINEERED NEEDLE TECHNOLOGIES FROM TIP-TOP GAINING RECOGNITION AMONGST SYRINGE MANUFACTURERS

UPDATE

In this article, Barry Liversidge, Managing Director at tip-top, provides an update on how discussions with pharmaceutical companies and syringe manufacturers have confirmed that tip-top's minim and mini-Max safety needle systems offer a simple, safe, and cost effective way to provide passive needlestick protection for prefilled syringes.

Today worldwide, there are five principal manufactures of standard glass syringes – BD, Gerresheimer, Schott, Nuova Ompi and MGlas and, to all intents and purposes, these companies make almost identical prefillable syringe products to very similar specifications.

However, none of these syringe producers markets a prefillable syringe with inbuilt integrated needlestick protection; which means that pharmaceutical companies buying from these syringe makers, must then secondary-package their injectable drug products, with 'clip-on' accessories to provide some form of needlestick protection – because this is the only way to comply with requirements for syringe-based injectable drugs to be marketed with safety-engineered sharps protection.

It is important to consider why there are five independent manufactures producing almost identical prefillable syringe products; especially as the expression "product differentiation" seems to dominate the drug delivery industry. Nevertheless it is a fact, that the vast majority of parenteral drugs are packaged almost identically because over many years the prefilled syringe has become a universally preferred way to supply a ready-to-use injectable drug, and therefore pharmaceutical compa-

"SYRINGE MANUFACTURERS AND PHARMACEUTICAL COMPANIES RECOGNISE HOW TIP-TOP'S MINI-MAX SYSTEM WILL INTEGRATE PASSIVE NEEDLESTICK PROTECTION ONTO READY-TO-FILL SYRINGES WITHOUT HAVING TO REDESIGN THE PRIMARY DRUG CONTAINER."

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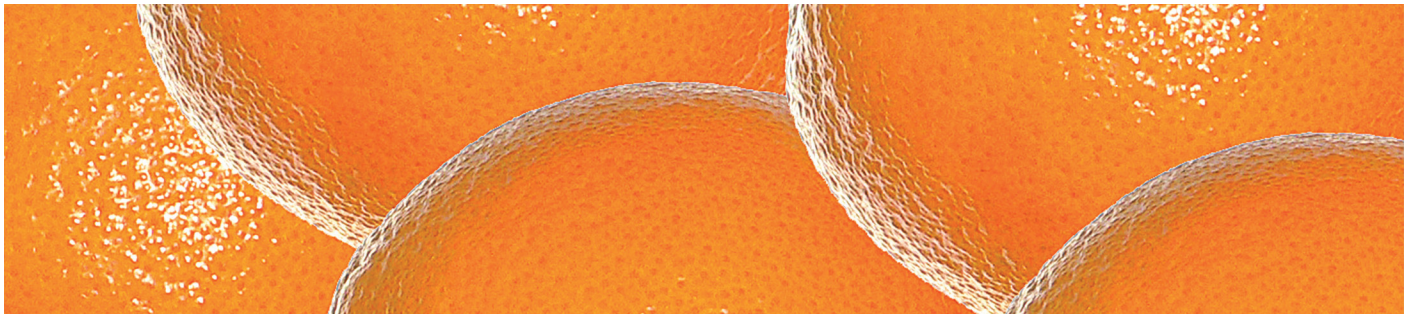


Historically, oranges were a popular choice for training injection techniques, because the outer peel and inner pulp simulates the "feel" of performing an injection.

Figure 1: mini-Max is fitted by the syringe manufacturer onto standard syringes. There are no compatibility issues with existing ready-to-fill infrastructures.

"IT IS IMPORTANT TO CONSIDER WHY THERE ARE FIVE INDEPENDENT MANUFACTURES PRODUCING ALMOST IDENTICAL PREFILLABLE SYRINGE PRODUCTS."

nies have generated a huge demand for a universal 'multi-sourced' product, and this demand has been satisfied by these five syringe producers.

Today however, the proliferation of needlestick legislation throughout the world, threatens the utility of the prefilled syringe because, whilst the ready-to-use convenience of the prefilled syringe defines its utility, if the syringe is not provided with safety-engineered needlestick protection, then it is not ready-to-use..!

The mini-Max system can enable existing manufactures to provide prefillable syringes with integrated passive needlestick protection, without having to redesign the primary drug container. And because the mini-Max system can be fitted to any manufacturer's syringe, the pharmaceutical industry's demand for a 'multi-sourced universal product', is easily satisfied.

Since their launch at the 2010 PDA *Universe of Prefilled Syringes and Injection Devices* conference in Las Vegas, NV, US, tip-top's innovative needlestick prevention technologies have been well received by both device manufactures and pharma companies. The minim and mini-Max devices, have attracted considerable interest from the major stakeholders in all quarters of the injectable drug delivery industry; and in particular syringe manufacturers and pharmaceutical companies recognise how tip-top's mini-Max system could integrate passive needlestick protection onto ready-to-fill syringes without having to redesign the primary drug container.

The mini-Max system is designed to maintain the fusion that exists between elastomeric

Figure 2: mini-Max comprises only a few plastic parts that do not require gluing or welding, and there is no metal spring.

component manufactures and syringe producers; so that passive needlestick protection can be integrated onto existing prefilled syringes, without major changes to Drug Master Files.

Furthermore, the mini-Max system is fitted by the syringe manufacturer onto standard syringes before the syringes are nested into the popular ready-to-fill Tray & Tub format. Thus, there are no compatibility issues with existing ready-to-fill infrastructures, due to the small size and shape of the mini-Max device (see Figure 1).

The advantages of mini-Max extend beyond the benefits of a system that will integrate seamlessly into existing syringe manufacturing and drug filing lines. mini-Max comprises only a few plastic parts (Figure 2) that do not require gluing or welding together, and there is no metal spring, yet the device is less than a quarter of the size and weight of clip-on secondary packaged safety-needle accessories.

Significantly, we estimate that 100 million prefilled syringes fitted with the mini-Max system, (instead of a clip-on accessory) would save 500 tonnes of plastic polymer, and that means 500 tonnes less plastic waste going into the environment.

Figure 3: Once assembled and packaged, staked-needle syringes fitted with mini-Max (left in blister pack and centre boxed) use only half the storage space, and are around 30% lighter, than the same syringes fitted with secondary-packaged clip-on safety shields (right).

Once filled and packaged, staked-needle syringes fitted with mini-Max take up around half the storage space, and are around 30% lighter, than syringes fitted with secondary packaged clip-on safety shields (see comparison in Figure 3).

The consequential savings arising from the mini-Max design cannot be understated. These significant savings are both financial and environmental:

- Reduced manufacturing cost of goods
- Reduced assembly and production costs – removing secondary packaging lines
- Reduced shipping and transport costs
- Reduced warehousing and cold-chain storage costs
- Freeing up costly space requirements on retail and hospital pharmacy shelves
- Reduced volumes of sharps waste – both storage and disposal
- Reduced environmental load – less waste and lowering demand for raw materials.

Syringes fitted with a mini-Max are used in the same way as the familiar, standard (non-safety-engineered) prefilled syringe; the difference is that mini-Max shields the needle before use, and automatically re-shields the needle after use, without the need for user intervention (Figure 4).

CONCLUSION

The key to understanding the mini-Max system is to recognise tip-top's commitment to facilitate the integration of passive needlestick protection onto EXISTING prefillable syringes, produced by EXISTING syringe manufacturers, for inclusion into EXISTING 'tray and tub' ready-to-fill formats.

tip-top's business model, is to make available the mini-Max technology, to enable syringe manufacturers to produce and supply products that fully comply with medical and pharma industries' requirement for better safety-engineered needle-based devices; whilst also removing the inconvenience and cost associated with having to provide secondary-packaging lines to fit needle-shielding accessories .

tip-top will be exhibiting (stand 24) at the 2011 PDA Universe of Prefilled Syringes and Injection Devices conference in Basel, Switzerland, this November.

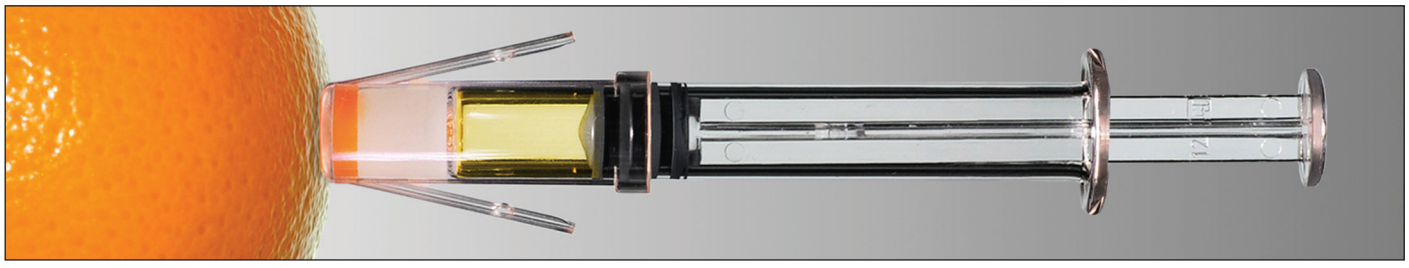
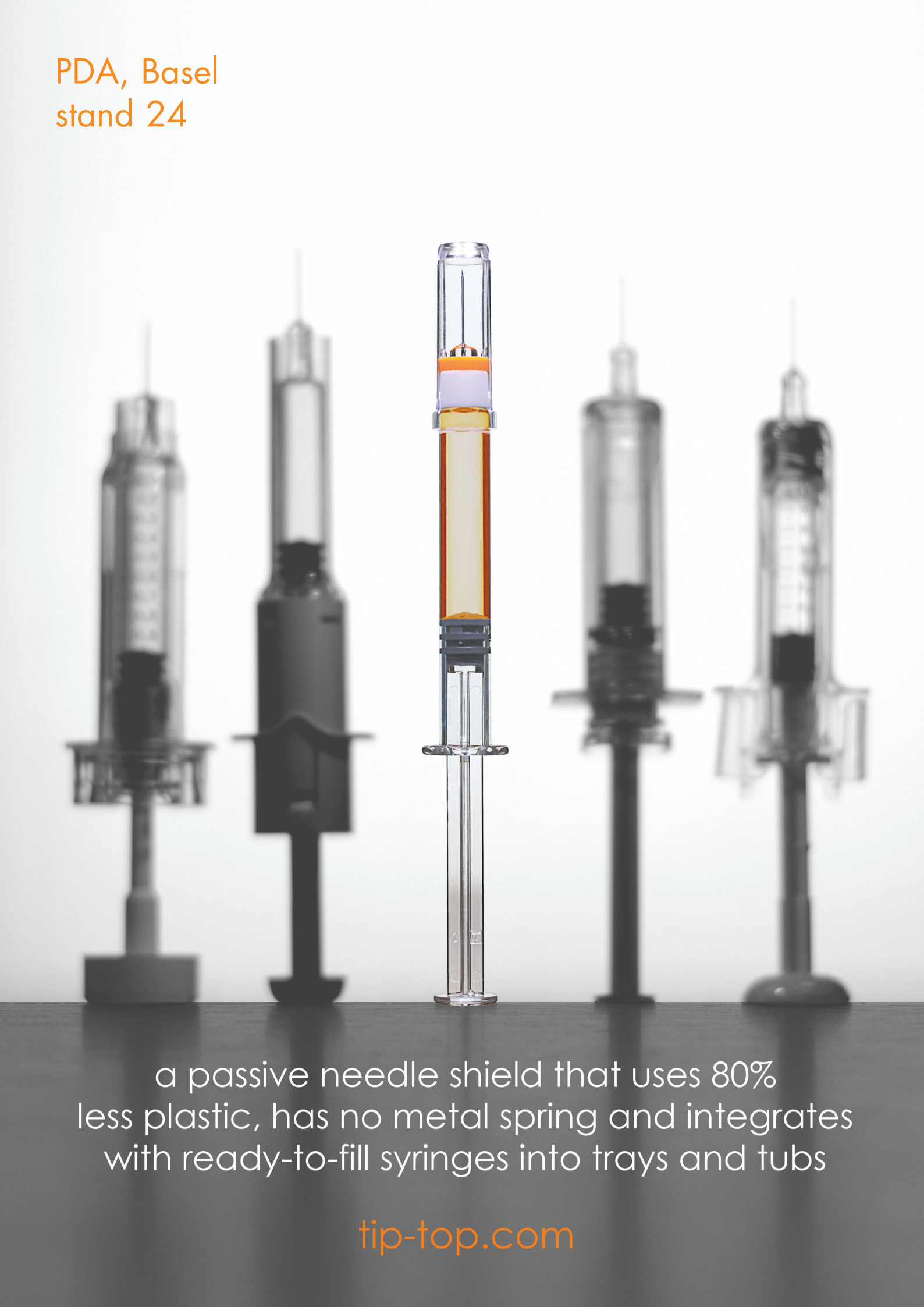


Figure 4: An industry-standard safety needle system by simply replacing the ordinary needle cover on a ready-to-fill glass syringe.

PDA, Basel
stand 24



a passive needle shield that uses 80%
less plastic, has no metal spring and integrates
with ready-to-fill syringes into trays and tubs

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TRANSFORMING A CLINICAL SAFETY DEVICE INTO A VIABLE SELF-INJECTION OPTION

This article by Alexander Jaksch, Vice-President, Business Development & Marketing, at Safety Syringes, Inc, highlights the importance of needlestick safety devices, describes business drivers, and outlines how a clinical safety product used by healthcare professionals all around the world is becoming a viable option for self-injecting patients. This is especially true with the integration of an add-on finger flange designed to help patients with debilitating diseases, such as rheumatoid arthritis, to administer injections.

Needlestick safety is especially important to many professionals in the healthcare industry. In March 2000 the US Centers for Disease Control & Prevention (CDC) estimated that more than 385,000 percutaneous injuries occur among healthcare workers from needles and other sharps used in the healthcare setting.[1] Published studies regarding needlestick safety and prevention have noted that the actual number could be as much as 70% higher.[2]

The cost and ramifications of an accident caused by a contaminated needle from a prefilled syringe can be disastrous. These events cause a risk of transmitting blood-borne diseases such as the Hepatitis B virus (HBV), the Hepatitis C virus (HCV) and the Human Immunodeficienty Virus (HIV). In the US, the short-term cost of caring for a needlestick injury is approximately US$2,500 (£1,590).[3] Safety-engineered devices have been shown to greatly reduce these injuries.[3] Some studies show a reduction of up to 80%.

As needlestick injuries become more recognised as occupational hazards, their prevention has become the subject of regulations in an effort to reduce and eliminate this preventable event from occurring.[4]

Several countries have implemented sharps injury prevention legislation mandating the use of safety devices. In 2000, the US enacted the *Needlestick Safety and Prevention Act,* Germany implemented *TRBA250* in 2007, Brazil passed rule *Norma Regulamentadora NR32* and last year the EU passed 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. Experts anticipate that this legislation will have a big impact on the presentation of injectable drugs, especially those in prefilled syringes.

Many pharmaceutical companies acknowledge this trend and, although these legislative measures are not targeting them directly yet, they see value for healthcare professionals as well as the need for hospital and doctor's offices to offer safer injection presentations.

BIOTECH PHARMACEUTICAL TREND

Over the past several years a continuously increasing number of biotech drugs have been offered in prefilled syringes. A widely cited report by the US Pharmaceutical Manufacturers Association (PhRMA) stated that by the end of 2008 approximately 633 biologics will be approved; the majority being monoclonal antibody therapies targeting chronic and auto-immune diseases like rheumatoid arthritis (RA), psoriasis or multiple sclerosis (MS).

These drugs typically need to be given either through an iv or a sc injection and the latter tends to be the preferred route of administration because patients can give the injection themselves. This method prevents them from having to go into a doctor's office for therapy, thus offering more convenience for the patient but also saving on healthcare costs.

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Figure 1: The UltraSafe Passive® Needle Guard.

Figure 2: Design Features of the Ultrasafe Passive® Needle Guard, Such As the Plastic Housing, Square Design and the Finger Flange, All Improve Handling and Comfort.

SELF-INJECTION DEVICES

Depending on the formulation, biotech drugs, and especially monoclonal antibody therapies, can be quite viscous, making them more difficult to inject. This is especially true for patients who suffer from debilitating diseases such as RA.

Self-injecting patients are trained to perform their own injection when they receive treatment for the first time. This situation cannot be compared with that of an experienced healthcare professional who has performed injections for many years and, thus, in the self-injection setting, pharmaceutical companies have attempted to meet their user's needs by offering auto-injectors in a variety of designs, shapes and with different actuation mechanisms.

In addition, pharmaceutical companies use injection device presentation increasingly as a product differentiator as certain target markets become more crowded – a prime example of this is the RA market. RA therapies are highly specialised and are traditionally very expensive for patients. There is a growing expectation among patients that these drugs be presented in higher-value devices – a "mere prefilled syringe" would neither meet their expectations, nor their needs.

Most of today's auto-injection devices are disposable (one-time use) and host a conventional 1 mL prefilled syringe. The majority of these products address needlephobia by hiding the needle from view before injection and covering it after completion. Covering the needle prevents accidental needlestick injuries.

As much as auto-injectors represent a convenient and preferred injection option for many self-injecting patients, they also bring disadvantages for the patient such as: increased size, noise (which can be associated with pain) and increased pain during the injection. This points to a considerable percentage of the patient population, who prefer the flexibility and control of a prefilled syringe over an auto-injector.

Many auto-injectors are not "off-the-shelf" products but are designed to inject a particular drug – which makes this technology less versatile for companies' differing drug portfolios. Pharmaceutical companies introducing an auto-injector for their specific drug must be prepared for a large upfront investment which could be up to US$10 million (£6.5 million), including capital equipment, labour, and design and development fees.

ULTRASAFE PASSIVE® NEEDLE GUARD

As an alternative to auto-injectors, pharmaceutical companies acknowledge that a safety device adds several advantages to a prefilled syringe. Consequently, in some instances, companies offer their injectable drug in both an auto-injector and safety device presentation. One example of this is Simponi (golimumab), an RA drug from Janssen Biotech, Inc (Horsham, PA, US).

Several studies have confirmed that the safety aspect of an injection device is highly valued with self-injecting patients and vastly preferred over a bare prefilled syringe.[5] However, it is important to carefully select the right product. Passive safety technology (automatic activation), like the UltraSafe Passive® Needle Guard (Figure 1), has been proven to be the most effective at avoiding accidental needlestick injuries.[6] This is compared with manual safety technology, which requires an additional manual operation after the injection is given. The superiority of passive safety technology arises perhaps because most needlestick injuries happen in the few seconds after needle withdrawal.[7]

It is crucial that the needle is shielded right after the injection without the user having actively or manually to initiate the safety mechanism. Any need for a deliberate action can leave open the possibility of simply omitting such a step resulting in an unshielded needle until disposal.

A bare prefilled syringe gives patients more control over their needle insertion, drug dispensing speed and injection angle than they would have with an auto-injecting device. However, handling is not optimal. Adding a safety device such as the UltraSafe Passive® Needle Guard (shown in Figure 2) increases handling comfort significantly over a bare prefilled syringe by adding the following design features:

- plastic housing: protects the glass syringe and increases gripping surface area
- plunger head: larger and concave shape offers additional support during injection
- finger flange: provides stability and additional leverage; especially helpful for more viscous drugs
- square design: prevents the device from rolling off of an uneven surface

Some of these design attributes were included in a poster presentation by Dr Anthony Andre, Co-Founder and Principal, Interface Analysis Associates (San Jose, CA, US, at the 2010 PDA Universe of Prefilled Syringes & Injection Devices conference in Las Vegas, NV, US) in which guidance was given on how to make prefilled syringes more ergonomic, usable and human-centered.[8]

ULTRASAFE PASSIVE® NEEDLE GUARD WITH FINGER FLANGE

Safety Syringes, Inc (SSI) has developed an add-on finger flange for its UltraSafe Passive® Needle Guard safety device to make it an even more attractive injection option for self-injecting patients. The device with finger flange is shown in use in Figure 3 (A) before and (B) after injection.

HUMAN FACTORS & DESIGN

The fundamental design of the add-on finger flange was carefully chosen by per-

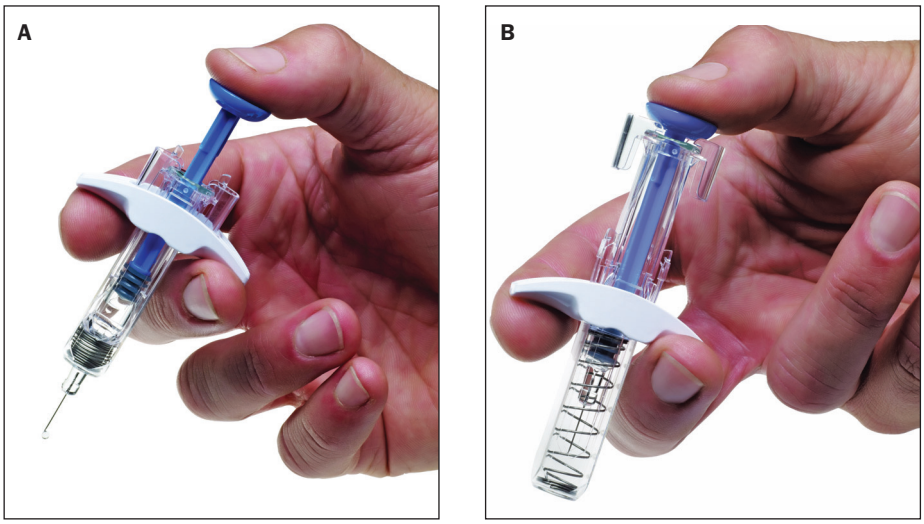

Figure 3: The UltraSafe Passive® Needle Guard with add-on Finger Flange Shown (A) Before Use and (B) After Use.

forming handling studies with self-injecting patients. Patients in this study suffered from RA, psoriasis or MS. These diseases can have very different effects on dexterity and these limitations were used in this study to select the optimal design.

Results of this market research found that patients with RA preferred to place the finger flange in the joint proximal to the finger tip. This way there was more leverage as opposed to using the end of the fingers, which can cause pain in inflamed joints. MS patients, on the other hand, preferred to place the finger flange on their finger tips. Because of this, a larger surface area was preferred, as MS patients suffer from a loss of sensitivity. Increased surface gives them more assurance and stability during their injection. The study required all patients to perform injections with eight finger-flange designs and rank them according to handling preference. Aesthetics, design fit, and confirmation that the designs did not create improper use of the syringe were also taken into account.

MANUFACTURABILITY

After the fundamental design (shape and size) of the finger flange had been determined, SSI consulted with leading assembly machine companies to ensure manufacturability of the finger flange was possible in an automated process. It was ideal to have this operation located close to the syringe/device assembly station to ensure the most efficient final product assembly.

Following this step of the design review process, SSI adjusted the side surface of the finger flange ensuring that there was enough space for suction cups to pick up the device and place it in a blister for final packaging (Figure 4).

MATERIAL AND MOLDABILITY

For optimised molding propensities such as favourable glass transition points and to fulfill ISO 10993 requirements, SSI chose a medical grade polymer. The final material characteristics had to be soft enough for an easy snap-on during automated assembly, yet ridged enough for the intended end-user applications.

The result of this was a design which not only met user criteria but also met manufacturing challenges for pharmaceutical companies. The finger flange should be commercially available in the first quarter of 2012.

SUMMARY

An increasing number of injectable drugs are being offered for self-injection. Patients, especially those with limited dexterity, have very specific needs and requirements for the injection device. Most self-injection drugs, in particular the high-value drugs, are offered today in auto-injecting devices, which offer convenience to a lot of patients but do not fulfill the entire spectrum of injection needs. Many patients want to control their injection and are wary of the technology behind auto-injectors. For this patient population, adding a safety device already brings enormous benefits to a prefilled syringe presentation – the option of extended finger flanges for this device/syringe combination makes it an even more desirable option for self-injection. A relatively small add-on feature can make a big difference for self-injecting patients.

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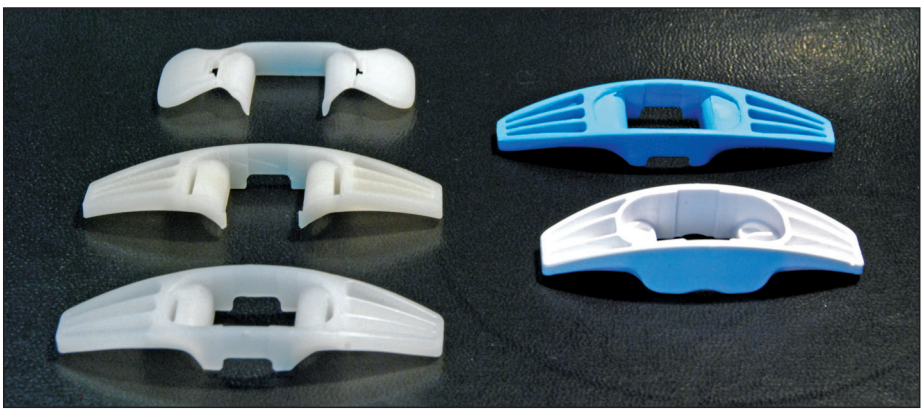

Figure 4: Development of SSI's Add-On Finger Flange with Final Design Shown Bottom Right.

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DIFFERENTIATION WITHOUT DISRUPTION

In this article, Alan Shortall, Chief Executive Officer, Unilife Corporation, describes a new paradigm now driving the pharmaceutical market for advanced drug delivery systems, where the composition of clinical development pipelines is being increasingly dominated by complex injectable drugs, such as biologics, with specific molecular and formulation requirements that are targeted for patient self-administration. He argues that in many cases the combination of these large-molecule drugs with delivery systems comprised of commodity components sourced from conventional device manufacturers can constrain or diminish their commercialisation and marketability across highly competitive therapeutic classes. Instead, pharmaceutical companies are seeking to build long-term partnerships with a new generation of device manufacturers who specialise in the design, development and commercial supply of innovative delivery systems that can enable the commercialisation of pipeline drugs, enhance or extend product lifecycles and generate strong brand differentiation.

Pharmaceutical companies with access to best-in-class delivery systems that can enhance patient care, protect healthcare workers or improve therapy compliance are well positioned to succeed across therapeutic classes facing heightened levels of competition amongst novel, generic or biosimilar drugs.

The development of these strong long-term partnerships between pharmaceutical companies and device manufacturers are ultimately focused on the development of the right device to deliver the right drug to the right patient. Collaborations between device manufacturers and pharmaceutical companies can commence early during the clinical development of the drug and span the entire commercial lifecycle of the combination product.

"UNLIKE CONVENTIONAL DEVICE MANUFACTURERS THAT SUPPLY "ME-TOO" COMMODITY COMPONENTS, UNILIFE SERVES AS A TOTAL SOLUTIONS PARTNER FOR ADVANCED DRUG DELIVERY SYSTEMS."

To succeed under this new industry paradigm requires device manufacturers to have a diversified portfolio of delivery systems, an advanced array of operational capabilities and the flexibility to respond to the needs of the pharmaceutical customer with speed, agility and reliability.

UNILIFE – AN EMERGING GLOBAL LEADER FOR ADVANCED DRUG DELIVERY SYSTEMS

Unilife is a fast-growing US-based developer and commercial supplier of advanced drug delivery systems. In direct response to the unmet needs of pharmaceutical companies, healthcare workers and patients, Unilife has developed one of the most complete and customer-focused portfolios of injectable drug delivery devices on the market. A rich portfolio is led by the Unifill range of ready-to-fill syringes with integrated safety features (Figure 1), and also includes patient self-administration systems such as auto-injectors and subcutaneous pump infusion systems, as well as other specialised devices for targeted organ delivery. The size and scope of this unique portfolio, the depth of our operational capabilities and our unparalleled capacity for device innovation together enable Unilife to address the specific molecular, formulation and

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patient requirements of injectable drugs supplied in either a liquid-stable or lyophilised form for reconstitution at the point of delivery.

Unlike conventional device manufacturers that supply "me-too" commodity components, Unilife serves as a total solutions partner for advanced drug delivery systems. Our centre of operations is a state-of-the-art manufacturing facility located in York, PA, US (Figure 2). This modern $32 million (£20 million) facility was opened in late 2010 and serves as an integrated centre for device innovation. At York, Unilife has brought together the people, production systems, design expertise and quality processes necessary to design and develop best-in-class drug delivery systems targeted for use across a range of therapeutic classes. Designed by pharmaceutical architects to be ahead of the curve in the design, production and supply of medical devices, the US FDA-registered site plays a key role in ensuring that we comply with stringent internal and industry standards for quality and reliability.

The 165,000 square-foot (15,300 m^2) facility includes 11 cleanrooms, a product development centre, quality labs, machine shops and a fully segregated warehouse. Activities undertaken at the site include device design, rapid prototyping, pilot and commercial production, bio-analytical testing, packaging, quality assurance and supply chain. All activities at Unilife are guided by advanced business systems, such as SAP ERP (SAP AG, Walldorf, Baden-Württemberg, Germany), that complement those of our pharmaceutical partners.

Our Quality Management System is fully certified to ISO 13485, and in compliance with 21 CRF 210/211 for pharmaceuticals and 21 CFR 820 for medical devices.

UNIFILL PLATFORM OF PRIMARY DRUG CONTAINERS WITH INTEGRATED SAFETY FEATURES

We have developed a full platform of Unifill ready-to-fill syringes that are designed for use with a broad range of liquid-stable and lyophilised drugs and vaccines targeted for delivery in a prefilled format. Unifill syringes function as a primary drug container, a safety device and a needle containment system all rolled into one.

Figure 1: The Unifill syringe, shown here before and after use, is the first and only known prefilled syringe with safety features fully integrated within the glass barrel.

Available in both single and multiple chamber formats with either a staked or an attachable needle, Unilife syringes feature a unique automatic needle-retraction mechanism that is activated upon full-dose delivery. With activation of the safety mechanism signaled by an audible, tactile click, Unifill syringes have a true end-of-dose indicator. Operators can control the speed at which the needle is withdrawn directly from the body into the barrel of the syringe. The plunger is then automatically locked to prevent the re-use of the device, circumvent product tampering, and encourage its convenient and compact disposal.

All Unifill components within the fluid path feature USP Class six-compliant materials sourced from established suppliers, with the devices designed for customer supply as per standard handling systems for equivalent syringes for integration into fill-finish systems. As a primary drug container with integrated safety features, Unifill syringes can streamline pharmaceutical industrial processes and significantly reduce transport, packaging and storage costs associated with the attachment of ancillary safety products.

"UNIFILL SYRINGES ARE ALSO SIMILAR IN SIZE TO AN EQUIVALENT PREFILLED SYRINGE AND SIGNIFICANTLY SMALLER THAN THOSE ATTACHED WITH AN ANCILLARY SAFETY PRODUCT TO REDUCE PACKAGING, TRANSPORT AND STORAGE VOLUMES BY UP TO 60-70%."

UNIFILL SYRINGE

The Unifill syringe is the world's first and only prefilled syringe with automatic safety features fully integrated within the glass barrel. It is

Figure 2: Unilife's Centre for Operations in York, PA, US, Designed by Pharmaceutical Architects and Purpose Built to be Ahead of the Curve.

Figure 3: Unifill Select combines the benefits of automatic, fully integrated safety features with the ability to attach interchangeable needles.

primarily designed for use with injectable drugs and vaccines between 0.2 mL and 1.0 mL in volume and indicated for subcutaneous injection. It is currently available with a staked (fixed) ½" needle in either a 27- or 29-gauge format.

The Unifill syringe is supplied to pharmaceutical manufacturers as per standard handling processes, and designed for integration into the fill-finish systems used for equivalent conventional ready-to-fill syringes. The Unifill syringe can eliminate the current requirement to purchase separately and attach ancillary safety products onto a standard prefilled syringe after dose filling and prior to packaging. Unifill syringes are also similar in size to an equivalent prefilled syringe and significantly smaller than those attached with an ancillary safety product to reduce packaging, transport and storage volumes by up to 60-70%.

The combination of automatic, operator-controlled retraction features within the Unifill syringe helps to virtually eliminate the risk of infection from needlestick injuries or other potential transmission modes including aerosolisation (splatter). Independent evaluations of the Unifill syringe comparing it with leading prefilled syringes supplied with ancillary safety devices found experienced healthcare workers strongly preferred it across all surveyed areas including safety, ease-of-use, handling and intuitiveness.

The Unifill syringe is now in initial production at our production facility in York, and available for supply to pharmaceutical customers for compatibility and stability testing.

UNIFILL SELECT

The Unifill Select range of ready-to-fill syringes combines the benefits of automatic, fully integrated safety features with the ability to attach interchangeable needles of up to 1½" in length (see Figure 3). Unifill Select syringes facilitate the use of injectable drugs and vaccines between 0.2 and 1.5 mL in volume that are supplied in either a liquid-stable form or lyophilised for reconstitution.

Unifill Select delivery systems are supplied as per standard handling systems for integration into fill-finish systems used for equivalent conventional 1mL standard, 1mL long or larger prefilled syringes. As primary drug containers with USP Class six-compliant materials within the drug fluid path, Unifill Select products are similar in size to equivalent prefilled syringes. Select products may be supplied ready-for-injection in a kit format with one or more needles for intuitive and convenient administration either directly to the patient or via an iv port.

"UNIFILL EZMIX SYRINGES FEATURE TWO OR MORE PRIMARY DRUG CONTAINERS WITHIN A SINGLE GLASS BARREL."

The safety and functionality benefits of the Unifill syringe and its unique ergonomic styling to prefilled devices can be utilised by pharmaceutical companies to extend product lifecycles, increase levels of market differentiation in competitive therapeutic areas, and expand the marketability of drugs for convenient self-administration by patients outside of the healthcare setting.

In addition to its targeted use with drugs supplied in a liquid-stable format, the Unifill Select can also be prefilled with a diluent and packaged with a vial adaptor for use with lyophilised drugs requiring reconstitution. As a unique delivery system for liquid-stable drugs targeted for im injection, or other lyophilised drugs, Unifill Select syringes are ideally positioned to generate brand differentiation for drugs marketed within competitive therapeutic classes to optimise product lifecycles.

UNIFILL EZMIX

Unifill EZMix syringes have been developed in direct response to the unmet needs of pharmaceutical companies seeking an innovative and convenient delivery system for the reconstitution and administration of lyophilised drugs and vaccines. Unifill EZmix syringes feature two or more primary drug containers within a single glass barrel to store a combination of liquid stable or lyophilised drugs along with up to 1mL of diluent for reconstitution.

In addition to being the world's first and only known dual or multi-chamber prefilled syringes with automatic (passive) safety features fully integrated within the glass barrel, the Unifill EZMix syringe offers minimal steps of use for healthcare workers and patients alike. The operator simply advances the plunger to mix the lyophilised powder with the diluent, before swirling the device to complete reconstitution. An audible, tactile click signals the injection of the full dose and the activation of a passive safety system that allows operators to control the speed of needle retraction directly from the body into the barrel. The Unifill EZMix syringe has been designed for development in either a fixed (staked) needle for drugs indicated for sc injection, or with attachable needles of up to 1.5 inches (3.8 cm) in length.

UNIFILL AUTO-INJECTORS

The Unifill range of auto-injectors has been designed for the accurate, intuitive and convenient administration of injectable drugs by patients outside of healthcare facilities. Developed for use in conjunction with Unifill prefilled syringes, Unifill Auto-Injectors are extremely compact, and enable patients to inject a measured dose of medication with the simple push of a button. Unlike conventional auto-injector technologies that are used with standard prefilled syringes, the incorporation of the Unifill syringe with its integrated safety features give Unifill Auto-Injectors several significant market advantages including a relatively small diameter and a true end-of-dose indicator.

Unifill Auto-Injectors are being developed in a range of single-use disposable and re-usable configurations for use across a wide spectrum of therapeutic drug classes. The devices can be custom-designed to support a range of drug viscosities and patient dexterity requirements. With the increasing standardisation of many injectable drugs across a number of therapeutic classes in both a stand-alone prefilled syringe format and

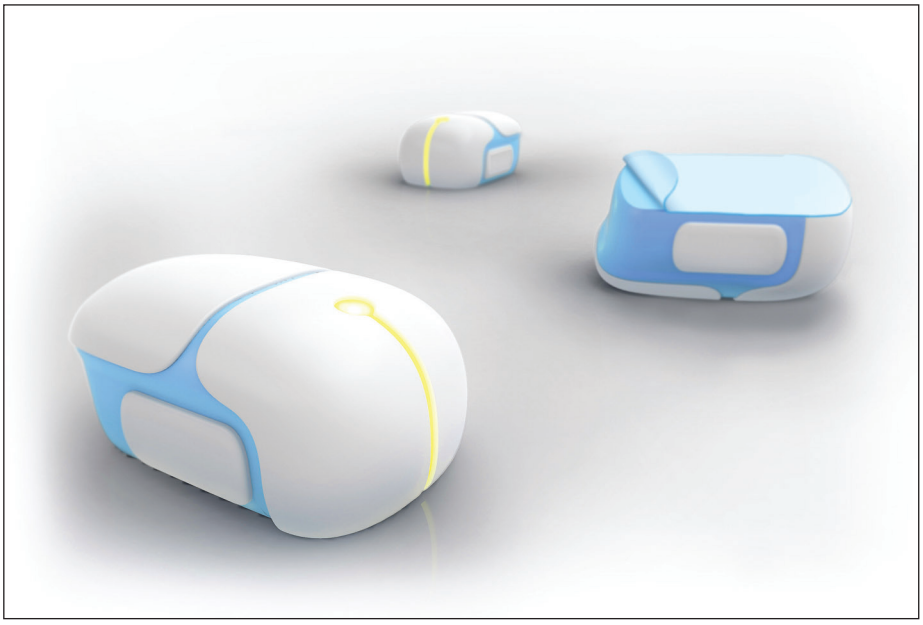

Figure 4: AutoInfusors are now available for human clinical trials in either prefilled or fill-at-time-of-use formats.

supplied with an auto-injector, the combination of the Unifill syringe and a compact, accurate auto-injector under one best-in-class technology platform can streamline the pathway to commercial launch and generate powerful brand differentiation during the product lifecycle.

AUTOINFUSORS

We have developed a proprietary range of single-use, disposable subcutaneous infusion pump systems for the patient self-injection of drugs between 3 mL and 10 mL in volume.

Unilife has developed its AutoInfusor technology (shown in Figure 4) to address the unmet needs of pharmaceutical and biotechnology companies with drugs that have complex formulations with higher viscosities and requiring large dose volumes. AutoInfusors are now available for supply to pharmaceutical companies for human clinical trials in either prefilled or fill-at-time-of-use formats. AutoInfusors are compact, single-use drug delivery systems that are designed for simple, intuitive and convenient use by patients outside of healthcare facilities. Consisting of a primary drug container, fluid delivery path, and drive mechanism, AutoInfusors are modular in design and can be customised to address the specific requirement of the drug and its target patient. They can be pre-set for infusion periods that can span minutes or hours in duration, as specified by the pharmaceutical customer.

> "ONCE THE PATIENT ATTACHES THE DEVICE ONTO THE INJECTION SITE AND PUSHES THE ACTIVATION BUTTON, THE AUTOMATIC INFUSION OF THE DRUG INTO THE SUBCUTANEOUS TISSUE COMMENCES."

Once the patient attaches the device onto the injection site and pushes the activation button, the automatic infusion of the drug into the subcutaneous tissue commences. With the size, shape and functionality of the AutoInfusor being ergonomically designed for optimal wearability, the patient can continue to go about their normal daily routines during the period of dose delivery. A series of audible, tactile and visual indicators can signal to the patient when the full dose has been delivered, at which time the AutoInfusor can be removed from the body for convenient disposal.

NOVEL DEVICES FOR TARGETED ORGAN DELIVERY

We work with pharmaceutical companies to develop specialised drug delivery systems to administer biologics and other macromolecular drugs that require high-precision administration to target organs of the human body. For these projects, we collaborate directly with our pharmaceutical customers early in the development phase to identify and address the specific molecular and patient requirements of a target pipeline drug.

By addressing the specific device innovation needs of our pharmaceutical customers in parallel with the development of the target pipeline drug, the specialised organ delivery systems that we deliver to our pharmaceutical customers can help to support successful clinical trial outcomes and the filing of regulatory applications with strong claims for the combination product. In addition, our proprietary organ delivery systems can help to generate strong brand differentiation for the target drug, and potentially obstruct the entry of other brand-name, biosimilar or generic competitors.

With Unilife, pharmaceutical and biotechnology companies now have the option of selecting a single partner in the development and commercial supply of innovative, differentiated devices that can help to enable, enhance and extend the commercial lifecycles of their injectable drugs and vaccines.

Pharmaceutical customers are encouraged to contact Unilife at info@unilife.com.

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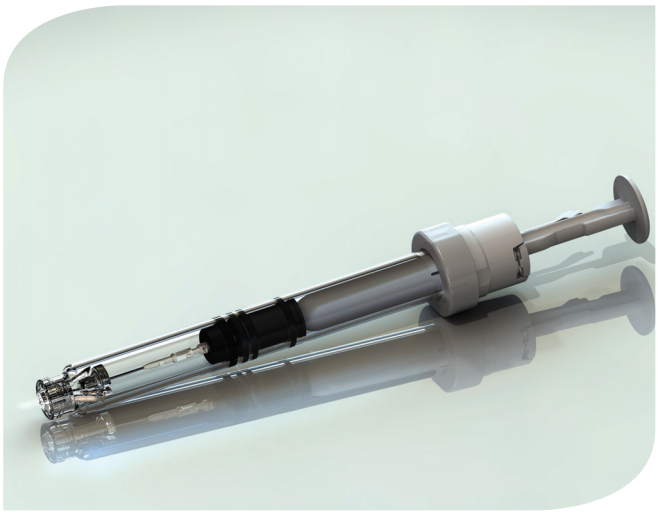

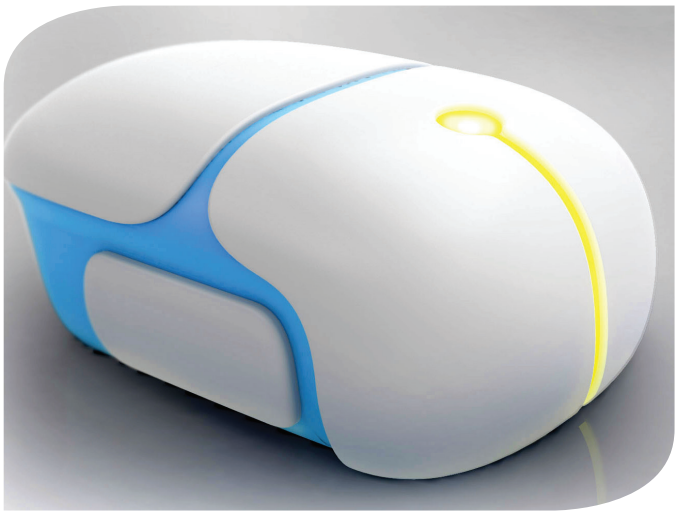

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PRODUCTION TECHNOLOGY

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 Maschinen und Anlagen GmbH 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.

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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.

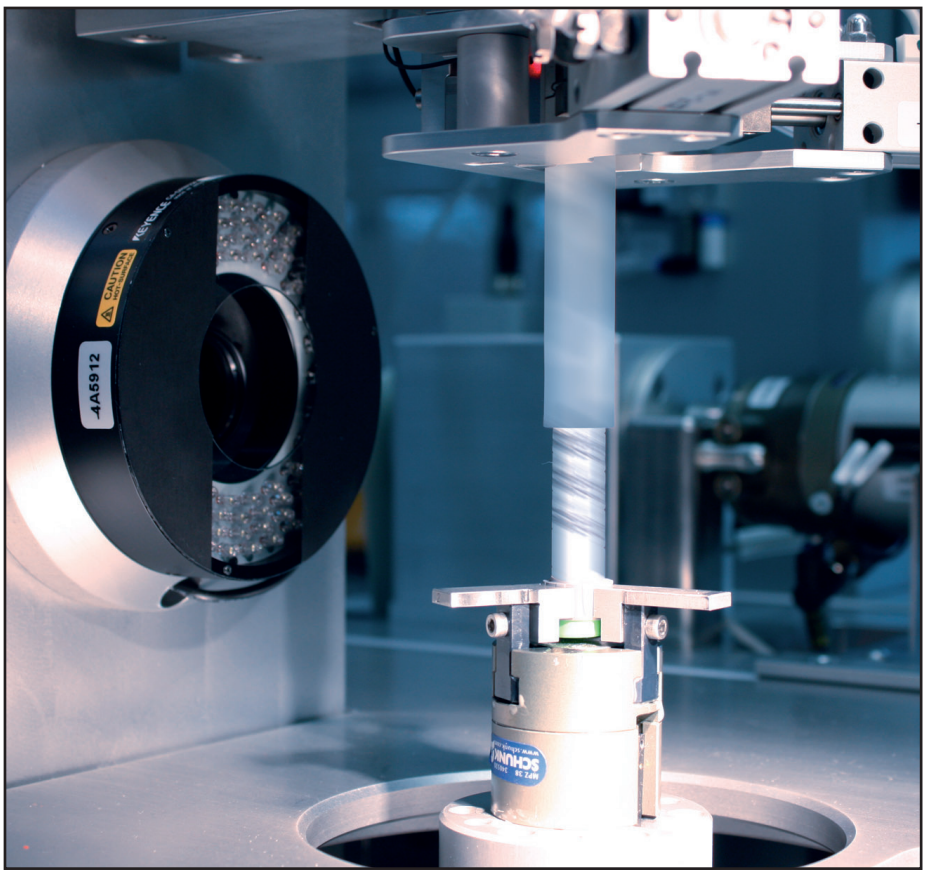

Figure 3: Integrated Pen Testing Application

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.

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DEVELOPING CONTAINERS AND DEVICES TO MEET EMERGING AND EVOLVING PARENTERAL NEEDS

Detailing as its backdrop the rise of biologics, this piece from Justin Wright, PhD, Director of Pharmaceutical Development at BD Medical - Pharmaceutical Systems, describes how the top-flight of prefilled syringe and component manufacturers must adapt and are adapting to the current market, regulatory and clinical changes taking place in the sector.

INTRODUCTION

Injection and infusion are the prevalent delivery option for most biologics. Fortunately, users of injectable biotherapeutics have at their disposal not just prefilled syringes but a wide choice of needle technologies, pens, auto-injectors, and other injection-ready devices, with the prospect of emerging injection systems yet to come.

Commercial strategies utilising delivery systems help differentiate products within a therapeutic class and are expected to become a factor in market acceptance of biosimilars, as well as franchise extension and differentiation of existing therapies.

As biologics and vaccines continue to become more complex in their chemical compositions, formulations, and end-user requirements, products under development today require container and delivery technologies that surpass those of even five years ago.

The progression of biologics and vaccines illustrates an interesting dynamic in the evolution of delivery systems. As drug product complexity rises and end-user requirements emerge, quality and regulatory expectations increase. As such, a robust platform of engineering, science, manufacturing and a keen regulatory perspective is needed in order to successfully develop and commercialise these products.

"AS BIOLOGICS AND VACCINES CONTINUE TO BECOME MORE COMPLEX IN THEIR CHEMICAL COMPOSITIONS, FORMULATIONS, AND END-USER REQUIREMENTS, PRODUCTS UNDER DEVELOPMENT TODAY REQUIRE CONTAINER AND DELIVERY TECHNOLOGIES THAT SURPASS THOSE OF EVEN FIVE YEARS AGO."

MARKETS

Thirty years into the biotechnology era, biologics are on the verge of attaining revenue parity with small-molecule drugs. In 2000, just two of the twenty top pharmaceutical products sold in the US were biologics; a decade later, six molecules made the list. A study by EvaluatePharma predicts that by 2016, ten of the 20 leading US drugs by sales – and seven of the top eight – will be biologics and

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comprise 88% – US$50.2 billion of $56.5 billion (£32.2 billion of £36.2 billion) – of sales.

The major product categories for these products, monoclonal antibodies and vaccines, have distinct requirements for formulation, delivery and prefilled container.

BD estimates that between 2010 and 2015 the use of vials will remain nearly constant for all injectable drugs: the use of prefilled syringe will grow by 6%; pens and cartridges will grow by 11% for all injectables and by 22% for biotech drugs.

Adoption of advanced delivery systems is driven primarily by medical need, administration setting, and end-user requirements. BD estimates that in 2010 the leading conditions for which patients self-inject were multiple sclerosis (61%) and rheumatoid arthritis (24%). By 2015, the rheumatoid arthritis market segment will remain constant, but new indications, for example, non-biologic diabetes drugs, will increase from 1% of the market to 5%.

Small-molecule and biologics will both be hit hard by the looming "patent cliff." But, where non-biologics lose 90% of market value due to patent expiration nearly overnight, biologics are expected to experience a relatively soft landing and only modest price erosion as the clarity on the regulatory pathway for follow-on biologics becomes more apparent.

Vaccines are in a unique position as they do not have the patent cliff to contend with, and many companies are diversifying their portfolio to include vaccines.

Biosimilar approvals in the US and EU have been limited thus far to well-characterised human growth hormone and haematopoietic cytokines. Nevertheless, the inevitable emergence of a robust market for biosimilars and biobetters has the potential to alter the drug delivery environment for both follow-on and originator molecules as sponsors seek differentiation strategies before prescribers, patients, and pharmacy plans.

BENEFITS AND CONSIDERATIONS

Prefilled, single-dose delivery systems provide convenience to healthcare providers as well as to patients with chronic illnesses and medical practices that serve them. These ready-to-use systems are inherently designed to improve safety by eliminating potential errors associated with dose manipulation and transfer. While at times the principal trade-off may come in the form of a slightly higher unit cost associated with the delivery system, the corresponding effects, from patient outcome to sytem wide, can far outweigh this trade off.

Within the context of this environment reimbursement is a key consideration not only for the drug, but for the delivery system and the combination. Moving forward, end-users, both patients and healthcare providers, will continue to demand delivery systems that provide improved features that impact their successful use. For patients, this might mean less injection pain and/or less-frequent dosing for injectable drugs – factors that will improve adherence and reduce the number of unused doses – all of which are important in the current reimbursement landscape.

"BETWEEN 2010 AND 2015 THE USE OF VIALS WILL REMAIN NEARLY CONSTANT FOR ALL INJECTABLE DRUGS: THE USE OF PREFILLED SYRINGE WILL GROW BY 6%; PENS AND CARTRIDGES WILL GROW BY 11% FOR ALL INJECTABLES AND BY 22% FOR BIOTECH DRUGS."

For healthcare providers, quantifying the value added by advanced delivery systems to medical environments like hospitals, clinics, pharmacies and the home is a complex task. Each setting and drug demands separate considerations. Properly assessing benefits and risks of advanced delivery systems can only occur when one considers healthcare economics from the micro (patient or healthcare worker) level, to the macro (institution or system reimbursement) level.

RISING NEEDS AND EXPECTATIONS

Top developers of delivery systems employ a "systems-based" approach to design, development, and deployment of these products. As part of this strategy, companies scrutinise compatibility of drug and container, consider human factors related to use and comfort (for both patient and, if not self-administered, for healthcare workers), focus on preventable defects, and establish solid post-marketing surveillance programs.

Emerging delivery technologies always receive close scrutiny from regulators, who are keenly aware of their complexities and potential for altering the drug's activity through materials of construction or design. And as more advanced delivery systems enter the marketplace stakeholders – including regulators – become more knowledgeable. From BD's perspective, the timeframe for significant changes or additions to delivery system regulations is approximately six to eighteen months with respect to expectations on testing and qualification. This timeframe includes data generation, submission and approval by the Agency. These regulatory uncertainties force developers to adopt risk management and operational excellence as a normal part of business.

Regulators, advocacy groups, and patients demand that developers assure safety and efficacy before products enter the healthcare system, and monitor them carefully thereafter. Components of a strategy to meet such expectations include consideration of a product's appropriateness, intuitiveness, safety, required training, and implications of its misuse.

Just a few years ago, when trained healthcare workers were the primary dispensers of injected drugs, many of these factors were not considered to the extent that they are today, even by regulators. As the migration of care expands beyond traditional clinical settings, new medical homes are adopted, and more patients self-administer, understanding and documenting the relevant factors become critical in the context of a regulatory filing.

Categorisation of device suppliers is still evolving at regulatory agencies. For example, the US FDA considers prefillable syringes from a supplier to be a component rather than a system/device. However, once these components are assembled the agency considers the drug plus delivery device a system, which brings with it a new set of expectations. In practice, BD views itself as an extension of the drug and drug manufacturing process.

Distinctions between these designations may seem immaterial, but they affect how a manufacturing organisation views and conducts itself with respect to development and qualification (design history files) and supply chain integration, both of which have become a hot topic for regulators and manufacturers alike. Best-in-class manufacturers recognise the significance of supply chain management and quality, not only for their own finished products, but for their secondary and tertiary suppliers.

Earlier this year, FDA/CDER conferred "super office" status on its Office of Compliance which will regulate, among other things, global supply chain. Additionally, the industry has formed its own standards organisation, the Rx-360 consortium, to ensure quality and safety across global supply chains. The two

initiatives both reflect the commonly recognised importance of maintaining quality across supply chains for drugs, of which devices are now a critical part.

No roadmap *per se* exists for designing new delivery systems. However, the FDA's Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics* (for both CDER and CBER) provides design considerations. Evaluating the points included in the guidance underscore the fallacy of a one-size-fits-all delivery system for biologics.

While *Container Closure Systems* is detailed in its recommendations, it does not suggest a specific test methodology that works for all products. Developers must settle on approaches that will generate quality data that satisfy the Guidance requirements and evaluate total system performance.

To deliver against these expectations BD advises that all components must be assessed for their discrete interactions and then as a system. Our philosophy is that the system cannot perform as expected unless each component also performs on its own merit. This approach provides the scientific data needed for regulatory filings, as well as a robust information base and rationale for post-filing changes.

INTEGRATION OF DRUG + DELIVERY SYSTEM

"Integration science" describes the systematic methodology and process of combining a drug and a delivery system, recognising that biologics and vaccines typically demand more rigor during development than other dosage forms. Since drug product and container closure systems are developed and used as one, developers must consider their compatibility from the earliest formulation work through the physiology of delivery – how the drug enters the body.

That was not always so. When prefilled delivery devices were first combined with biologics, formulations, drug containers, and devices in many cases, were developed independently.

Integration science has created a new paradigm for scientifically designing delivery systems. This data-driven model incorporates a novel process for assessing interactions between drug, primary container, device, device material and patient, and a re-thinking of basic formulation, protein analysis, and even consideration of fill-finish operations. Underlying this approach are sound engineering and quality by design for the assembled product and all components of the system.

Complicating this exercise is the reality that the delivery device is also a container closure system for long-term storage. For example, upon storage, issues of material permeability, piston forces, and the interaction of formulation ingredients with system components must be thought of for both drug product constitution and stability, and the ultimate functionality of the delivery system in the hands of the end-user.

Device makers must also consider the non-trivial issue of drug-device robustness, which is related to designed-in quality and how it holds up at large scale. The last thing a sponsor wants to see is a system, which, when marketed and used by several million patients, does not operate as robustly as it appeared to during clinical trials.

"BEST-IN-CLASS MANUFACTURERS RECOGNISE THE SIGNIFICANCE OF SUPPLY CHAIN MANAGEMENT AND QUALITY, NOT ONLY FOR THEIR OWN FINISHED PRODUCTS, BUT FOR THEIR SECONDARY AND TERTIARY SUPPLIERS."

And since biologics are orders of magnitude more value-dense than small-molecule drugs, device suppliers must apply the strictest manufacturing quality standards to reduce wastage and deliver value at scale. This can be achieved only when best-in-class developers strive to a lower-total-cost-of-ownership model, as it relates to the fill-finish process, supply chain optimisation, and continuous improvement across an entire franchise.

INNOVATION THRESHOLD

Predicting a biopharmaceutical developer's delivery needs is often difficult. Many manufacturers, for perfectly viable reasons, have a low innovation threshold. Limited are those manufacturers who demand the most features and operate at the frontiers of science and regulation. There is a strong preference by manufacturers to work with suppliers who have strong experience and history with regulatory agencies globally as well as a proven track record of continuously bringing to market advanced scientific developments and innovative delivery devices.

Prefilled injection devices have evolved from mere market differentiators for biologics and vaccines into an absolute necessity for many products. Innovation in delivery systems for today's complex biologics requires the convergence of numerous competencies, and transparent interaction between drug and device organisations. Because regulations change rapidly, developers must design programs around the collection of scientific data that demonstrate both compliance with appropriate regulatory guidances and deep understanding of the product.

The most successful approaches involve methodical evaluation of the system from the ground up, beginning with discrete components and ending with the system in clinical use. Conducting a development program in this manner provides the best chance of producing a delivery system that meets the needs of patients, development partners, and regulators.

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INTEGRATED DRUG CONTAINMENT AND DELIVERY SOLUTIONS TO MEET EVOLVING PATIENT AND MARKET NEEDS

In this article, Graham Reynolds, Vice-President, Marketing & Innovation, Pharmaceutical Delivery Systems at West Pharmaceutical Services, describes four key elements necessary for the development of a successful integrated delivery system, and how the needs of the patient, more than the product, must be at the essence. Mr Reynolds also introduces the SmartDose electronic patch injector as an example of such a successful patient-centric system.

Adherence to long-term therapy for chronic conditions is for many patients a painful and stressful daily routine. In fact, according to the WHO, adherence to long-term treatment recommendations hovers at just 50% in developed countries.[1] While much of the responsibility for such treatment is complex and falls directly to the patient or caregiver, the healthcare industry can help make adherence easier through the use of innovative delivery system technologies.

"MANUFACTURERS MUST SHIFT FROM A PRODUCT-CENTRIC FOCUS TO A PATIENT-CENTRIC FOCUS ... TO DO SO REQUIRES GOING DIRECTLY TO THE END-USER TO DEVELOP A DEEPER UNDERSTANDING OF THE EMOTIONAL AND PHYSICAL NEEDS."

Novel materials, unique devices and enhanced administration systems, as well as partnerships between pharmaceutical and packaging manufacturers that help to ensure patient needs for safety and efficacy are built into the drug product's packaging from early-stage development, may improve the overall effectiveness of a drug therapy, and ultimately, the health, safety and comfort of the patient.

Even the most innovative drug can provide the appropriate therapeutic benefit to the patient only if it can be delivered effectively and the patient adheres to the necessary treatment regimen. In addition, drug therapies must deliver the appropriate clinical value to ensure payer acceptance.

A successful integrated system must therefore combine the following four key elements:

1) The needs of the patient, caregiver and healthcare professional: Clinical benefit, as well as the ease-of-use and ability to adhere to a treatment schedule, should be considered.
2) The drug: A drug product must provide effective treatment in an appropriate form that enables effective delivery with an optimum delivery rate and frequency.
3) A primary containment system: The drug must be held in a container that maintains effectiveness, safety and optimum quality over a period of time.
4) A delivery device or system: The drug should be compatible with the containment system and designed to enhance the drug delivery experience for the patient or caregiver.

As the trend toward self-care continues and patients take an even greater role in decisions

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regarding their treatment, easy-to-use, safe and effective delivery systems will be essential

EFFECTIVE DELIVERY SYSTEMS BEGIN WITH THE PATIENT

The relationship between the delivery system design and the end-user is a critical factor in a drug product's success. Manufacturers must provide an easy-to-use delivery system that is not only compliant with regulatory requirements and suitable for the safety and efficacy of the drug product, but also enhances the quality of care for the patient.

There is a strong correlation between drug product administration and patient adherence, so manufacturers must shift from a product-centric focus to a patient-centric focus when designing an effective drug delivery system. To do so requires going directly to the end-user to develop a deeper understanding of the emotional and physical needs of the intended user. West has partnered with an experienced expert in this area, Insight Product Development (Chicago, IL, US), to ensure that patient and user requirements are clearly understood and integrated into the design of our delivery systems.

EFFECTIVE DRUG CONTAINMENT IS FUNDAMENTAL TO SUCCESSFUL DELIVERY SYSTEMS

Historically, pharmaceutical manufacturers have focused – and rightly so – on the efficacy and safety of the drug product. However, if the drug is to achieve its therapeutic objective, then its primary container and closure system must be both compatible with the drug and stable over time. By partnering with an experienced manufacturer such as West, with a range of technology solutions and recognised expertise in primary container systems, pharmaceutical companies can ensure an optimised container and delivery solution.

Current syringe-based systems are typically based around glass. However, in recent years, issues with glass delamination, breakage, syringe variability, cosmetic defects and particulate contamination have driven the healthcare market towards the use of innovative plastic vials and prefillable syringes manufactured from polymers such as cyclic olefins. This transition is already well established in Japan, and continues in Europe and the US. An example of such a material, Daikyo Crystal Zenith® cyclic olefin polymer, has been developed specifically for the unique needs of drug containment by West's Japanese partner, Daikyo Seiko, Ltd, and has been approved for marketed drugs in all major global markets.

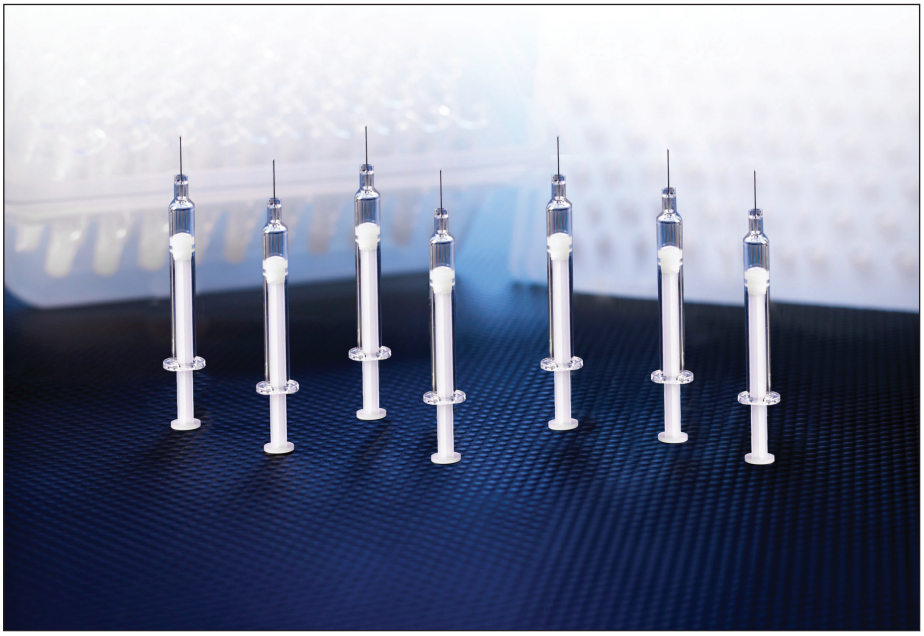

Figure 1: Innovative, silicone-free syringe systems such as the Daikyo Crystal Zenith® 1 mL insert needle syringe offer an optimised syringe system that forms part of an integrated system.

In addition to the benefits of the material, the containment system has to be manufactured, validated and presented in such a way that it can be effectively filled and handled. Once again, the requirement to develop a complete system becomes apparent.

ing the use of a glass prefillable syringe in an auto-injector, manufacturers must ensure that the stress placed on the glass does not cause breakage or that the force in the auto-injector is enough to overcome variability in dimensions, functional performance and siliconisation

"SMARTDOSE OFFERS A SUBCUTANEOUS, PROGRAMMABLE ELECTRONIC INJECTION SYSTEM THAT ADHERES TO THE SKIN AND CAN DELIVER THE DRUG OVER TIME."

Experience has shown that if the interface between the primary container and the delivery device or system is not effectively understood, the performance of the ultimate delivery system can suffer. For example, when consider-

effectiveness to ensure complete dosing. An early understanding of the interface can help to enhance performance and reduce issues associated with glass. Innovative, silicone-free syringe systems such as the Daikyo Crystal Zenith 1mL

Figure 2: West's SmartDose® electronic patch injector system features a Crystal Zenith® cartridge designed specifically to hold high-volume doses of sensitive biologics.

Figure 3: West's ConfiDose® auto-injector system can be combined with the Daikyo Crystal Zenith® 1 mL insert needle syringe to help prevent breakage and other issues associated with glass prefillable syringes.

insert needle syringe (Figure 1), once again, highlight the opportunity to offer an optimised syringe system that overcomes the limitations of glass and forms part of an integrated system.

Manufacturing skills, developed specifically to meet the challenging requirements of sterile containment systems as well as the complexities of multi-component delivery systems, are also essential parts of the overall system offering.

EVOLVING DELIVERY SYSTEM TECHNOLOGY

When manufacturers are able to combine the four key elements with expertise in container closure systems and design technology, including a thorough understanding of the pharmaceutical manufacturer's filling requirements, and high-quality manufacture at all stages, they will better meet the needs of the end-users while improving overall value and reducing time to market.

New designs are evolving around the needs of today's growing biopharmaceutical market. Trends toward higher-molecular-weight biologics mean that delivery devices and systems must be designed to accommodate higher dose volume and reduced dosing frequency. Since cyclic olefin polymers can be molded into a variety of shapes and designs, unique systems with larger fill volumes and tighter dimensional tolerance can be used while still remaining compatible with established filling technologies.

Proprietary systems, including West's SmartDose® electronic patch injector system, are being developed to aid patients with self-administration (see Figure 2). The SmartDose system, which features a Crystal Zenith cartridge designed specifically to hold high-volume doses of sensitive biologics, offers a subcutaneous, programmable electronic injection system that adheres to the skin and can deliver the drug over time.

User interfaces optimised through patient studies, including electronic indicators and wireless reporting capability, can aid in patient adherence and caregiver monitoring. The SmartDose system can be tailored to a specific patient's needs and is an excellent example of the balance between an effective drug containment system and a user-friendly delivery system. In spite of the internal system complexity, SmartDose has been designed for simplicity and patient comfort, while facilitating the delivery of innovative drug products.

"PHARMACEUTICAL AND BIOTECHNOLOGY COMPANIES SHOULD SEEK OUT A PARTNER WITH EXPERTISE AND EXPERIENCE IN ALL FOUR ELEMENTS ESSENTIAL TO THE CREATION OF AN INTEGRATED DELIVERY SYSTEM."

Other options include designs that center on more traditional containers, such as vials or prefillable syringes. Auto-injectors have long been recognised as a convenient method for delivering drug products, especially for patients who may have dexterity or needlephobia issues. However, many sophisticated delivery systems are still based around conventional glass syringes designed primarily for manual injection. Costly recalls caused by broken syringes, and slow or incomplete delivery of a drug from an auto-injector system, have pushed manufacturers to develop safer systems for use in every healthcare setting.

Auto-injector systems such as West's ConfiDose® auto-injector system (Figure 3) can be combined with the Daikyo Crystal Zenith 1 mL insert needle syringe to help prevent breakage and other issues associated with glass prefillable syringes. The ConfiDose auto-injector system is designed to minimise the force an auto-injector places on a syringe system's weakest areas, so the system can overcome many of the issues that may occur when glass systems are combined with viscous products. In addition, the CZ syringe has the potential to contain a higher volume of drug than a conventional glass syringe.

PARTNERSHIPS BUILD EFFECTIVE PRODUCTS

Pharmaceutical and biotechnology companies should seek out a partner with expertise and experience in all four elements essential to the creation of an integrated delivery system. West is uniquely placed to help enable its customers to provide innovative drug delivery systems that optimise the quality of life for patients by effectively managing the interrelationship of the four primary components: the drug; the end user; the primary container; and the delivery system. West applies proprietary technologies, manufacturing excellence, market and patient understanding to ensure that it works seamlessly with partners to provide innovative solutions that help mitigate risk, encourage patient adherence and enhance value.

Daikyo Crystal Zenith® is a registered trademark of Daikyo Seiko, Ltd. Daikyo Crystal Zenith technology is licensed from Daikyo Seiko, Ltd. ConfiDose® is a registered trademark of West Pharmaceutical Services, Inc, in the US and other jurisdictions. SmartDose® is a registered trademark of Medimop Medical Projects, Ltd, a West company. The SmartDose electronic patch injector and ConfiDose auto-injector systems are marketed by West as multi-component system. Final assembly is completed by a pharmaceutical partner.

REFERENCE:

1. *"Adherence to Long-Term Therapies: Evidence For Action." 2003, WHO, Geneva, Switzerland.*

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*West markets these products as multi-component systems only. Final assembly of the prefilled component is completed by the pharmaceutical company.

#6355

COMPANY PROFILE - BESPAK INJECTABLES

bespak Injectables

Bespak Injectables specialises in the design, development and manufacture of innovative devices for the delivery of injectable drugs. Designed to accommodate prefilled syringes, Bespak's disposable autoinjectors enable patients and other non-clinicians to easily undertake comfortable and safe injections in a convenient manner.

OTS™ AUTOINJECTOR - MEETING MARKET NEEDS

When Bespak Injectables set about developing an off-the-shelf delivery device to incorporate the most common syringe and needle configuration, its market research consistently identified three key needs.

The first was a high degree of flexibility, from both the product and its provider. Secondly, the new product would need to provide exceptional performance to succeed in an already competitive environment. Third, it was clear that pharmaceutical companies were looking to partner with an organisation that could demonstrate a solid track record of innovation and manufacturing success with drug delivery devices.

With the launch of OTS™ Autoinjector, Bespak has met these needs. By bringing together an established technology platform, a novel and flexible product embodiment and world-class manufacturing facilities, Bespak has created a market-ready device that is equally suited to meeting the low-volume needs of clinical trial work and the high volumes associated with commercially-successful drug products (Figure 1).

OTS™ AUTOINJECTOR - FLEXIBILITY

- **Established technology.** OTS™ Autoinjector is based on Bespak's patented platform. With a fully automated injection process, the simple yet effective platform has already been customised across a number of design variants.
- **Simplicity.** The simplicity of the platform allows the external geometry of OTS™ Autoinjector to be adapted and optimised swiftly, without the risks, costs and timescales commonly associated with device customisation programmes (see Figure 2).
- **Responsiveness.** Bespak's willingness to incorporate and undertake product optimisation is integral to its service offering and is backed by fully resourced in-house design and engineering expertise.
- **Market-ready.** OTS™ Autoinjector can be supplied either "off-the-shelf" or quickly and easily tailored to address specific needs in relation to actuation mechanism, injection volume and external device geometry.
- **Supply volumes.** Bespak's manufacturing flexibility enables the company to supply OTS™ Autoinjector in volumes ranging from sample quantities to facilitate early-stage decision making, through to commercial supply.

OTS™ AUTOINJECTOR - PERFORMANCE

- **Industry standard.** OTS™ Autoinjector incorporates industry standard 1ml "long" prefilled syringes with ½-inch staked needles.
- **Simple, effective design.** OTS™ Autoinjector has one of the smallest component counts of any comparable product on the market. Clinicians and patients alike benefit from a device that is both robust and easy to use.
- **Choice of actuation.** Two-step "push" and three-step "button" actuation options make OTS™ Autoinjector ideal for a range of patient populations, for example where physical dexterity may be an issue.
- **Viscous liquids.** Bespak leads the field in the delivery of viscous formulations. Liquids up to 40 Cps can be routinely handled by OTS™ Autoinjector with a capability to deliver beyond this figure where necessary.

ABOUT BESPAK INJECTABLES

Bespak, a Consort Medical company, is a leading global supplier of drug delivery devices for injectable and inhaled products. Headquartered in the UK and with representation in a number of key territories, the company was established in 1959 and today employs nearly 650 staff in the UK and overseas.

Figure 1: OTS™ Autoinjector - Shown (Left) Before and (Right) After Use.

Figure 2: Examples of the OTS™ Autoinjector as an Optimisable Device.

More than 500 million medical devices are manufactured by the company each year, supporting device programmes from pilot-scale to commercial supply. The company's solid manufacturing credentials are demonstrated by many long-established partnerships with leading pharmaceutical and biotechnology company clients, with a number of products successfully launched and marketed worldwide.

Bespak has experience with a wide range of technologies including inhalers, nasal, ophthalmic and diagnostic systems in addition to its injectors portfolio.

Bespak Injectables (formerly The Medical House) was acquired by Consort Medical PLC (Hemel Hempstead, Hertfordshire, UK) in 2009, and specialises in the design, development and supply of innovative devices for the delivery of injectable drug products. Bespak Injectables offers customised injection devices for specific applications, as well as off-the-shelf products. Its patented technology portfolio includes both auto-injectors and needle-free jet injectors.

Come and talk to Bespak Injectables about your autoinjector requirements at the **PDA Universe of Prefilled Syringes & Injection Devices Conference** in Basel, Switzerland, **Stand #60.**

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DATWYLER

omniflexCP
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COATED PLUNGERS: PEACE OF MIND...

In this article, Patrick Grueninger, Global Marketing & Business Development Manager at Datwyler Pharma Packaging (formerly Helvoet Pharma), describes the benefits of the company's coated plungers, OmniflexCP and how, whilst their purchase price is higher compared with traditional plungers, there are potentially considerable cost savings in the longer term.

The pharmaceutical industry's demand for elastomeric components for prefilled syringes (PFS) has grown significantly in the last few years. More drug products are being offered in this, without question, most convenient packaging option for parenterals. Today, expensive products with very complex and extremely sensitive active pharmaceutical ingredients, especially but not limited to those produced by the booming biotech industry, are filled in prefilled syringes. This diversification and growth into new therapeutic classes brings with it a clear demand for more sophisticated elastomeric components besides the traditional materials.

First steps were undertaken some years ago by not only improving the quality of the individual ingredients used for a elastomeric component formulation but also simply reducing the number of ingredients used. A further step was optimisation of siliconisation levels of the components and increasing the silicone oil viscosity from 1,000 cSt to 30,000 cSt resulting in a significant reduction of visible and subvisible particles.

Another development, within the industry, was the shift of the component preparation function away from the pharmaceutical companies to the syringe manufacturer, creating the ready-to-sterilise and ready-to-use product offerings.

Despite these efforts, the industry asked for something more on this point. More favourable extractable and leachable profiles and the reduction or elimination of silicone oil were the demands of the market. The solution was found in coated plungers. Soon, refined fluoropolymer coatings were proven to be ideally suited for this application.

A fluoropolymer layer is employed to separate the elastomer from the drug product, creating an efficient barrier. Besides the barrier function, fluoropolymer coatings show low "stiction", which eliminates the need for additional silicone oil. Although fluoropolymers are by far the most commonly used material for coatings, other materials like polyethylene terephthalate (PET) or Parylen have also found some applications.

Two technologies have established themselves in the market place:

A) Laminate or film coating technology: A very thin film of fluoropolymer covers the direct contact area of the plunger to the drug product. The coating takes place in between the "moulding" and "trimming" operation steps. The sides of the plunger require some silicone or silicone-like coating to assure that products are not sticking to each other.

B) Spray coating: The coating material is sprayed onto the plunger surface and a chemical reaction covalently bonds it to the rubber. The spray coating covers the direct drug contact area as well as the side of the plunger including the trimming edge. It is applied to the final product. Therefore, no additional silicone coating is required.

Both technologies result in products with outstanding performance characteristics.

Datwyler's response to coated plungers is OmniflexCP. Omniflex stands for a proprietary spray coating technology. The base material or substrate for OmniflexCP is FM257/2, a formulation with a long and very successful track record in prefilled syringe applications. A 2.25 ml luer-cone syringe with an OmniflexCP plunger is shown in Figure 1.

FM257/2 is a bromobutyl compound showing a very favourable hardness of 52°ShA. This formulation presents a very low gas and vapour permeability as well as low compressions set (ability of returning to its original shape after being compressed). It is also resistant to ozone ageing.

The substrate plunger is produced in the same way as a traditional plunger, which is

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Figure 1: 2.25 ml Luer-Cone Syringe with OmniflexCP.

a great advantage for controlling production costs within compound mixing, moulding and vulcanisation, die trimming and finally washing. Specialised geometries like "undercut" (where the trimming edge does not touch the syringe barrel) can thus be applied on uncoated as well as coated products.

After these stages, traditional plungers would be packed and shipped to the customer, but for the OmniflexCP substrates, the coating process starts. Specially designed spray coaters carefully build up the coating onto the plunger surface then a post-treatment step assures proper bonding and structure. The final OmniflexCP is washed once more and packed in the specified way; either going straight to the customer or being shipped out for further treatment such as sterilisation for ready-to-use.

The geometrical design of OmniflexCP has been altered to improve its performance in the syringe. The original design (DIN ISO 11040-5) showed elevated breakaway and gliding forces, which limited its applications. Slight alterations

Figure 3: PBSI, Build-Up for Compression Testing.

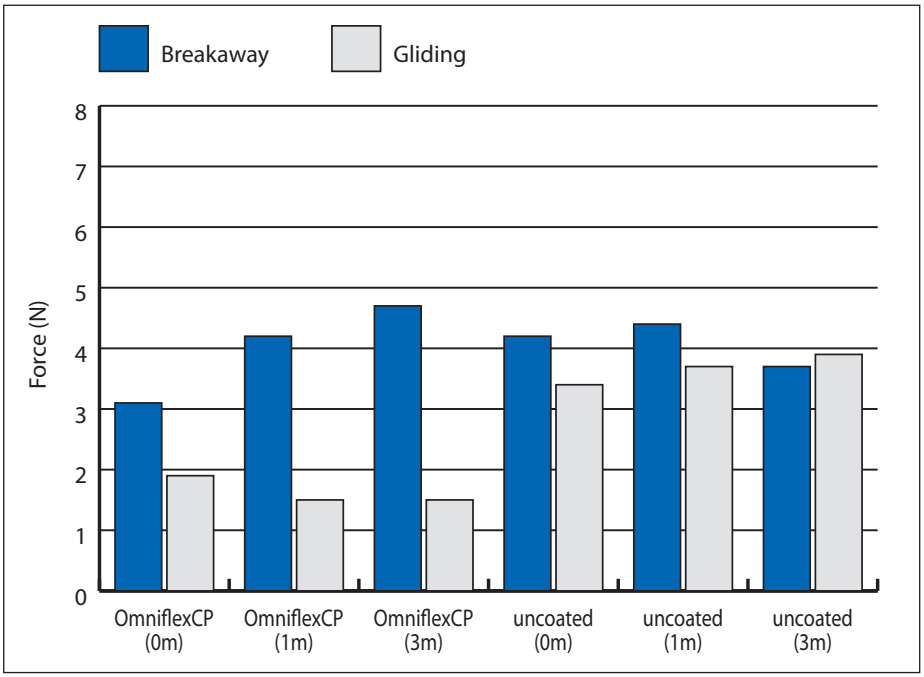

Figure 2: Break-Away and Gliding Forces after Storage.

on the rills, resulting in a decreased contact surface with the syringe barrel, improved the mechanical behaviour in the system significantly without compromising the plunger-barrel seal integrity (PBSI).

Figure 2 shows breakaway and gliding forces after zero, one and three months' storage, for OmniflexCP plungers compared with uncoated plungers.

PBSI testing is – perhaps surprisingly – not yet defined through the DIN ISO11040 guidelines for prefilled syringes. In order to have a common understanding and technique to perform a seal integrity test, the test for "Sterile Hypodermic Syringes for Single Use", described under DIN ISO 7886-1, is usually applied (see Figure 3).

The test is simple and defines a pressure and time for which a plunger has to provide a perfect seal against an aqueous solution with a dye. If the dye surpasses the first rill, the plunger fails the test. The test is performed in two modes, one with overpressure (300 kPa for 30s) and the other with negative pressure (88 kPa for 60s). Naturally, OmniflexCP passed these tests comfortably.

In addition to the outstanding extractable and leachable profile obtained through OmniflexCP (see Figure 4), and a total absence of any additional lubricant like silicone oil helping to

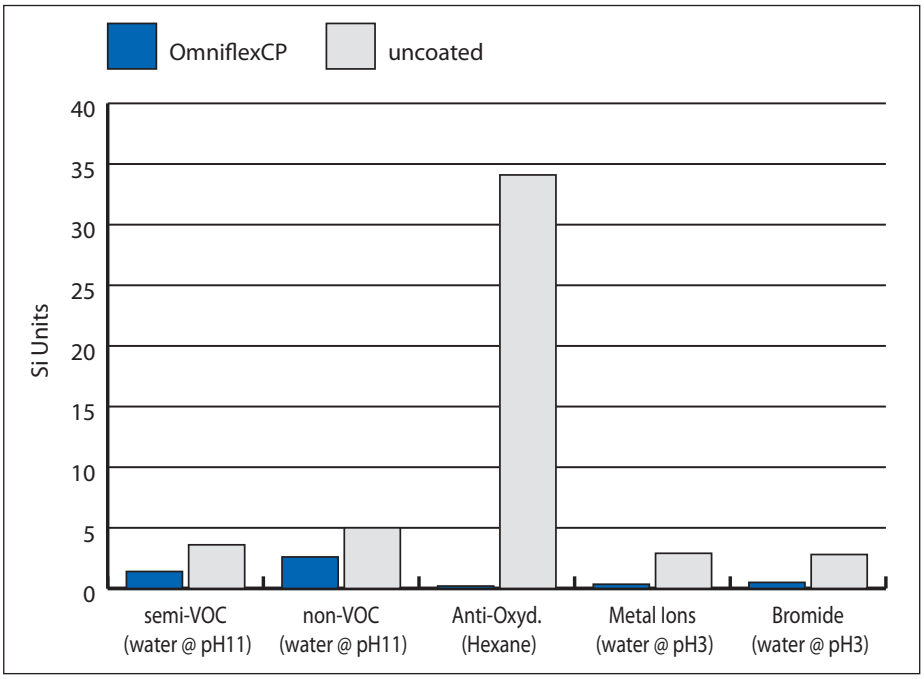

Figure 4: Extreme Conditions Extractables and Leachables Testing.

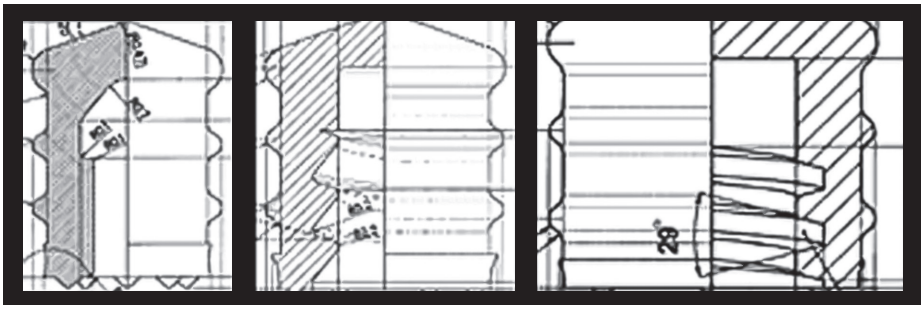

Figure 5: Standard OmniflexCP Designs.

reduce particles and protein degradation, very positive results were obtained for the machinability of OmniflexCP on all equipment brands.

It has also been reported that OmniflexCP is suitable for both of the two most common plunger placement systems. Vacuum stopper placement was usually the preferred method for coated plungers since the stress / deformation the plunger has to undergo is far less than the traditional insertion or vent tube.

Laminated plungers have a tendency to present wrinkles at the flanks of the plunger if placed under high stress / compression. Most of the time, these wrinkles do not affect the sealing integrity at all but they do have an impact on the visual appearance (magnified by the convexity of the syringe barrel) which, depending on the target market for the drug product, might have an influence on the acceptance of the entire system. A spray-coated plunger such as OmniflexCP, has shown to be more robust and forgiving to compression, and wrinkles are significantly less marked. This makes OmniflexCP suitable for both plunger placement technologies, vacuum and insertion tube, be it that vacuum is to be considered as the safer of the two.

Datwyler is proud to offer three formats to the pharmaceutical industry: the 0.5 ml (V9417); 1-3 ml (V9416); and the 1 ml long (V9403), as shown in Figure 5. Besides these standard formats, customised designs are also possible. OmniflexCP is available in bulk, ready-to-sterilise and ready-to-use formats, in multiple bags or rapid transfer port (RTP) bags.

SUMMARY

Coated plungers have proven to be a real step forward in helping the pharmaceutical industry to reduce risks related to packaging failures and control the total cost of ownership. Coated plungers may be able to improve the shelf life of the drug product, reduce visible and subvisible particles, and improve the compatibility between closure and drug product, which might lead to a reduction of unwanted interactions with rubber extractables and the accumulation of leachables in the drug product.

The biggest hurdle for a widespread introduction and use of coated plungers is the perceived cost related to these kinds of component. They are without doubt more expensive than uncoated versions, and a simplistic comparison of purchasing prices might cause concern.

However, a deeper analysis shows that, in real terms and over time, coated plungers provide increased value relating to the whole packaging cost and the quality of the resulting product. When the cost of a possible failure due to inferior packaging and, in the worst case, a market recall are taken into account, the investment in a coated product appears the more financially prudent strategy.

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DATWYLER

IMPROVING PARTICULATE & MICROBIAL CLEANLINESS OF ELASTOMERIC CLOSURES

The closure of an injectable drug product's container, because of its contact with the drug, is a potential source of contamination and must meet a certain number of "cleanliness" criteria. The cleanliness of elastomeric components is particularly important for prefilled syringe components, especially plungers, where there is a large contact surface between the drug and the plunger and where contact is prolonged. This cleanliness principally concerns the parameters of visible particles, bioburden and endotoxins. These parameters have to be constantly improved to ensure the maximum control and safety to the pharmaceutical laboratories and drug applications. Here, Stelmi details the measures it has implemented in the production process to decrease and master the risk of potential contamination, and the resulting achievements over time.

In the field of particulate and microbiological cleanliness, many actions have been implemented over time, notably in terms of environment, automation and finishing process, in support of the ever increasing requirements of pharmaceutical laboratories.

Indeed, the characteristics of microbiological and particulate "cleanliness" are closely connected to the manufacturing process and in particular to the finishing process, which consists of washing, rinsing, drying, siliconising and packaging the components.

Figure 1: Prefilled Syringe Plungers.

THE WASHING PROCESS: A SIGNIFICANT STEP

Washing rubber parts, (Figure 1), effectively and efficiently, requires equipment specially designed for this purpose. Stelmi has therefore developed its washing technology and uses machines (Figure 2) designed to its own specifications.

Various washing procedures (differing in terms of environment, quality of fluids used, cycle length and consequently guarantees) are proposed depending on the regulations in force. These procedures lead to different results in bioburden, endotoxins and PCI (particulate index).

US requirements and regulations result in the greatest particulate and microbiological cleanliness of closures. The UltraClean 6 *evolution* washing process meets these criteria. Indeed, in accordance with FDA regulations, the UltraClean 6 *evolution* process follows this sequence:

- washing followed by first rinsing operations of the components in European Pharmacopoeia (EP) **"highly purified water"** and in accordance with the United States Pharmacopeia (USP).
- a final rinsing of the components in **apyrogenic distilled water** in accordance with the "Water for injectable products" monograph in the EP and the USP. This final rinsing phase uses a system exclusive to Stelmi making it possible to guarantee optimum

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Figure 2: Component Washing Process.

cleanliness of the stoppers, both in terms of particles and microbiology.

Moreover, to limit the risk of contamination:

- The washing, rinsing, drying and siliconising operations are performed in an ISO 7 environment at rest while the primary packaging takes place in an ISO 5 environment at rest.
- The washing and drying cycles are automated and piloted by a programmable robot, which allows a reduction in human presence.
- Finally, the components are packaged so that they are handled as little as possible to minimise the further contaminations inevitable during each transfer.

The registration of the finishing process in a single type V Drug Master File for all production sites ensures the rigorous application of Good Manufacturing Practices, offers the additional safety assurance of a multiple source supplier, and makes it possible to meet the regulatory needs of pharmaceutical laboratories.

These measures enabled levels of cleanliness to be obtained, as detailed in Figure 3, which compares Stelmi's finishing process complying with FDA regulations with the finishing not complying with this regulation in terms of guarantees. Furthermore, implementing a policy of constant improvement in this field and analysing trends lead to progress as shown by the results below:

MICROBIOLOGICAL RESULTS ULTRACLEAN 6 EVOLUTION FINISHING

BIOBURDEN Trend 2010: 0.01 CFU/cm²

ENDOTOXINS Trend 2010: 0.01 EU/ml

	Finishing complying with FDA regulation	Finishing NOT complying with FDA regulation
Endotoxins	< 0.03 EU / ml	< 0.125 EU / ml
Bioburden	< 0.25 CFU / cm²	< 0.5 CFU / cm²
PCI (Particulate Count Index)	< 2.9	< 2.9

Figure 3: Guarantees from Stelmi's FDA-Compliant Finishing Process (Left) Compared with a Finishing Process Not Complying with this Regulation.

EVOLUTION OF NEEDS

The evolution of the needs of pharmaceutical laboratories lead to the development of new products which present new challenges in terms of particulate and microbiological cleanliness, notably:

- Ready-to-use (sterile) closures which require the highest degree of assurance as they are used directly by the drug manufacturer.
- "Cosmetic quality" (visual aspect of components) for which the particulate cleanliness has to be increased.

Both types of products are washed with the UltraClean 6 *evolution* process but additional precautionary measures are taken regarding critical risks.

STERILE CLOSURES: LIMITING THE RISK OF BIOBURDEN CONTAMINATION

Since the end of 2003, Stelmi has been offering guaranteed sterile plungers, greatly simplifying use for its clients.

The "ready-to-use" concept is meant to limit the potential risk of contamination to handling when transferring the components to the aseptic area where the drug products are packaged. The advantages sterile closures bring are not merely financial (the costs of associated validations, improved productivity, reduction in investment regarding sterilisation machines, clean rooms or clean fluids required for these operations, reduction in storage levels) but also concern the stopper cleanliness by reducing the number of human operations, thus limiting the risks of contamination during these preparation stages.

Sterile "ready-to-use" products, whether stoppers or plungers, undergo a manufacturing process specific to Stelmi before being sterilised by gamma radiation. The objective is to obtain components with a bioburden and bacterial endotoxin load that is as low and steady as possible.

From this perspective, a risk analysis was performed to determine the critical stages and the various factors in potential bacterial contamination. Following the study, the various contaminants were identified as per the *Ishikawa* diagram shown in Figure 4. So, at each stage of the component production process, special precautions are taken in the light of the identified risks of potential contamination. Physico-chemical, aspect, particle, microbiological and endotoxin controls are performed on each production batch before the products are irradiated.

Taken as a whole, the measures implemented result in a very low bioburden in the components before sterilisation, which proves the mastery of the process, as shown by the results obtained for the year 2010 (Figure 5). This low level of bioburden means that the components can be sterilised by gamma radiation using a low dose that limits any impact on the properties of the components, while ensuring their sterility.

COSMETIC QUALITY (VISUAL ASPECT)

Changes in perception and the potential impact of certain defects in the appearance of pharmaceutical primary packaging components require the establishment of stricter Acceptable Quality Levels (AQL) to keep up with the latest demands of pharmaceutical laboratories to:

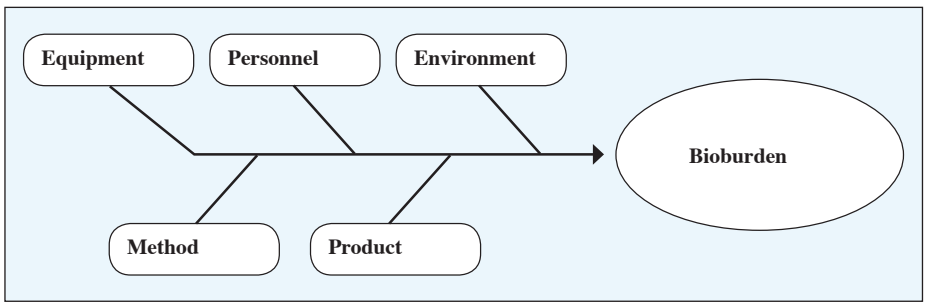

Figure 4: Ishikawa diagram

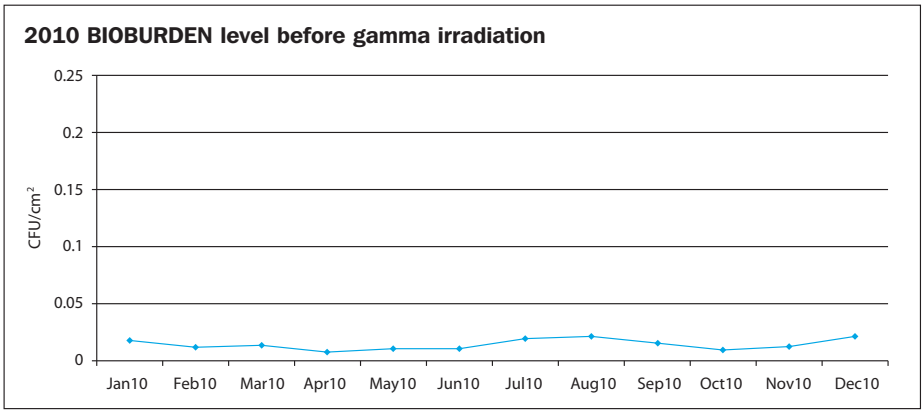

Figure 5: 2010 Bioburden.

- Meet new requirements of some specific markets in the matter of visual inspection and especially "cosmetic" defects.
- Reduce the rejection ratio of finished products (drugs) during the final visual inspection.

An approach was developed to integrate the cosmetic quality at each step of the production process and a risk analysis enabled the implementation of additional measures of precaution at critical stages to eliminate appearance defects at the source.

Indeed, beyond the installation of visual inspection automatic machines at the end of production, visual quality is above all the result of a total control of the manufacturing process with regards to endogenous and exogenous contamination.

These measures of precautions enable:

- A very low level of embedded particles
- An improved particulate cleanliness (loose particles), particularly loose fibers (PCI)
- A reduction in other types of defects

In terms of particulate index, this process enabled a decrease in the level guaranteed from PCI<2.9 to PCI<1.5 for stoppers.

DEVELOPMENT OF A NEW PRODUCTION CONCEPT

Combined with an efficient washing process, the next step to reduce the risk of microbiological and particulate contamination still further is to act upstream in the production process and obtain components as clean as possible before the washing process.

In keeping with its culture of continual improvement, Stelmi has developed a new production concept – PremiumFill (see Figure 6) – in-line in a controlled area aiming at optimising cleanliness levels in the production of sterile (ready-to-use) and cosmetic quality components (visual aspect).

Along with the further implementation of clean rooms in production while maintaining conformity to ISO 9001 and ISO 15378 standards, this new concept incorporates the findings of a risk analysis. Each production step has been evaluated and appropriately re-designed to further limit the potential risk of contamination (endotoxins, bioburden and particulates) and achieve greater assurance in the upstream production before final processing (washing of the components) and release.

Various measures have been implemented such as:

- Molding (see Figure 7) and trimming in segregated ISO classified areas
- Reduction of human presence and restricted access
- Maximum automation
- New conception of machines
- Specific garments
- Implementation of process monitoring in real time

This concept enables us to reduce and control the potential risk of contamination in terms of particles, fibers and micro-organisms.

CONCLUSION

Implementing a policy of constant improvement is essential when supplying the pharmaceutical industry especially in terms of microbiological and particulate cleanliness. Incorporating pharmaceutical procedures, Stelmi permanently improves and develops new production processes to obtain a level of quality compatible with the requirements of laboratories and regulatory agencies. The latest process implemented, PremiumFill Concept, starts to give very promising results in the search for increased safety for the patients.

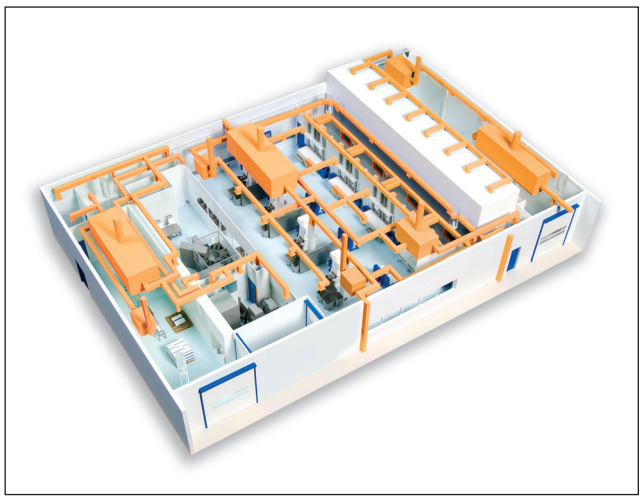

Figure 6: Cell PremiumFill Concept.

Figure 7: PremiumFill Concept Molding Area.

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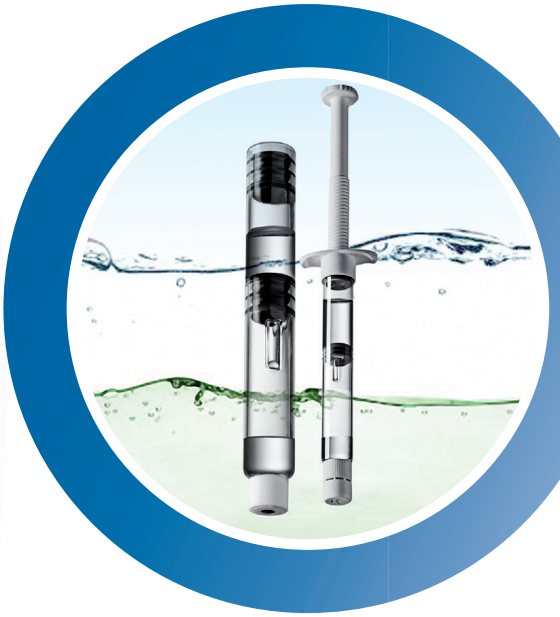

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ADVANCED TECHNOLOGY FOR A NEW GENERATION OF STERILE NEEDLE-FREE PLASTIC PREFILLED SYRINGES

In this article, Danielle Labreche, Director, Business Development & Innovation at Aguettant, outlines some of the company's research into recent market trends and surveys of medical practices and incidents, and describes how Aguettant's products can meet current and future needs.

Syringes are used not only for delivering drugs directly to patients, but also as a means to reconstitute, dose or dilute an injectable drug before it is infused. More than half of injectable drugs are presented in powder or lyophilised form and thus require reconstitution, and a not insignificant proportion of injectable hospital drugs are marketed as concentrated formulations that need to be diluted and/or individually dosed for each patient.

Although the history of hypodermic syringes goes back nearly 160 years in the therapeutic arena, there are still a number of risks associated with drug preparation today, especially when it is not performed in a pharmaceutical industrial environment where quality, integrity, sterility can be systematically monitored and guaranteed.

"WOULD THE INDUSTRY AND MEDICAL PROFESSIONALS VALUE A SIMPLIFIED, SAFER AND MORE SECURE PROTOCOL FOR THE RECONSTITUTION OF POWDER AND LYOPHILISED FORMULATIONS?"

MEDICATION ERRORS & READY-TO-USE

In 2009, The French Health Authority (AFSSAPS) published a report on the medication errors, based on four years of operations of their adverse effect events reporting entity, the *"Guichet des Erreurs Médicamenteuses"*.[1]

In this study, the most common errors were attributable as follows:

1. errors with the active drug (41.8%)
2. dilution errors (27.7%)
3. incorrect dosing (7.3%)
4. using the wrong route of delivery (5.5%).

Amongst the sources of such errors were: similar packaging (31.9%); not following the correct procedure (26.7%); and missing information (10.2%).

For example, in anaesthesia alone, medical errors occur at each step of the therapeutic process (namely prescription, dispensing, reconstitution and delivery) at a rate of between 1% and 10%. In this particular therapeutic area, half of medication errors involve syringes and ampoules or vials.[2]

A US study scrutinising compounded preparations in hospitals showed that medication errors were reported among all healthcare disciplines. Specifically, errors involved: nurses (32%); pharmacists (24%); physicians (21%); and pharmacy technicians (17%).[3]

The French health authorities reported in 2005 that there could be as many as 190,000 avoidable severe adverse effect events each year, which were likely to cause death, disability, or prolong the hospitalisation.[4] Similar data from other countries confirms these results.

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The pharmaceutical industry is expected to commercialise ready-to-use drug formulations that are packaged in their final delivery device.

NOSOCOMIAL INFECTIONS & STERILITY

In February 2010, a US study reported in the Archive of Internal Medicine revealed the impact of infections acquired during hospital operations.[5] The study analysed 69 million discharge records from hospitals in 40 US states issued between 1998 and 2006. The study estimates that the most common contracted infections during hospitalisation, pneumonia and sepsis, were the cause of at least 48,000 deaths in the US in 2006.

The study stated that, "many of these health care-associated infections result from failures in the process of care at hospitals and may be preventable". Additional costs related to prolonged hospitalisation due to nosocomial infections reached €6 billion (US$8.1 billion) in 2006 alone.

An article published in 2005 on medication errors in intravenous drug preparation, observed that aseptic procedures required for the safe preparation of doses were frequently violated.[6]

Clearly single-dose sterile ready-to-use drugs will contribute to reducing the risk of contamination and its consequences.

ACCIDENTS, RISK OF BLOOD EXPOSURE AND NEEDLE-FREE

A study by the French network for reporting, investigating and monitoring nosocominal infections (*Réseau d'alerte, d'investigation et de surveillance des infections nosocomiales; RAISIN*), which investigated accidents in the hospital environment, reported that 71.5% of such accidents are needle-stick injuries.[7]

Since the international standardisation of the Luer Lock and Luer Fit connections, developed by BD (Franklin Lakes, NJ, US), the progression of needle-free systems (syringes, catheters, infusion bags and injectors), creates an opportunity to dramatically reduce the injuries in hospitals, offer a safer environment to the healthcare professionals and protect them from blood contamination.

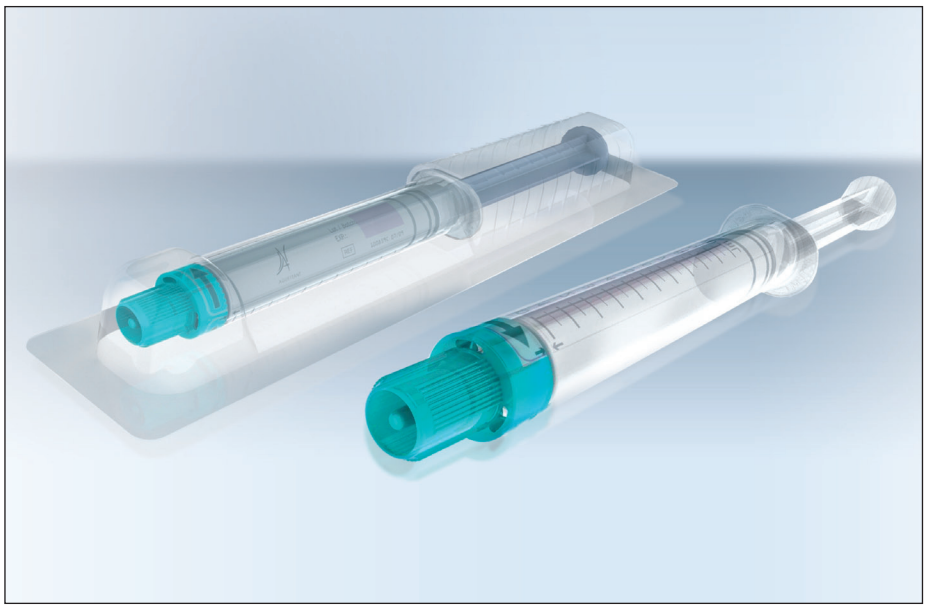

Figure 1: Aguettant's Internationally Patented Sterile Needle-Free Plastic Prefilled Ready-to-Use Syringe.

ROBUSTNESS OF GLASS, COC / COP AND POLYPROPYLENE

Empty syringes are predominantly offered in plastic, while prefilled and prefillable syringes used for parenteral drug delivery are mostly manufacture from glass, cyclic olefin polymer (COP) or cyclic olefin copolymer (COC).

Glass is well known for its oxygen barrier properties and capacity to procure drug stability. The downfall is that for volumes of 5 ml or more, the syringe becomes heavy in addition to being breakable, and not cost effectively adaptable for the incorporation of creative design features required by the pharmaceutical industry such as tamper evidence and different back stops designs.

Polymer and copolymer syringes are lighter-weight than their glass alternatives, visually as transparent, yet present less of a barrier against oxygenation. For certain molecules, polypropylene can be an excellent alternative, being robust and less expensive, while delivering more than 24 months of drug stability.

Despite lower performance in certain characteristics, such as oxygen barrier function, plastic syringes may bring a benefit over glass as they provide improved robustness against breakability and better ergonomics, while delivering an adequate stability performance level regarding water/gas permeability as well as acceptable extractables/leachables profiles for a range of molecules.

BUDGET, WASTAGE AND THE ENVIRONMENT

Finally, economic studies show that using a prefilled syringe can reduce costs and waste:

As stated in a survey of UK practice (in the area of anaesthetics for obstetric emergencies), the use of prefilled syringes would eliminate concerns regarding efficacy and sterility, and reduce wastage and the potential for drug error.[8]

Another study, comparing the overall cost of a prefilled syringe with that of an ampoule, revealed a saving of €0.50 per unit, despite the purchasing price of the prefilled syringe being three-times more than the ampoule (€3.40 versus €1.10).[9] It is important to note that this study did not take account of the additional benefits from prefilled syringes arising from the reduced preparation time, reduced medication errors and reduced nosocomial risks.

Aguettant has patented worldwide and, in 2009, launched its new generation of Sterile Needle-Free Plastic Prefilled Syringe for emergency wards and operating rooms. The syringes aim to address critical issues, such as:

Risks and concerns	Aguettant's answer
Medication errors	Ready to use , Clear label and double graduation
Nosocomial infections	Sterile and Tamper Evident
Accident & exposure to blood	Needle Free
Robustness	Light Weight, Ergonomic and easy to use
Supplies, logistics	Environmental Friendly
Budget constraint	Affordable even for low priced drugs

THE PFS MARKET OUTLOOK TO 2025

A 2010 visiongain report estimated that two billion prefilled syringe units were sold in 2009. It predicted that growth in prefilled syringes units sold is to continue, reaching 3.62 billion units in 2015 and rising to 6.83 billion units in 2025.[10]

Ready-to-use syringe application is a fast growing segment in many therapeutic areas and is urgently expected in **emergency wards** because it provides immediate access to treatment where time is of essence, reduces medication errors, facilitates and shortens preparation time and reduces supply wastage. It is also expected to dominate the homecare market wherever possible, because a risk-free handling procedure is favourable in a less controlled environment.

A 2008 study conducted for Aguettant by Access Research (unpublished) revealed that in the UK critical care arena the implementation of prefilled syringes was already underway, with many molecules already being presented in prefilled syringes format. Surprisingly, in Germany, none or very few prefilled syringes found in the critical care area meaning that the German market still seemed to represent an opportunity for development.

DRUG RECONSTITUTION WITH PFS

Is there an unmet need for drug reconstitution using sterile diluent PFS?

If for drug stability reasons, a ready-to-use PFS containing the active pharmaceutical ingredient is not an option, we ask: would the industry and medical professionals value a simplified, safer and more secure protocol for the reconstitution of powder and lyophilised formulations?

If one believes so, our studies show that the priority must be to address the need in the most common syringe volumes, namely 2ml, 5ml and 10ml. These diluent prefilled syringes would be marketed within a kit, packaged with the drug, thus providing simplified ordering and logistics for hospital pharmacists and homecare nurses.

Branded drugs are ideal candidates for a prefilled syringe for reconstitution, as this solution will be more expensive than a vial and reconstitution supplies, and branded pricing models will be able to absorb, if in return the market shares are maintained or increased.

We ask again: could a user-friendly packaged drug professionalise the work of the nurse and encourage the doctor to prescribe a safer drug in a given therapeutic area?

It is known that a few multinational companies have worked on the concept and launch of glass and plastic syringes dedicated to the preparation of powder / lyophilised drugs from 0.5 mL to 50 mL (WFI, NaCl). Data reveals that several million units are sold, mainly in North America, but not yet in Europe… We wonder why is that?

There is a higher cost but there is also an opportunity for new revenue flow. Can this also present a threatening barrier to competitors, if exclusivity is secured?

Having had a look at the market and with the help of a research company, in 2011 Aguettant identified a few sectors with potential for a prefilled syringe in the reconstitution field, namely **haemophilia, analgesia and anti-inflammatories for the retail market**. These branded drugs "to be reconstituted" are sold at a price that can absorb the induced costs of a kit package and yet we think the brand would most likely benefit from an improved quality of care for patients, ease of use for medical staff and additional protection against generic competition.

Aguettant has developed an innovative delivery device, being part of the "AGUETTANT System" range, which is covered by two international patent applications: WO 2007/028876 and WO 2007/083034. Aguettant is looking to establish partnerships to develop molecule applications and is dedicated to adding value to drug preparations, for the hospital and the homecare markets.

AGUETTANT'S PREFILLED R2U SYRINGE

Aguettant's internationally patented sterile needle-free plastic prefilled ready-to-use syringe (shown in Figure 1) is:

- **Ready to use** to avoid medical errors and reduce preparation time
- **Needle free** to provide a secure and safe connection to interface devices via a Luer Lock design
- **Sterile** for immediate use into the sterile field as it is packaged in a sterilised blister
- **Tamper evident** to guarantee sterility via its innovative tip cap design & pre-perforated label
- **Ergonomic**, lightweight, double graduation and colour-coded drug identification
- **Environmentally friendly** as it reduces drug and supply waste traditionally associated with syringe preparation and caused by the short shelf life when prepared by hospital
- **Affordable**

Aguettant is the first company in France to commercialise a plastic sterile ready-to-use prefilled syringe. It is Aguettant's plan to launch another critical care molecule in its domestic market and through its affiliates in the UK and in Belgium during the course of 2012.

Committed to an international deployment, Aguettant has entered into licensing agreements for Scandinavia and Australia this year. Agreements for Spain, Portugal and Canada should follow and discussions are ongoing for other European countries, such as Germany.

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MATCHING A RANGE OF INJECTORS WITH BOTH PATIENTS' AND PHARMA PARTNERS' NEEDS

In this article, Ian Thompson, Vice-President, Business Development, Delivery Systems, at Ypsomed, focuses on the injection technology landscape for the development and manufacture of pens and auto-injectors, and introduces Ypsomed Delivery Systems' range of Custom Products.

PHARMA DEVELOPMENT LANDSCAPE FOR INJECTION TECHNOLOGY

The number of new injectables in development and reaching the market continues to increase, as does the demand for the cartridge and syringe-based devices needed for their easy, safe and reliable administration. Over the last 25 years, self-injection devices, pens and auto-injectors have continuously been developed to meet the needs of patients in the key areas of diabetes (insulin / glucagon-like peptide-1 (GLP-1)), growth hormone and other hormone replacement therapies, hepatitis C, multiple sclerosis (MS), cancer treatment, autoimmune diseases and emergency injections for treating anaphylactic shock and migraine.

Many existing injectables are biotech drugs which are being reformulated and improved. Improvements include liquid-stable formulations, long-acting formulations for less frequent dosing and multidose preserved formulations which help differentiate against generic / biosimilar competition.

Another trend is that biotech cancer therapies that are currently infused are being reformulated to allow subcutaneous self-injection. In addition, self-injectable therapies in new therapeutic areas such as Alzheimer's and cardiovascular diseases are in development. Some injectable therapies are facing up to competition from substitution technologies; examples include dipeptidyl peptidase 4 (DPP-4) inhibitors *versus* GLP-1s in diabetes, and oral drugs for treating MS.

PHARMA NEEDS

As self-injection device technology has matured, the drive to customise platform products rather than develop completely new devices has intensified. Due to infrequent dosing or multidose drug presentations, many therapies require nominal device quantities even for relatively large patient populations. Apart from diabetes and certain autoimmune disease treatments, most injectable therapies require no more than several hundred thousands to a few million disposable devices per year. This means that the use of standardised device platforms that can be leveraged across a number of therapies is part of each pharma company's strategy to maintain quality, minimise risk and reduce costs.

> "AS SELF-INJECTION DEVICE TECHNOLOGY HAS MATURED, THE DRIVE TO CUSTOMISE PLATFORM PRODUCTS RATHER THAN DEVELOP COMPLETELY NEW DEVICES HAS INTENSIFIED."

In addition, through consolidation and experience, the pharma industry has acquired a high level of knowledge about complex medical devices such as injection devices. There is gen-

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Figure 1: The Spring-Driven Reusable ServoPen (Left); the Value Reusable Ypsopen Twist (Centre); and the UnoPen (Right).

eral awareness of which devices are best to use for which therapies. This combined with cost pressures on big pharma means that they are looking for off-the-shelf solutions which reduce investment during Phase III clinical trials until it is clear that the drug is going to be launched successfully. Pharma companies want to be able to move into the clinic with a device which can be manufactured in the required volume with a minimum of modifications. It is therefore important for device suppliers to leverage platform products and minimise costs based on the use of common tooling, assembly and printing systems throughout the manufacturing process.

DISPOSABLE PREFERRED TO REUSABLE DEVICES

Pens and auto-injectors have reached a high level of patient-friendly functionality and there is a clear trend to disposable devices instead of reusable devices as this provides a higher level of convenience for patients. The main area of demand for reusable devices is for reusable insulin pens in developing markets that are moving away from vials to cartridge-based insulin injections and where disposable pens are not yet affordable.

INSULIN PENS – ESTABLISHED MARKET DRIVER

Currently approximately one billion insulin cartridges are filled each year with half being assembled into disposable pens and the other half used with reusable pens. Most insulin pens today have standard "dial-and-dose" functionality that is well accepted by clinicians, caregivers and patients allowing for easy dose selection and delivery. The key features of dosing up to 60 or 80 insulin units, easy-to-read dose displays, dose correction and clear injection control and feedback are a must for variable dose, multidose pens.

An in-depth understanding of pen gearing mechanisms, material selection and the patent situation is necessary to be able to develop and manufacture both reusable and disposable pens in the large quantities required by insulin manufacturers. The most recent insulin pen development activities have focused on moving from manual geared pens to spring-driven pens that further simplify the injection process for the patient.

Ypsomed Delivery Systems provides a range of state-of-the-art "dial-and-dose" reusable and disposable insulin pens to fulfil market demand in established and developing insulin markets (see Figure 1). The spring-driven reusable ServoPen features an attractive combination of user-orientated design and improved functionality based on a robust lightweight aluminium housing and a spring-assisted injection mechanism. The value reusable Ypsopen Twist is ideal for developing markets and non-insulin therapies where device cost is sensitive. The UnoPen disposable insulin pen has been developed for the new ambitious and fast-growing insulin providers.

PENS FOR OTHER INDICATIONS

Insulin pen technologies are ideally leveraged for use with other hormone-based therapies such as human growth hormone (hGH) and follicle stimulating hormone (FSH) requiring variable dosing. The move to spring-driven injection technology is ideal for patient populations which may have problems injecting themselves with manual geared pen technology such as MS patients or children treated with growth hormone. Core insulin pen technology can also be applied to therapies that require small or larger multiple fixed doses such as GLP-1 in diabetes, parathyroid hormone in osteoporosis, and niche therapies such as apomorphine in Parkinson's.

Frequent large doses are today often injected from prefilled syringes. As part of the lifecycle management of these therapies there is also the opportunity to develop preserved formulations that can be injected from pen-based cartridges. An example of this is beta-interferon for treating multiple sclerosis which is available in both prefilled syringes and cartridges.

AUTO-INJECTOR DEMAND CONTINUES TO INCREASE

While the market for traditional reusable auto-injectors is limited to frequently injected MS therapies and emergency injections for migraine, the market for disposable autoinjectors continues to grow driven by the demand for less-frequently injected drugs such as TNF-inhibitors for the treatment of rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease (IBD). A positive development is also the introduction of needle safety mechanisms for the leading epinephrine emergency auto-injector.

AUTO-INJECTORS BRING REAL PATIENT BENEFITS

The "arms race" to develop full-feature auto-injectors, many of which are button activated, has been largely completed. Pharma companies are now recognising that there are a number of alternative devices in the "scale of convenience" between a bare prefilled syringe and the full-feature auto-injector. In particular, simpler two-step autoinjectors with push-on-skin activation are smaller, very patient friendly, and provide more scope for customisation than their button-activated cousins.

Auto-injectors based on spring mechanisms built inside the plunger rod help to reduce the size of the device. Most devices have good visualisation and clicks to provide the patient with excellent audible and tactile injection feedback. Very important is the need for an automated or patient-controlled dwell time at the end of the injection to ensure that the entire drug volume has been injected.

"PHARMA COMPANIES ARE NOW RECOGNISING THAT THERE ARE A NUMBER OF ALTERNATIVE DEVICES IN THE "SCALE OF CONVENIENCE" BETWEEN A BARE PREFILLED SYRINGE AND THE FULL-FEATURE AUTO-INJECTOR."

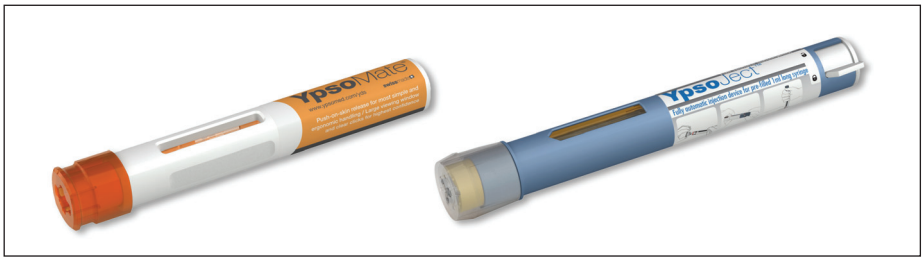

Figure 2: Ypsomed Delivery Systems' Range of "Push-on-Skin" Disposable Auto-injectors Include YpsoMate (Left) and YpsoJect (Right).

Figure 3: DuoPen is Ypsomed Delivery Systems' Cartridge or Syringe-Based Variable Monodose Device for Use in Combination with Needle-Safety Devices.

AUTO-INJECTOR-COMPATIBLE SYRINGES AND NEEDLES

Prefilled syringes are now being specified and manufactured for use with disposable auto-injectors. Ideally the syringe should be held on the front syringe shoulder rather than the finger flange as the latter could break. If the syringe has a rigid needle shield with a larger diameter than the syringe this makes assembly into the auto-injector's syringe holder more difficult, but there are a number of systems available to accommodate this.

A key improvement of the prefillable syringe is the availability of different diameter thin-wall cannulæ. By providing a range of needle sizes such as 29G, 27G up to 25G a broad range of drug viscosities can be covered by a standard auto-injector device. This avoids the need to develop bulky devices with high injection forces that require additional spring mechanisms that are external to the plunger rod.

Ypsomed Delivery Systems' range of "push-on-skin" disposable auto-injectors provide intuitive handling, syringe visualisation and end-of-injection patient feedback. YpsoMate is Ypsomed's latest 2-step push-on-skin autoinjector with a slim and easily customisable design. YpsoJect is highly rated by patients for its patient-controlled needle retraction mechanism (see Figure 2).

VARIABLE MONODOSE INJECTIONS

Variable monodose injections from a cartridge or syringe are sometimes needed to accommodate weight-based dosing or dose titration. In some cases prefilled syringes containing different doses are provided to the patient, but it may be more practical to provide a simple standardised cartridge or syringe-based dosing mechanism that can be used by most patients, such as DuoPen (Figure 3).

DUAL-CHAMBER-BASED INJECTORS

Dual-chamber cartridges and compatible injectors designed for the simple reconstitution of lyophilised drug and diluent have been on the market for more than 20 years. Examples include multidose pens for therapies such as hGH and PTH. All insulin pen technologies can be modified to accommodate a dual-chamber cartridge allowing simple reconstitution prior to use.

Today however, the dual-chamber cartridge is more often used for monodose therapies where it is difficult to develop a liquid-stable drug formulation. This requires disposable monodose pen devices which are essentially the equivalent of the disposable auto-injector for dual-chamber cartridges. Monodose dual-chamber-based injectors may include needle safety or, even better, the needle safety is provided by a dedicated safety pen needle.

HELPING THE PATIENT TO RECONSTITUTE AND INJECT

Manual twist-motion reconstitution of a dual-chamber cartridge and priming is easy to visualise and easy to perform for patients. Automating these steps may help patients with motor disabilities but this adds complexity and cost to the device. Whether manually or automatically operated, the device must ensure that all the steps are performed in the correct order. Regardless, the device must always be held in the correct position during reconstitution to prevent incomplete mixing or inadvertent expelling of the drug. Injection may be performed manually or automatically depending on the needs of the patient.

Ypsomed Delivery Systems' LyoTwist family of devices (see Figure 4) all include intuitive and proven manual reconstitution and priming and also provide excellent visualisation of the dual-chamber cartridge. The handling steps can only be performed in a certain order. Needle safety is provided in combination with Clickfine AutoProtect safety pen needles.

CONCLUSION

The technology for pens and auto-injectors is maturing in a market which continues to grow at above average rates. Pharma partners are experiencing increasing cost pressure and are looking for standardised device platforms that can be leveraged across different therapies.

Ypsomed Delivery Systems offers a complete range of self-injection systems based on proven and patent-protected designs customisable to pharma partner needs. The possibilities of developing new technical solutions to provide safe and reliable injections have not been exhausted, while the correct choice of device relies upon careful selection and close collaboration between the drug manufacturer and the device company.

Figure 4: Ypsomed Delivery Systems' LyoTwist Family of Devices with Needle Safety Provided in Combination with Clickfine AutoProtect Safety Pen Needles.

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